
# EFECTE DE LA VARIABILITAT GENÈTICA DE DDR1 EN LA MATÈRIA BLANCA CEREBRAL I EN LA VELOCITAT DE PROCESSAMENT EN PACIENTS AMB UN TRASTORN DE L'ESPECTRE DE L'ESQUIZOFRÈNIA I ALTRES PSICOSIS

Cinta Gas Prades

UNIVERSITAT ROVIRA i VIRGILI

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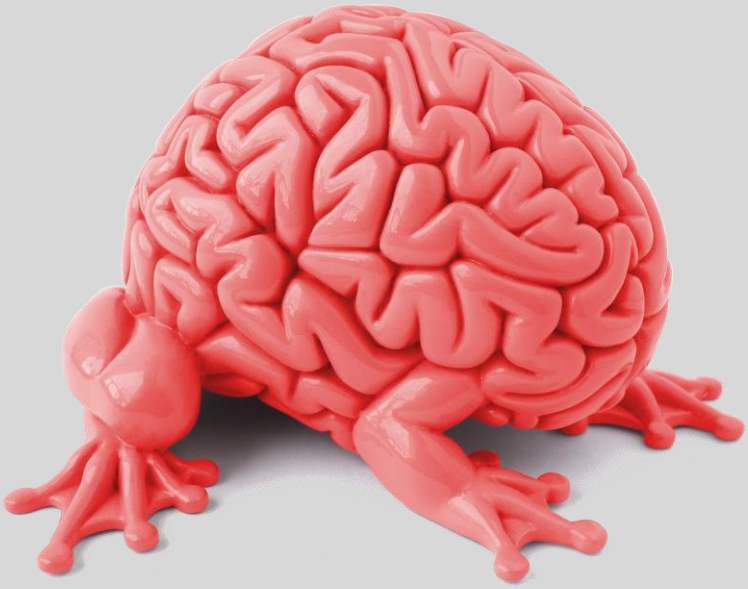
CINTA GAS PRADES



**TESI DOCTORAL**

**2021**

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**TESI DOCTORAL**

**Dirigida per la Dra. Elisabet Vilella Cuadrada**

**Departament de Medicina i Cirurgia de la Universitat Rovira i Virgili**

**Reus 2021**

UNIVERSITAT ROVIRA i VIRGILI

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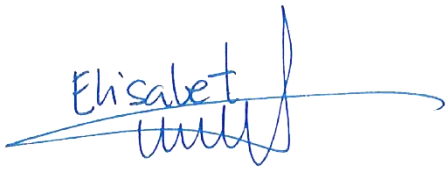
FAIG CONSTAR que aquest treball titulat "**Efecte de la variabilitat genètica de *DDR1* en la matèria blanca cerebral i en la velocitat de processament en pacients amb un trastorn de l'espectre de l'esquizofrènia i altres psicosis**", que presenta Cinta Gas Prades, ha estat realitzat sota la meva direcció al Departament de Medicina i Cirurgia d'aquesta Universitat i acompleix tots els requeriments necessaris per a l'obtenció del títol de Doctora.

Reus, 18 de març de 2021.

La directora de la tesi doctoral:



Dra. Elisabet Vilella Cuadrada

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*a Manel,*
*el meu company de viatge*

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# AGRAÏMENTS

En primer lloc, vull agrair a l'Elisabet Vilella, no només el lideratge d'aquesta tesi sinó també els valors, la dedicació i la motivació que transmet per la recerca.

En segon lloc, vull manifestar el meu agraïment a l'Institut Pere Mata i al grup de recerca, encara que físicament últimament ens hem trobat poc. I a la Irene, amb qui hem compartit (entre altres coses) moltes hores de formació.

Als participants dels estudis, per la important contribució.

A tots els que m'heu donat un cop de mà (o dos!) amb l'estadística: a la Mª José C., Quim, Gerard i sobretot a l'Ana Gavíria, amb qui em vaig iniciar i més hores vam invertir; heu aconseguit que m'agradi!

A l'equip de FIDMAG, que em va acollir durant la rotació externa: Edith Pomarol, Erick, Quim, Anna, Alicia i els que em deixo. També a l'equip de recerca de Psiquiatria de la UCL: Elvira Bramon i Álvaro; va ser una estada curta però intensa.

Als companys del CSMA de Tortosa, que compenseu les dues hores de viatge. A la Sandra, per la brillant idea dels "dimecres a recerca".

A les amigues i amics: els "tortosins" Lau, Robert, Marc i Cris (mil gràcies pels retocs artístics), les "barcelonines", els "tarragonins" dels "dimecres quedem" i "reusencs", pel suport i perquè continueu formant una part tan important de la meva vida. Entre les quals les coRs i resis adoptats: "xiquetes + xiquets"; va ser una gran sort trobar-nos! Gràcies, Alba, Ramon i Emilio per l'ajuda en la part tècnica i artística. I Mª José, pels moments compartits.

A tota la meva família, especialment als meus pares, al meu germà Lluís i a la meva cosina Montse, pel suport incondicional.

I, *last but not least*, a Manel.

A totes i a tots, moltes gràcies!

**Imatge de coberta:** *Jumping brain*, d'Emilio Garcia.

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# ÍNDEX

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# JUSTIFICACIÓ

El 2010, com a MIR de Psiquiatria, vaig tenir l'oportunitat d'iniciar-me en la recerca quan vaig entrar a formar part del grup Genètica i Ambient en Psiquiatria (GAP) a l'Hospital Universitari Institut Pere Mata, concretament en la línia de recerca del *receptor domini de la discoidina 1* (*DDR1*) i l'esquizofrènia.

Fa més d'una dècada que el grup va proposar el *DDR1* com a nou gen amb relació a l'esquizofrènia. El grup, prèviament, havia publicat un treball en què es demostrava la presència de *Ddr1* durant el neurodesenvolupament de ratolins. Posteriorment es va demostrar que *Ddr1* també estava implicat en la remielinització en un model murí de desmielinització-remielinització. Pel que fa als humans, el grup va publicar un treball que demostrava que en un cervell humà el *DDR1* s'expressa majoritàriament en oligodendròcits i també que l'expressió de la isoforma c és la que significativament correlaciona amb l'expressió de gens clàssics de mielina, i que aquesta isoforma es troba augmentada en cervells de pacients amb esquizofrènia.

Les alteracions en el neurodesenvolupament, fonamentades en estudis genètics, d'imatge i moleculars, sembla que són les responsables de la susceptibilitat pels trastorns de l'espectre de l'esquizofrènia i altres psicosis (TEEAP). Estudis en pacients amb esquizofrènia han evidenciat alteracions de la mielina i han identificat gens relacionats amb la mielina i els oligodendròcits com a gens susceptibles per a l'esquizofrènia.

Amb aquests antecedents ens vàrem plantejar la hipòtesi que les variants del *DDR1* podien associar-se a una alteració de la mielina que podia portar a un rendiment cognitiu pitjor, avaluable a través de la velocitat de processament (VP) com a funció directament associada a la integritat de la mielina en pacients amb TEEAP.

Donada la part eminentment clínica de la meva formació, el Màster en Investigació en Psiquiatria, Neurotoxicologia i Psicofarmacologia per la URV (2010-2012) em va permetre adquirir coneixements i aptituds en l'àrea de la recerca.

La rotació externa durant el MIR en el grup de recerca de la FIDMAG Germanes Hospitalàries (del gener al març de 2014) especialitzat en neuroimatge dels trastorns psiquiàtrics, així com la formació rebuda en el Diploma d'Especialització en Genètica i Imatge del Cervell Humà (Fundació Universitat Rovira i Virgili, 2015), em van ajudar a poder analitzar la relació entre el gen *DDR1* i la matèria blanca cerebral.

L'afirmació teòrica que l'afectació cognitiva és un dels aspectes clau de l'esquizofrènia que contribueix a conferir un pronòstic pitjor respecte a altres trastorns, afegida a

l'experiència clínica com a psiquiatra adjunta, i, més concretament, formar part d'un equip multidisciplinari d'atenció a la psicosi incipient, van aportar més interès a aprofundir en la relació de les variants del gen *DDR1* amb la cognició, concretament amb la VP.

La present tesi continua la línia d'investigació de *DDR1* amb els TEEAP, per estudiar la relació entre les variants del gen *DDR1* i els TEEAP en associació amb alteracions en la matèria blanca cerebral i la VP.

# ABREVIATURES

**A2RE:** *A2 response element*

**ADN:** àcid desoxiribonucleic

**ARN:** àcid ribonucleic

**ARNm:** ARN missatger

**CIM:** Classificació Internacional de Malalties

***CNP:*** *2',3'-cyclic nucleotide 3'phosphodiesterase*[*]

**CNV:** *copy-number variation*

***COMT:*** *catechol-o-methyltransferase*[*]

***CSMDI:*** *CUB and sushi multiple domains 1*[*]

***DDR1:*** *discoidin domain receptor 1*[*]

***DISC-1:*** *disrupted-in-schizophrenia 1*[*]

**DNMT:** ADN metiltransferasa

**DSM:** *Diagnostic and statistical manual of mental disorders*

**DTI:** *diffusion tensor imaging*

**DUP:** *duration of untreated psychosis*

**EM:** esclerosi múltiple

**FA:** *fractional anisotropy* (anisotropia fraccional)

**GWAS:** (de l'anglès) estudi d'associació de genoma complet

**HDAC:** *histone deacetylase* (histona desacetilasa)

**HMT:** *histone methyltransferase* (histona metiltransferasa)

**LD:** (de l'anglès) desequilibri de lligament

***MAG:*** *myelin-associated glycoprotein*[*]

**MATRICS:** *Measurement and Treatment Research to Improve Cognition in Schizophrenia*

**MCCB:** MATRICS *Consensus Cognitive Battery*

**MHC:** (de l'anglès) complex d'histocompatibilitat principal

**NIMH:** *National Institute of Mental Health*

***NRG1:*** *neuroregulin 1*[*]

***NRXN1:*** *neurexin 1*[*]

***OLIG2:*** *oligodendrocyte lineage transcription factor 2*[*]

**OPC:** *oligodendrocyte progenitor cell* (cèl·lules progenitores d'oligodendròcits)

**OR:** *odds ratio*

**PRS:** *polygenic risk score*

**RM:** ressonància magnètica

***RTN4R:*** *reticulon 4 receptor*[*]

**SNC:** sistema nerviós central

**SNP:** *single nucleotide polymorphism*

**TEEAP:** trastorns de l'espectre de l'esquizofrènia i altres psicosis

**TMT:** *Trail Making Test*

**TMT-A:** Part A del TMT

**VBM:** *voxel-based-morphometry*

**VP:** velocitat de processament

**ZFPM2:** *zinc finger protein, FOG family member 2*[*]

[*]Nom oficial del gen

# RESUM DE LA TESI DOCTORAL

El gen del receptor domini de la discoidina 1 (*DDR1*) està situat a la regió 6p24.21, que conté el complex d'histocompatibilitat principal que ha estat relacionat amb l'esquizofrènia. El DDR1 és un receptor tirosina-cinasa que és activat per col·lagen i al cervell és predominantment expressat per oligodendròcits. Els oligodendròcits formen la beina de mielina al sistema nerviós central (SNC), i la hipòtesi que estan involucrats en el desenvolupament dels trastorns de l'espectre de l'esquizofrènia i altres psicosis (TEEAP) pren força. S'ha observat una associació entre l'esquizofrènia i els *single nucleotide polymorphisms (*SNPs) del *DDR1* rs1049623, rs2267641 i rs2239518. L'SNP rs1049623 està en alt desequilibri de lligament amb el rs1264323, que està localitzat a la regió reguladora. D'altra banda, l'SNP rs2267641 està localitzat en una seqüència A2RE del gen *DDR1* que està involucrada en l'empalmament alternatiu de les isoformes *DDR1*b i *DDR1*c i el transport dels ARNm abans de ser traduït a proteïna. S'ha evidenciat que l'expressió de l'ARNm *DDR1*c es troba incrementada en cervells de pacients amb esquizofrènia.

Els TEEAP són trastorns altament heretables que es caracteritzen per símptomes positius i negatius així com per dèficits cognitius. Múltiples estudis mitjançant neuroimatge han evidenciat alteracions en la microestructura de la matèria blanca *in vivo* en aquests pacients.

**Hipòtesi:**

Amb els antecedents de què disposàvem ens vam proposar replicar l'associació de *DDR1* amb TEEAP en una altra mostra i estudiar si les variants del gen *DDR1* conferien susceptibilitat per presentar un TEEAP en associació amb variacions de la microestructura blanca cerebral i els dèficits neurocognitius com la velocitat de processament (VP).

**Objectius:**

1) Fer una recopilació sistemàtica de la informació disponible sobre l'expressió gènica i proteica de *DDR1* en SNC, tant en humans com en models animals i en els diversos tipus de cèl·lules, i descriure la relació de *DDR1* amb malalties del SNC.
2) Replicar l'associació de *DDR1* amb TEEAP en una mostra gran de pacients i controls procedents de tot l'Estat espanyol.
3) Determinar la influència dels SNPs de *DDR1* (rs1264323 i rs2267641) en la VP en una mostra de pacients amb diagnòstic de TEEAP establert.

4) Determinar la influència dels SNPs de *DDR1* (rs1264323 i rs2267641) en la VP en dues mostres independents de pacients en primeres fases de la psicosi i en controls sans.
5) Explorar mitjançant l'anisotropia fraccional (FA, en anglès) la relació entre la microestructura de la matèria blanca cerebral, la VP i el genotip *DDR1* en una mostra de pacients amb diagnòstic de TEEAP establert.

**Mètodes:**

En primer lloc vam fer una revisió bibliogràfica sistemàtica sobre el paper de *DDR1* en el SNC.

En segon lloc, per replicar la relació entre els TEEAP i les variants del gen *DDR1* es va realitzar un estudi amb un disseny cas-control en què pacients i controls (n=1193 i n=1839, respectivament) van ser genotipats pels SNPs rs1264323 i rs2267641 de *DDR1* i es van comparar les freqüències.

Per explorar la relació entre els SNPs (rs1264323 i rs2267641) de *DDR1* i la VP en els TEEAP establerts, es va avaluar la VP en 194 pacients per mitjà de la part A del *Trail Making Test* (TMT-A) i es van obtenir els genotips per *DDR1*. Per comparar la VP i els grups genotípics de *DDR1*, vam fer una anàlisi de covariància. D'altra banda, es va estudiar també aquesta relació en dues mostres independents de pacients en primeres fases de la psicosi (n=75 i n=312, respectivament) comparant-los als respectius controls sans (n=57 i n=160, respectivament).

En darrer lloc, es va seleccionar un grup de pacients (n=54) segons el genotip rs1264323 i van ser reavaluats, incloent una prova de *diffusion tensor imaging* (DTI) per ressonància magnètica cerebral. Per testar les associacions entre VP, la microestructura de la matèria blanca i el genotip *DDR1*, primer es van localitzar les regions de matèria blanca on la FA va correlacionar amb la VP, i després es va testar si la FA mostrava diferències entre els genotips de rs1264323.

**Resultats:**

Es van aportar dades ordenades i exhaustives sobre l'expressió de *DDR1* en els diversos tipus cel·lulars de SNC tant en rosegadors com en humans, informació sobre la variabilitat genètica de *DDR1* i patologies del SNC i perifèric, i l'evidència respecte el rol rellevant de *DDR1* en el procés de mielinització. També es va apuntar el seu paper important en la fisiopatologia d'algunes malalties neuropsiquiàtriques.

Es va replicar l'associació de *DDR1* amb TEEAP (rs1264323, p=0.015) i es va observar que els portadors del genotip rs1264323AA combinats amb el rs2267641AC/CC

presentaven risc per TEEAP comparats amb les altres combinacions genotípiques. Pel que fa a la relació de les variants de *DDR1* amb els pacients amb els TEEAP establerts, vam observar que els pacients amb el genotip rs2267641CC presentaven una disminució de la VP en comparació amb els pacients amb el genotips AA i AC ($p=0.009$). En canvi, vam trobar que la combinació genotípica de risc (rs1264323AA-rs2267641AC/CC) estava associada a un increment de la VP en els pacients en primeres fases de la psicosi però no en els controls sans.

Finalment vam observar que els pacients amb TEEAP establert amb el genotip rs1264323AA van mostrar una disminució de la FA en regions de la matèria blanca associades a una disminució de la VP.

**Conclusions:**

Les variants de *DDR1* sembla que poden conferir un risc per als TEEAP mitjançant alteracions en la microestructura de la matèria blanca, que poden conduir a una disfunció cognitiva. Els resultats suggereixen que les variants de *DDR1* tenen una associació directa amb la VP en les primeres fases del trastorn però una associació indirecta a mesura que el trastorn progressa.

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# I. INTRODUCCIÓ

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## 1. Generalitats dels trastorns psicòtics

Entre els trastorns de l'espectre de l'esquizofrènia i altres trastorns psicòtics (American Psychiatric Association, 2013), l'esquizofrènia és una de les patologies més greus i la més comuna de l'espectre (Kahn et al., 2015). Definida clàssicament per la presència de símptomes positius (com són al·lucinacions, deliris o comportament desorganitzat) i negatius (com l'abúlia, l'aplanament afectiu o la retracció social), en les darreres dècades s'ha anat consolidant l'evidència que l'afectació cognitiva és també una alteració nuclear d'aquests trastorns i que contribueix que sigui una de les principals causes de discapacitat al món (Vos et al., 2015).

Tot i la gran variació en els components metodològics dels estudis, en la revisió del 2018 de Moreno-Küstner i altres col·laboradors (Moreno-Küstner et al., 2018), s'apunta una prevalença global dels trastorns psicòtics al llarg de la vida d'un 0,75%.

Una altra característica d'aquests trastorns és que generalment apareixen per primer cop al final de l'adolescència o a l'inici de l'edat adulta (Owen et al., 2016), amb un pic entre els 18 i els 25 anys (Insel, 2010). Si es presenta després dels 40 anys d'edat, el trastorn es considera d'aparició tardana (Suen et al., 2019; Van Assche et al., 2017). Sovint l'àmplia variabilitat de les primeres fases del trastorn en fa difícil el diagnòstic, i per això s'ha arribat al consens d'anomenar-los de forma general *trastorns psicòtics incipients* (inclouen des de símptomes psicòtics aïllats, formes subsindròmiques i incompletes del trastorn, trets o estructures de personalitat amb risc, fins a diagnòstics de trastorns psiquiàtrics específics), tot esperant, amb l'evolució de la malaltia, com s'acaba definint. La psicosi incipient s'entén així com un fenomen dimensional (McGorry & Nelson, 2016).

L'etiologia d'aquests trastorns continua sent poc definida tot i la inversió de moltes dècades d'investigació en aquest camp. A la segona meitat del segle XX, quan van emergir els fàrmacs neurolèptics, una de les hipòtesis que va agafar més força va ser la dels neurotransmissors, concretament la de la dopamina (Carlsson, 1988), però també s'han postulat altres sistemes de neurotransmissors com el glutamat (Coyle, 2006), en focalitzar-se en els símptomes cognitius. Tanmateix, la investigació centrada en els fàrmacs (Yang & Tsai, 2017) en lloc del trastorn, fins ara ha proporcionat pocs avanços en la fisiopatologia dels TEEAP. Un dels models més acceptats és el del neurodesenvolupament, proposat fa més de dues dècades (Feinberg, 1982; Weinberger, 1987), que defineix la malaltia com una progressió que s'inicia durant el neurodesenvolupament, en què amb l'impacte de certs factors ambientals s'acaben manifestant els símptomes propis del trastorn psicòtic. Aquest model encaixa bé amb l'evidència científica de la intervenció tant de factors genètics com de factors ambientals (Van Os et al., 2008; Zwicker et al., 2018). Entre els factors ambientals relacionats amb

la psicosi s'han descrit l'exposició prenatal a infeccions virals, la història de maltractament durant la infància, la residència al medi urbà, la migració, el baix estatus socioeconòmic dels pares o el consum de cànnabis (Zwicker et al., 2018). D'altra banda, la contribució dels factors genètics a la psicosi és significativa i la descriurem més detalladament a la secció 2 d'aquesta introducció.

En la revisió feta per Raduà i altres (Radua et al., 2018) es va observar que un dels factors personals que estava més fortament lligat a la psicosi era el fet de tenir antecedents d'estat mental d'alt risc. A més a més, és crucial la identificació dels individus amb risc per l'esquizofrènia en les fases inicials del trastorn, ja que hi ha una associació clara entre una evolució pitjor de la malaltia i el temps de la psicosi sense tractar (DUP, de l'anglès *duration of untreated psychosis*). Si es reduís la DUP, es podria reduir la prevalença de símptomes negatius i millorar el pronòstic dels primers episodis psicòtics (Fusar-Poli et al., 2017). Els estudis en primers episodis són particularment importants, ja que tenen menys factors de confusió, com els efectes del tractament psicofarmacològic, de l'edat, els efectes a llarg termini de l'abús de substàncies o de patir un trastorn crònic.

Per dur a terme un diagnòstic psiquiàtric es fa una avaluació clínica mitjançant l'entrevista psiquiàtrica i l'exploració psicopatològica. S'utilitzen proves complementàries per al diagnòstic diferencial, per exemple amb quadres orgànics o tòxics, però actualment no es disposa de proves específiques per al diagnòstic. Per al diagnòstic clínic s'utilitzen uns criteris operatius que recull el *Manual de diagnòstic o estadística* (DSM, en anglès) de l'*American Psychiatric Association* (American Psychiatric Association, 2013) o la Classificació Internacional de Malalties (CIM) de l'Organització Mundial de la Salut. L'esquizofrènia, com la majoria de diagnòstics psiquiàtrics, continua sent un concepte sindròmic (Owen et al., 2016).

Al llarg de la tesi em referiré en general als trastorns de l'espectre de l'esquizofrènia i altres psicosis (TEEAP) seguint el sistema més actual, del DSM-5 (American Psychiatric Association, 2013), que introdueix el concepte del *continuum* en la psicosi i que utilitza el grau, el nombre i la durada dels signes i símptomes psicòtics per diferenciar diverses formes de símptomes psicòtics (Guloksuz & Van Os, 2018) (taula 1). En alguns moments em referiré més concretament als trastorns psicòtics incipients com a fase inicial dels trastorns psicòtics o a l'esquizofrènia, ja que és un dels trastorns psicòtics més freqüents i més estudiats.

| TRASTORNS DE L'ESPECTRE DE L'ESQUIZOFRÈNIA I ALTRES PSICOSIS (TEEAP) SEGONS DSM-5 |
|---|
| **Característiques clau:** deliris, al·lucinacions, pensament (discurs) desorganitzat, comportament motor molt desorganitzat o anòmal (inclosa la catatonia) i símptomes negatius |
| **Trastorn esquizotípic (de la personalitat)** |
| **Trastorn delirant** |
| **Trastorn psicòtic breu** |
| **Trastorn esquizofreniforme** |
| **Esquizofrènia** |
| **Trastorn esquizoafectiu** |
| **Trastorn psicòtic induït per substàncies/medicaments** |
| **Trastorn psicòtic degut a una altra afecció mèdica** |
| **Catatonia relacionada amb un altre trastorn mental** |
| **Trastorn catatònic degut a una altra afecció mèdica** |
| **Altre trastorn de l'espectre de l'esquizofrènia especificat i altre trastorn psicòtic (inclou síndrome de psicosi atenuada)** |
| **Trastorn de l'espectre de l'esquizofrènia no especificat i altre trastorn psicòtic** |

**Taula 1.** Trastorns de l'espectre de l'esquizofrènia i altres psicosis (TEEAP) segons el DSM-5 (American Psychiatric Association, 2013).

La recerca pot aportar informació rellevant per avançar en la identificació de marcadors per millorar el diagnòstic, el tractament i la qualitat de vida de les persones que pateixen un trastorn psiquiàtric.

## 2. La genètica dels TEEAP

Els TEEAP formen part de les malalties complexes, ja que no s'expliquen amb la genètica mendeliana, i, com hem comentat, en l'etiologia s'hi veuen implicats factors tant genètics com ambientals i la seva interacció.

Els estudis fets a la segona meitat del segle XX amb diversos dissenys que comprenien estudis d'agregació familiar, estudis amb bessons i estudis d'adopció, van aportar evidència per suficient confirmar que els TEEAP tenen un fort component genètic (Kety, 1987; McGuffin, P. & Gottesman, 1999). Amb les dades d'aquests estudis, es calcula que l'heretabilitat dels TEEAP se situa al voltant del 80% (Hilker et al., 2018). El risc de desenvolupar TEEAP al llarg de la vida sent familiar de primer grau d'un membre afectat va del 48% en els bessons monozigòtics al 13% en fills o 6% en pares (Gottesman, 1991).

# I. INTRODUCCIÓ

Els estudis d'associació de genoma complet (GWAS, *genome-wide association study*) han permès identificar variants polimòrfiques d'un sol nucleòtid (SNP, de *single nucleotide polymorphism*) i alteracions de fragments de l'ADN (pèrdua o guany) anomenades CNV (de l'anglès *copy-number variation*) associats a diversos trastorns psiquiàtrics, entre els quals l'esquizofrènia (Wendt et al., 2020), i la seva identificació pot ser d'utilitat en la pràctica clínica (Bouwkamp et al., 2017).

Amb relació als SNPs, amb el darrer gran esforç internacional en el qual s'han analitzat >60.000 casos i >10.0000 controls, ja s'han identificat >300 SNPs associats als TEEAP (Lam et al., 2019; Lee et al., 2019; Ripke et al., 2014). Amb el conjunt de variants del tipus SNP es pot calcular el *polygenic risk score* (PRS), que explica un 25% aproximadament de la base genètica en el cas de l'esquizofrènia i té potencial per ser utilitzat en l'avaluació del risc (Wendt et al., 2020).

Pel que fa a les CNVs associades als TEEAP, s'han identificat diverses CNVs recurrents: 1q21.1, 2p16.3 (*NRXN1*), 3q29, 7q11.2, 15q13.3, distal 16p11.2, proximal 16p11.2 i 22q11.2 (Kirov et al., 2014; Marshall et al., 2017). Una de les més freqüents és la causada per la deleció al cromosoma 22q11.2 que dona lloc a la síndrome velocardiofacial o síndrome de DiGeorge. Amb una incidència d'1/2.000-4.000 naixements, el 80% dels portadors d'aquesta síndrome desenvolupen un trastorn psiquiàtric (el 25-30% desenvolupen una psicosi) (Sullivan, 2019).

Aquests estudis cas-control amb rastreig a tot el genoma han permès identificar variants comunes i variants rares de susceptibilitat (Tiwari et al., 2010; Van Os et al., 2008), però no causants (Farrell et al., 2015). Queda més clar que els TEEAP tenen una base genètica poligènica amb centenars de variants comunes (freqüència >1%) i baix impacte fenotípic (OR lleugerament superior a 1), que en conjunt s'associen al diagnòstic. D'altra banda, presenten variants de baixa freqüència (<1%) en forma de variants funcionals i variants estructurals, aquestes majoritàriament representades per CNVs, però amb un gran impacte individual i una forta associació amb el diagnòstic (OR amb valors entre 2 i 60). A més, poden coincidir els dos tipus de variants; per exemple un portador de la deleció 22q11.2 amb un alt PRS per esquizofrènia tindrà un fenotip més sever (Davies et al., 2020).

Cal destacar que els GWAS han revelat un grau sorprenent de superposició genètica en els trastorns psiquiàtrics (Smoller et al., 2013), especialment en esquizofrènia, trastorn depressiu major, trastorn bipolar, trastorn d'ansietat i trastorn per dèficit d'atenció i hiperactivitat, mentre que els trastorns neurològics són genèticament més diferents (Anttila et al., 2018). Aquests resultats posen de manifest les disparitats entre la classificació clínica dels trastorns psiquiàtrics i la biologia subjacent. Dilucidar l'abast i la

importància biològica de les influències genètiques de trastorns creuats té implicacions per a la nosologia psiquiàtrica, l'elaboració de medicaments i la predicció de riscs (Lee et al., 2019).

Amb relació a la interacció entre la variabilitat genètica i els factors ambientals, progressivament es van identificant els mecanismes epigenètics associats a les patologies psiquiàtriques. El moment (edat de la persona) que els factors ambientals impacten sembla que és important en el cas de les malalties psiquiàtriques; s'han definit finestres de màxima susceptibilitat al període perinatal, a la infantesa i a l'adolescència, coincidint amb els canvis hormonals associats (Guintivano & Kaminsky, 2016). S'han identificat diversos mecanismes epigenètics que diferencien els controls sans de casos amb TEEAP, com són la metilació, la modificació d'histones i els nivells de microARNs. I en aquest sentit, tot i que som en una etapa molt preliminar, es planteja una nova classe de tractaments dirigits a modular el senyal epigenètic, com ara els inhibidors de la histona demetilasa (HMT, en anglès), els inhibidors de la histona desacetilasa (HDAC, en anglès) i els inhibidors de l'ADN metiltransferasa (DNMT) que actuen sobre la metilació de l'ADN (Smigielski et al., 2020).

## 3. Funcions de la mielina i alteracions en els TEEAP

### 3.1. Estructura i funcions de la mielina

El sistema nerviós central (SNC) es compon de matèria blanca i gris. La matèria blanca conté principalment fibres nervioses mielinitzades acompanyades de fibres no mielinitzades i cèl·lules de la neuròglia (com els astròcits, oligodendròcits o la micròglia). L'abundant mielina, amb alta composició en greixos, que recobreix els axons, li confereix la coloració blanquinosa. La matèria gris està formada per acumulacions de cossos cel·lulars de les neurones i les seves dendrites, juntament amb axons no mielinitzats (Gartner & Hiatt, 2011). La mielina és una capa de membrana citoplasmàtica concèntrica produïda pels oligodendròcits que cobreix els axons de les neurones al SNC (figura 1) i per les cèl·lules de Schwann al sistema nerviós perifèric (Muzio & Cascella, 2020). La mielina actua com a aïllant dels axons, els dona més capacitat per reproduir els estímuls elèctrics, de manera que la velocitat de conducció nerviosa depèn de les propietats estructurals de les fibres connectores, incloent el diàmetre axonal i el gruix aïllant de la beina de mielina (Aboitiz et al., 1992; Bartzokis, 2002).

Hem de tenir en compte que els oligodendròcits són molt sensibles a l'estrès oxidatiu, al trauma, als atacs immunomediats, als tòxics o a la hipoperfusió, factors que poden provocar la mort de l'oligodendròcit i la desmielinització (Kuhn et al., 2019). Nous

oligodendròcits diferenciats derivats de cèl·lules progenitores d'oligodendròcits (OPC, en anglès) poden substituir els oligodendròcits morts i restablir la beina de mielina al voltant dels axons desmielinitzats (remielinització), però la mielina regenerada té menys gruix que la beina de mielina original (Kuhn et al., 2019).

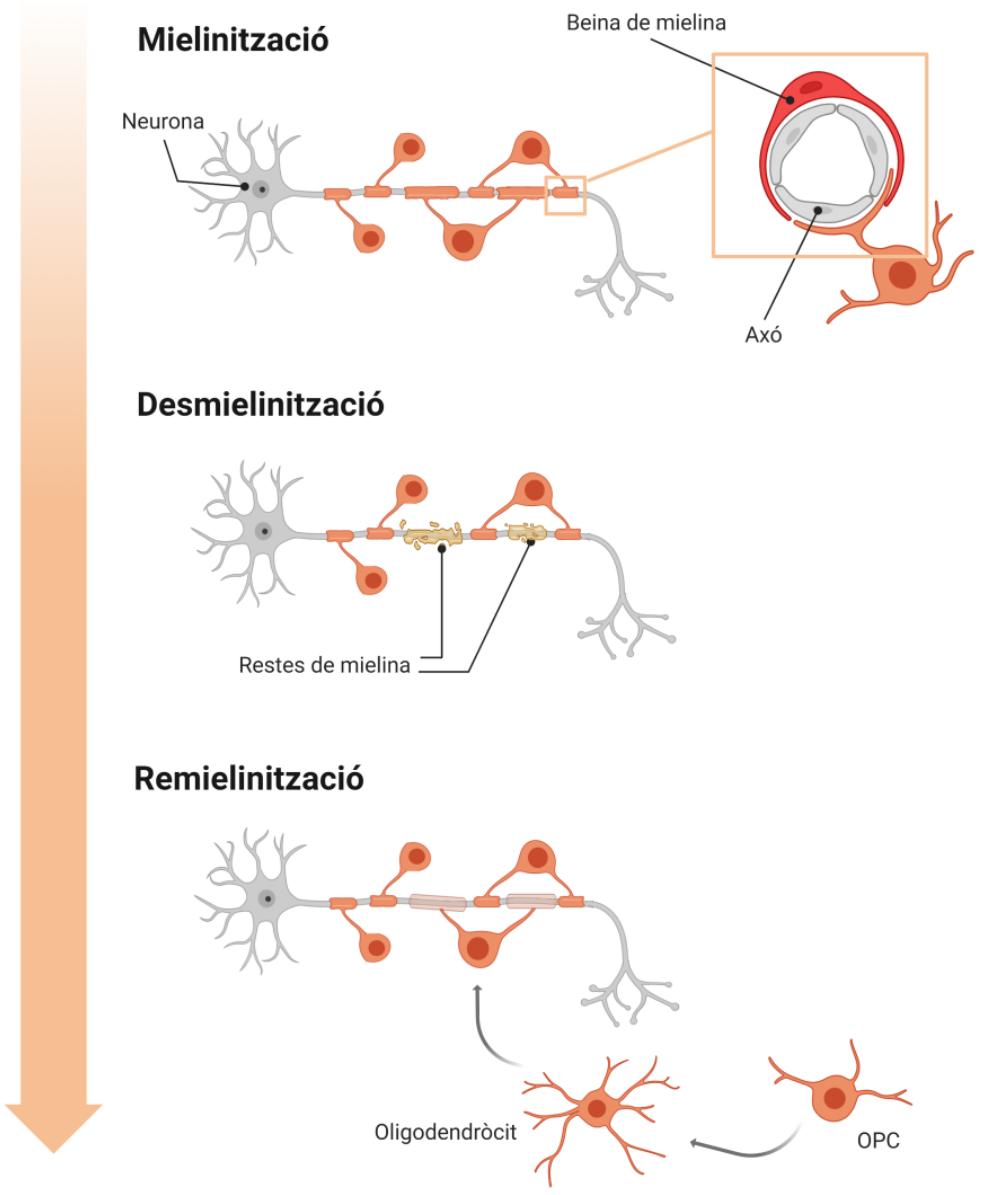


**Figura 1.** Oligodendròcits en la mielinització, desmielinització i remielinització. Adaptat de Kuhn et al. 2019 (Kuhn et al., 2019).

La visió clàssica de la mielina com a aïllant estàtic ha canviat en conèixer que es genera nova mielina contínuament, fins i tot al cervell adult (Young et al., 2013). I encara més

important: els estudis han demostrat que l'activitat neuronal modula la producció de mielina (Gibson et al., 2014). Un exemple clar d'aquesta estreta relació la trobem en les lesions cerebrals produïdes en l'esclerosi múltiple (EM), en què el dany provocat a la mielina pels autoanticossos causa, com a conseqüència, la degeneració de l'axó (Lemus et al., 2018). Aquestes observacions suggereixen que la mielinització pot ser essencial per a la funció neuronal i la plasticitat en el cervell adult (Tomassy et al., 2016).

### 3.2. Alteracions de la mielina en els TEEAP

Si tenim en compte la important funció dels oligodendròcits i la seva vulnerabilitat, no és estrany que diversos estudis apuntin que l'alteració dels oligodendròcits i la consegüent disfunció de la mielina poden contribuir al desenvolupament de TEEAP mitjançant l'alteració de la funció sinàptica i el processament de la informació (Giotakos, 2019; Mighdoll et al., 2015; Raabe et al., 2019; Takahashi et al., 2011). La hipomielinització i l'alteració de la integritat de la matèria blanca pot contribuir a la desincronització i desconnectivitat de la transmissió, mentre que el fracàs de la diferenciació astrocítica provoca anormalitat en la cobertura glial i en el suport a les sinapsis (Dietz et al., 2020). Aquesta hipòtesi encaixa molt bé en la hipòtesi més general de la causalitat dels TEEAP coneguda com la teoria de la desconnectivitat neuronal, que s'ha identificat com una anomalia central en l'esquizofrènia (Coyle et al., 2016; Konrad & Winterer, 2008) i suggereix que la integració cerebral anormal pot fonamentar el dèficit cognitiu i els símptomes presents en el trastorn (Bartzokis, 2002; Giotakos, 2019).

La dinàmica del curs de la matèria blanca al llarg de la vida i la consistència dels dèficits de connectivitat en els TEEAP donen suport a la integritat de la matèria blanca com un fenotip prometedor per avaluar els dos models proposats en l'etiologia i el curs d'aquests trastorns: el model del neurodesenvolupament i el model neurodegeneratiu (Kochunov & Hong, 2014). Els models del desenvolupament, com hem comentat anteriorment, plantegen que els factors de risc genètics i ambientals actuen durant el període prenatal, perinatal i en els períodes inicials de l'adolescència, de manera que n'alteren la trajectòria del desenvolupament i condueixen a l'aparició dels trastorns en l'adolescència i en la primera etapa de l'edat adulta. Els models neurodegeneratius descriuen els TEEAP com a trastorns de trajectòria neurodegenerativa progressivament desfavorable, un tema de recerca actiu ja des de l'observació de Kraepelin del declivi mental dels pacients amb esquizofrènia. S'han proposat diversos models per descriure la trajectòria del desenvolupament al llarg de la vida dels canvis en la matèria blanca en pacients amb esquizofrènia, com el model neurotòxic, el del desenvolupament i el que inclou el model del desenvolupament més el degeneratiu. Actualment, l'evidència dona més suport a

l'últim model esmentat, que combina el neurodesenvolupament amb el declivi posterior (Peters & Karlsgodt, 2015) (figura 2). Aquest model inclou diferències primerenques en la trajectòria del desenvolupament, així com un declivi continuat després de l'aparició, que pot ser degut als efectes de la medicació, a la toxicitat de la malaltia o a l'alteració dels efectes de l'envelliment.

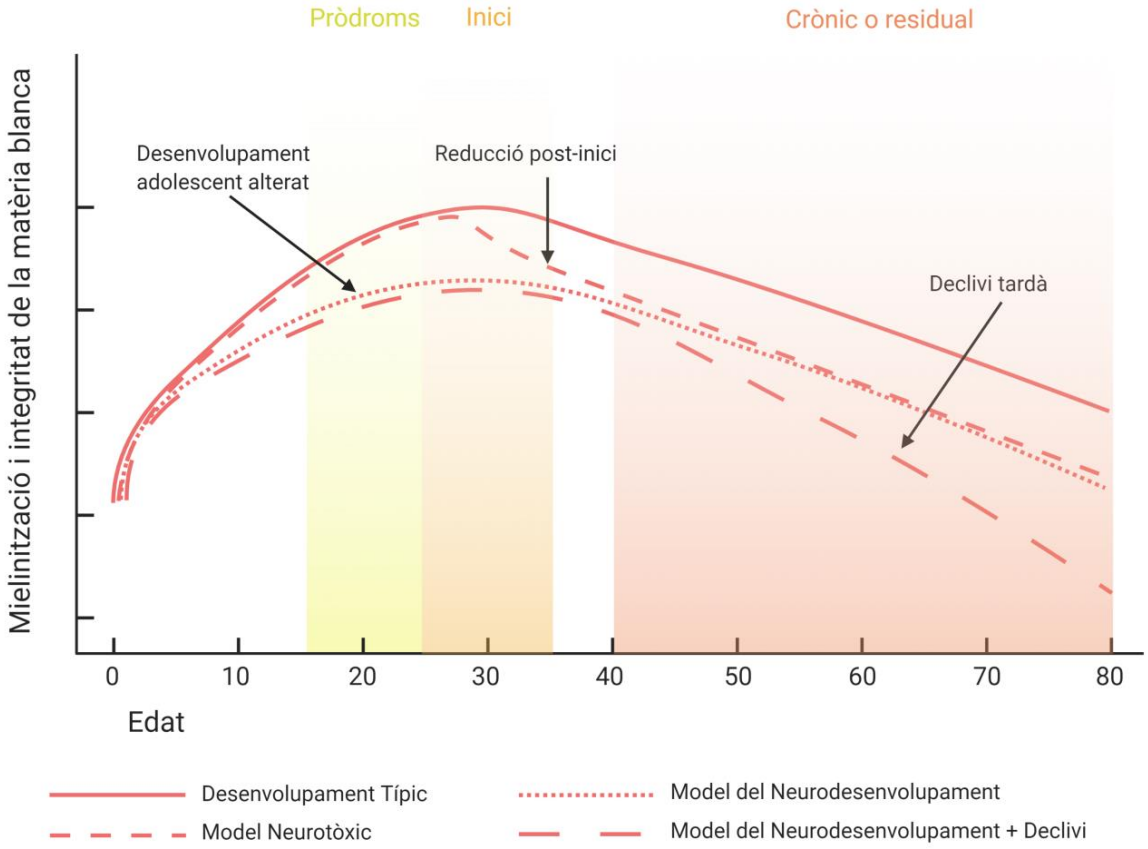


**Figura 2.** Models hipotètics dels canvis en el desenvolupament de la matèria blanca en les diverses etapes de l'esquizofrènia, en comparació amb canvis saludables en la matèria blanca al llarg de la vida. Adaptat de Peters and Karlsgodt 2015 (Peters & Karlsgodt, 2015).

A continuació, descriurem diversos enfocaments tècnics que han proporcionat evidències científiques sobre l'alteració de la mielina en els TEEAP.

### 3.2.1. Estudis histopatològics de la mielina

Estudis *post mortem* en pacients amb esquizofrènia han reportat una reducció del 14% al 22% en la densitat i la quantitat d'oligodendròcits (Kochunov & Hong, 2014; Takahashi et al., 2011), especialment en tractes de fibra que connecten els còrtexs prefrontals.

Mitjançant microscòpia electrònica (Uranova et al., 2001), van demostrar oligodendròcits apoptòtics i alteracions en la formació de les beines de mielina en forma de cossos lamel·lars concèntrics en cervells de pacients amb esquizofrènia, juntament amb irregularitats de l'heterocromatina i mitocondris en els oligodendròcits.

### 3.2.2. Tècniques de neuroimatge per estudiar la mielina

La màquina de ressonància magnètica (RM) permet obtenir imatges de teixits. Es basa en el nucli de l'àtom d'hidrogen (H), per les seves propietats magnètiques i perquè és el més abundant en els teixits. Permet detectar àrees que presenten danys, variació en la densitat del teixit, anàlisi de la volumetria, girificacions i gruix cortical. Hi ha diverses modalitats, entre les quals, l'estructural, la funcional i la de difusió.

La RM estructural permet examinar alteracions cerebrals utilitzant mesures quantitatives del teixit cerebral. Els estudis volumètrics dels cervell complet vòxel a vòxel (unitats mínimes de resolució en tres dimensions), en anglès *voxel-based-morphometry* (VBM), permeten comparar la densitat de matèria en cada un dels vòxels cerebrals entre els grups de subjectes a estudi i establir correlacions entre determinades característiques clíniques i la distribució espacial dels diversos tipus de teixits. La majoria d'estudis de VBM fan referència a anàlisis de la matèria gris, però també és possible treballar amb altres tipus de teixits o mesures anatòmiques (com la matèria blanca o el gruix cortical). Diversos estudis confirmen que els pacients amb psicosi presenten una dilatació dels ventricles laterals i una disminució del volum cerebral total i del volum cortical, en comparació amb controls (Fusar-Poli & Meyer-Lindenberg, 2016).

La DTI (*diffusion tensor imaging*) és la tècnica d'imatge per RM avançada que ha permès progressar en l'estudi de la integritat dels tractes de mielina al sistema nerviós central (Garin-Muga & Borro, 2014). Aquesta tècnica permet, de forma no invasiva i *in vivo*, obtenir mapes quantitatius de l'organització microestructural dels teixits i identificar de forma tridimensional el procés de difusió de molècules, principalment aigua. La difusió de les molècules d'aigua al cervell oscil·la entre la llibertat completa en totes direccions (*isotropia*) o la restricció en direccions concretes (*anisotropia*) en funció dels components del teixit d'una regió determinada (Basser & Jones, 2002). Les beines de mielina dels axons fan que la difusió de l'aigua sigui paral·lela al sentit d'orientació de les fibres. La reducció significativa de l'anisotropia indica una alteració de la integritat de la matèria blanca, ja sigui per modificació de l'orientació de la fibra, reduccions del nombre dels axons o alteracions de la mielinització (Scheel et al., 2013). L'anisotropia fraccional (FA, en anglès) és una mesura utilitzada freqüentment, i indirectament proporciona la

integritat microestructural, reflectint suposadament tant la mielinització com l'organització dels tractes de mielina. Les mesures secundàries aconseguides amb la DTI són la difusivitat radial i l'axial, que es relacionen amb la mielinització i l'organització axonal respectivament (Wozniak & Lim, 2006). L'estudi de DTI s'ha aplicat a trastorns neurològics de la matèria blanca, com l'EM, les leucodistròfies o les lesions cerebrals traumàtiques. També en trastorns psiquiàtrics com l'esquizofrènia, el trastorn bipolar, el trastorn depressiu major i l'autisme (Alba-Ferrara & de Erausquin, 2013; Koshiyama et al., 2020; Mighdoll et al., 2015; Pasternak et al., 2018; Pomarol-Clotet et al., 2010). La majoria dels estudis de DTI en esquizofrènia han mostrat una marcada disminució de la FA a les regions de la corona radiada anterior, el cos callós, el fòrnix i les circumvolucions cingulades (Kelly et al., 2018; Koshiyama et al., 2020). Aquestes llargues fibres de connexió sembla que faciliten la comunicació interregional i donen suport a una àmplia gamma de funcions cognitives (Karlsgodt, 2016).

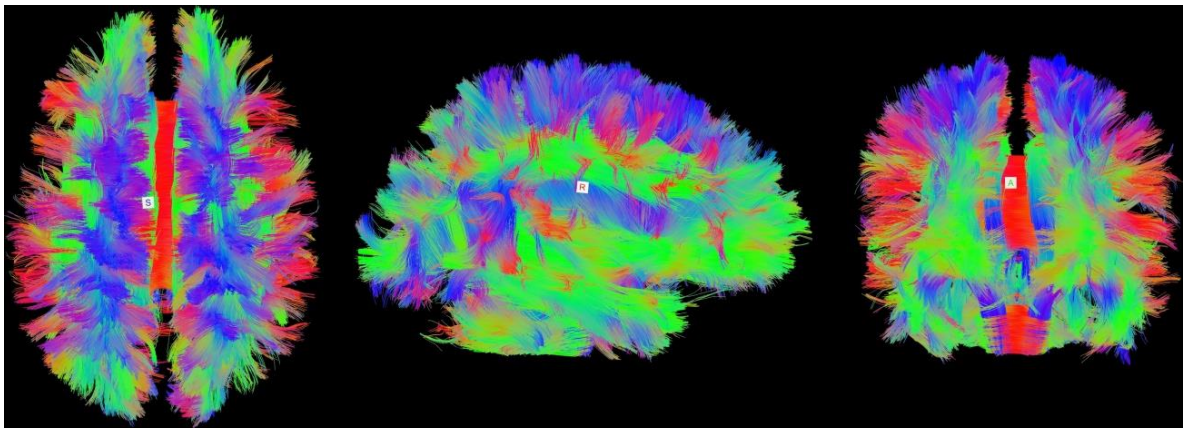

**Figura 3.** Imatges dels tractes de mielina del cervell humà obtingudes mitjançant DTI. La tractografia és la representació en 3D de DTI i es pot plasmar mitjançant un mapa de color. Cada segment de fibra reconstruïda s'ha acolorit d'acord amb la seva orientació espacial, i els segments en direccions intermèdies s'acoloreixen mitjançant una combinació d'aquests tres colors en funció de la proximitat en cada una d'aquestes orientacions. Segments en direcció esquerra-dreta: vermell; inferosuperior: blau; anteroposterior: verd. Imatges cedides per FIDMAG Germanes Hospitalàries Research Foundation.

L'alteració de la matèria blanca és present des dels estadis incipients, tant avaluada amb neuroimatge estructural (Andreou & Borgwardt, 2020) com per DTI (Carletti et al., 2012; Domen et al., 2017). Tot i això, és important apuntar que les alteracions observades en DTI en pacients amb primers episodis són menys robustes que en pacients crònics (Peters et al., 2010; Samartzis et al., 2014).

### 3.2.3. Gens relacionats amb la mielina en els TEEAP

Hi ha múltiples línies d'evidència derivades de dades de neuroimatge, moleculars i genètiques que donen suport al paper dels gens relacionats amb l'oligodendroglia i la mielina i a les vies moleculars en l'esquizofrènia (Alba-Ferrara & de Erausquin, 2013; Gouvêa-Junqueira et al., 2020; Roussos & Haroutunian, 2014; Takahashi et al., 2011; Voineskos, 2015). Alguns dels gens altament expressats en oligodendròcits revisats per Roussos i Haroutunian (Roussos & Haroutunian, 2014) amb més suport científic per l'associació amb l'esquizofrènia són *NRG1* juntament amb el receptor ERBB4, *DISC-1*, *RTN4R*, *OLIG2, CNP* i *MAG*.

També s'han realitzat alguns estudis que han evidenciat que els efectes de les variants dels gens relacionats amb la mielina en el rendiment cognitiu estan mediats per la integritat dels tractes de matèria blanca en pacients amb esquizofrènia, com els de Poletti i col. amb la *COMT* (Poletti et al., 2016), i Voineskos i col. amb *MAG*, *OLIG2* i *CNP* (Voineskos et al., 2013). Giddaluru i col. van fer un estudi de GWAS en població sana i van proporcionar noves dades sobre la genètica de les vies de la matèria blanca i la velocitat de processament destacant el paper del gens *ZFPM2* i *CSMD1* (Giddaluru et al., 2016).

Com hem comentat, la beina de mielina ajuda a preservar l'amplitud i a augmentar la velocitat de conducció de la propagació del potencial d'axó. Giotakos (Giotakos, 2019) apunta que, donat que el complex d'histocompatibilitat principal (MHC, en anglès) és el responsable de la superposició genètica tant en l'EM com en l'esquizofrènia, i tenint present la relació interdependent dels oligodendròcits i els axons que mielinitzen, podríem suggerir que trastorns com l'esquizofrènia o l'EM tenen en comú un processament desordenat de la informació al SNC, i en el cas dels TEEAP dona lloc als símptomes cognitius (figura 4).

Aquests estudis s'han realitzat amb hipòtesis centrades en cada un dels gens en particular. En l'era dels estudis de genoma complet ens podem preguntar quin paper tenen els gens expressats en oligodendròcits en el marc general d'identificació de variants de tipus SNP de susceptibilitat pels TEEAP. La sofisticació de les tècniques d'anàlisi de les dades genètiques permet, avui en dia, agrupar les variants genètiques que es troben en gens amb una expressió característica d'oligodendròcits (o dels altres tipus cel·lulars del SNC), de manera que s'ha pogut identificar quina és la proporció de cada tipus cel·lular en la susceptibilitat genètica deguda a SNPs. El que s'ha reportat és que el percentatge més alt de SNPs es troben en gens de neurones, però a continuació es troben variants de gens propis d'oligodendròcits (Skene et al., 2018).


**Figura 4.** Desmielinització, desconnectivitat cerebral i el resultant trastorn del procés de la informació en la psicosi. Adaptat de Giotakos 2019 (Giotakos, 2019).

## 4. El gen *DDR1* i els TEEAP

La regió cromosòmica 6p24.21, a prop de la regió del MHC, s'ha relacionat amb l'esquizofrènia (Owen et al., 2004) i inclou el locus que codifica el gen del receptor domini de la discoidina 1 (*DDR1*) (Edelhoff et al., 1995; Valent et al., 1996). El DDR1 és un receptor tirosina-cinasa i s'han identificat 5 isoformes de *DDR1* generades per empalmament alternatiu anomenades *isoformes a-e* (figura 5). El DDR1 és present en nivells baixos en teixits epitelials i en quantitats superiors al cervell, on és expressat majoritàriament per oligodendròcits (Roig et al., 2010). L'expressió de la isoforma c està altament correlacionada amb les proteïnes relacionades amb la mielina MAG i OLIG2 del cervell humà (Roig, Abasolo et al., 2012).

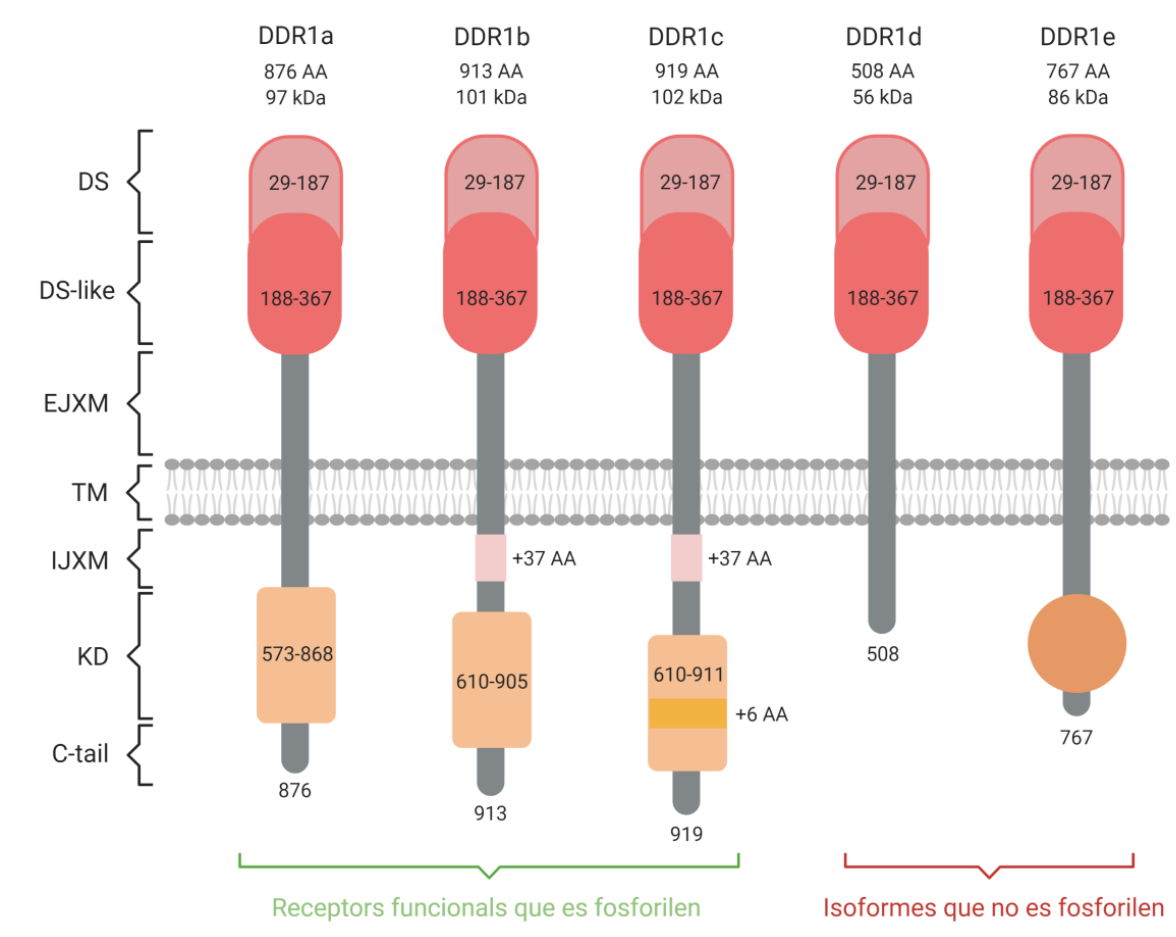


**Figura 5.** Isoformes a-e de *DDR1*. DS: domini discoidina, DS-like: domini similar a la discoidina, EJXM: regió extracel·lular juxtamembrana, TM: segment transmembrana, IJXM: regió intracel·lular juxtamembrana, KD: domini cinasa, AA: aminoàcid. Adaptat de Rammal i col. (Rammal et al., 2016).

Fins al moment només s'ha descrit el col·lagen com a únic lligand capaç d'activar DDR1 (Leitinger, 2014) (figura 6).

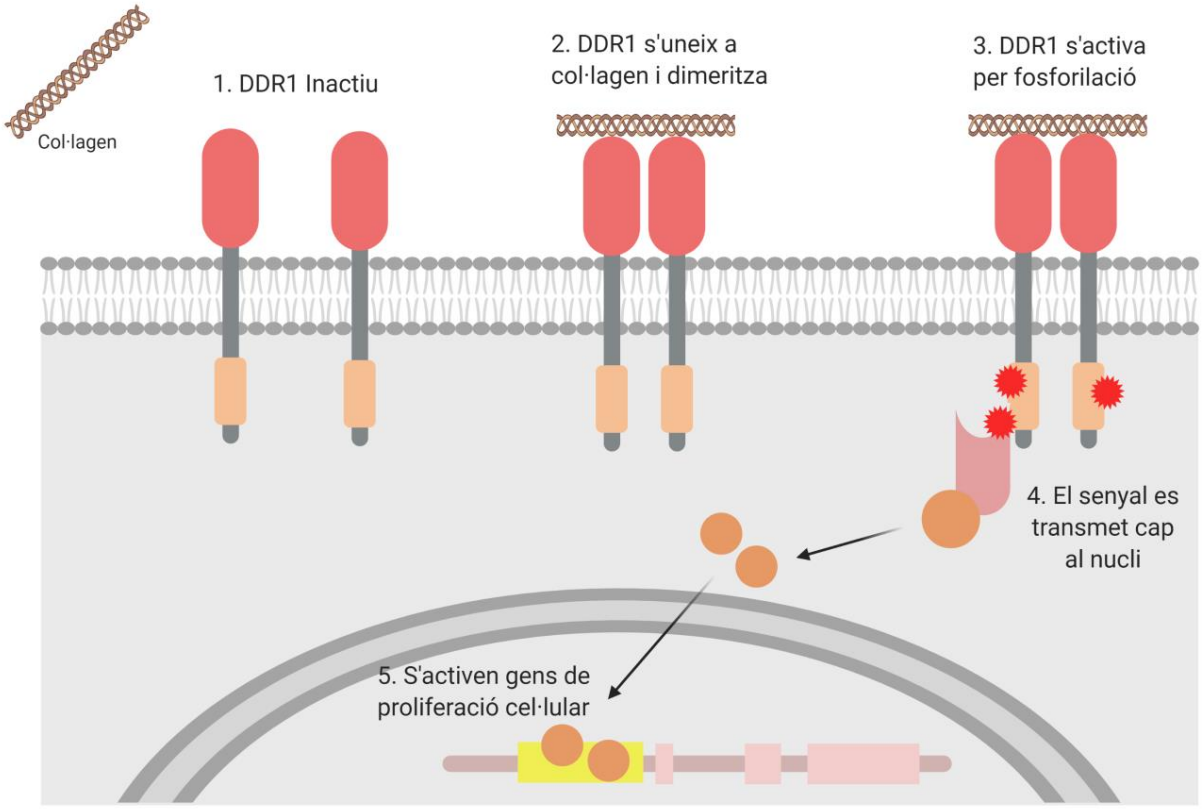


**Figura 6.** Activació de DDR1 per unió amb col·lagen.

El *DDR1* s'expressa durant el procés de mielinització del neurodesenvolupament (Franco-Pons et al., 2006a) i en la remielinització (Franco-Pons et al., 2009), tal com s'ha observat en estudis amb ratolins. En un article publicat el 2007 per Roig i col·laboradors, es va trobar una relació significativa entre un SNP (rs1049623) d'aquest gen amb l'esquizofrènia, particularment en homes (OR=2,03, 95% CI=1,51-2,73; P=0,0001). Aquesta associació es va confirmar en una anàlisi d'haplotip, que va mostrar una relació significativa entre els SNPs rs1049623, rs2267641 i rs2239518 i l'esquizofrènia (Roig et al., 2007), alhora que es va observar que l'expressió d'ARNm de *DDR1* en limfòcits de individus portadors d'al·lel G (rar o de risc) de rs1049623 era inferior que en els portadors del genotip heterozigot (AG) i per l'homozigot AA. Cal assenyalar que cap dels SNPs causa un canvi d'aminoàcid, però tant el rs2267641 com el rs1264323 estan implicats en l'expressió gènica (Roig et al., 2007; Roig, Abasolo et al., 2012; Roig,

Moyano et al., 2012) (figura 7). El rs1264323, probablement per la seva posició a la suposada regió promotora, està inclòs en la base de dades de variacions genètiques que afecten la regulació de l'expressió dels gens (eQTL) per la seva expressió diferencial en el nervi tibial humà i altres teixits. L'SNP rs2267641 es troba a la seqüència A2RE que participa en l'empalmament alternatiu de les isoformes *DDR1*c i *DDR1*b i en el transport de l'ARN missatger abans de ser traduït a proteïna (Roig, Moyano et al., 2012). En un estudi posterior, es va observar una elevació del ARNm de la isoforma *DDR1*c en el teixit de l'escorça prefrontal dorsolateral cerebral en pacients amb esquizofrènia respecte dels controls (Roig 2012a). Aquests resultats concorden amb estudis previs, comentats anteriorment, en què es mostra l'expressió alterada de gens de la mielina en pacients amb esquizofrènia.

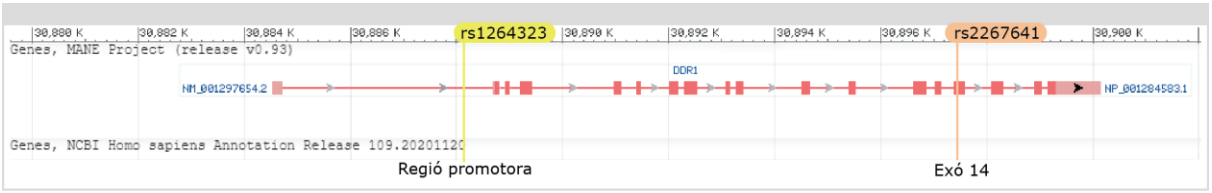


**Figura 7.** Posició dels SNPs analitzats al gen *DDR1* (Cromosoma 6. GRCh38. p13). Font: https://www.ncbi.nlm.nih.gov/gene/780. Data de consulta: 13/02/21.

## 5. Neurocognició

### 5.1. Qüestions generals

El terme *neurocognició* s'utilitza per descriure funcions compreses en regions del cervell o les seves xarxes, i com es relacionen amb els processos de pensament i del comportament humà. Inclou capacitats com la percepció, la velocitat de processament, l'atenció, la memòria, el processament del llenguatge, la capacitat visuoespacial i les funcions executives.

Per poder avaluar aquestes dimensions, s'utilitzen tests que s'han agrupat en bateries per facilitar l'avaluació i estimular el desenvolupament de nous enfocaments per millorar el tractament de les alteracions cognitives. En aquesta direcció, el 2002, el *National Institute of Mental Health* (NIMH) va establir la *Measurement and Treatment Research to Improve Cognition in Schizophrenia* (MATRICS) per aconseguir més consens en els dominis cognitius claus en l'esquizofrènia. Van dissenyar una bateria cognitiva denominada MCCB i van considerar com a rellevants els factors següents:

atenció/vigilància, velocitat de processament, memòria de treball, aprenentatge verbal, aprenentatge visual, raonament i resolució de problemes i cognició social (Nuechterlein et al., 2004).

### 5.2. Funció cognitiva i TEEAP

A part dels símptomes clàssics positius i negatius, l'esquizofrènia es caracteritza per alteracions cognitives. Els dèficits cognitius són comuns i clínicament rellevants, i són índexs importants de la funcionalitat i del tractament en els pacients. Fins i tot es va suggerir que els criteris diagnòstics haurien d'incloure un criteri relatiu a la capacitat cognitiva, fet que faria augmentar la consciència de la disfunció cognitiva a la pràctica clínica (Bora et al., 2010), però no hi va haver consens suficient. En particular, els dèficits cognitius persistents són uns predictors molt fiables de la recaiguda (Andreasen et al., 2005). La seva identificació ajuda a treballar la consciència del dèficit i és útil per millorar la individualització dels programes de tractament.

Diversos estudis han provat que els dèficits cognitius són evidents en les fases inicials de la malaltia (Menkes et al., 2019) fins i tot a l'inici del neurodesenvolupament, molt abans de l'aparició de la psicosi (Bora & Murray, 2014; Sheffield et al., 2018).

El dèficit cognitiu generalitzat és el més clar i fiable, però aquestes alteracions inclouen dificultats atencionals, de velocitat de processament, de memòria, de funcions executives i de cognició social. Les dades suggereixen dèficits específics en la memòria verbal en els trastorns psicòtics afectius i no afectius, i específicament la velocitat de processament en l'esquizofrènia (Dickinson et al., 2007; Sheffield et al., 2018).

El deteriorament neurocognitiu reflecteix un dèficit primari i es relaciona amb una vulnerabilitat genètica. No obstant els nombrosos estudis realitzats, els substrats neuropatològics de l'alteració cognitiva en l'esquizofrènia encara no s'han pogut establir.

### 5.3. Velocitat de processament

#### 5.3.1. Generalitats

La velocitat de processament (VP) reflecteix la quantitat d'informació que pot ser processada per unitat de temps. És una variable vagament definida que s'utilitza amb freqüència per explicar el rendiment tant en individus sans com en els que han patit una lesió cerebral (Tirapu Ustárroz et al., 2008).

En la VP, hi ha diversos factors que poden condicionar una resposta ràpida o lenta, com són l'atenció, motivació, la pràctica, el nivell d'activació, la comissió d'errors en l'execució de la tasca, l'existència d'alteracions anímiques, la impulsivitat, el consum de substàncies, la presència de símptomes neuropsicològics o dificultats motores. Algunes depenen de l'entorn, mentre que altres característiques són pròpies del subjecte (Tirapu Ustárroz et al., 2008).

Com hem apuntat anteriorment, la VP és una de les funcions més afectades en els pacients amb esquizofrènia amb aproximadament 1,5 derivacions estàndard per sota de la mitjana dels controls sans (Dickinson et al., 2007) i està relacionada amb la funcionalitat dels pacients (Brébion et al., 2009).

Ojeda i col·laboradors (Ojeda et al., 2008) van assenyalar la VP com un factor central en la relació entre símptomes cognitius i resultats funcionals en l'esquizofrènia crònica. També s'ha detectat una disminució de la VP en familiars de primer grau de pacients amb esquizofrènia, així com en individus amb un alt risc de desenvolupar el trastorn (Bolt et al., 2019; Dickinson et al., 2007; Paolo Fusar-Poli et al., 2012; Keefe et al., 2006), fet que suggereix que la VP pot ser un marcador biològic de l'esquizofrènia. Centrar-se a estudiar la VP pot proporcionar-nos, a més a més, una mesura més precisa del deteriorament cognitiu en els pacients sense evidències clares de deteriorament, com en l'estudi realitzat per González-Blanch i col·laboradors (González-Blanch et al., 2010).

### 5.3.2. Relació amb la integritat de la mielina

Les tècniques de neuroimatge i del registre de l'activitat cerebral han aportat informació rellevant pel que fa a les estructures subjacents a la VP. La VP s'ha relacionat més amb la matèria blanca cerebral que amb la matèria gris (Tirapu Ustárroz et al., 2011). Estudis conductuals mitjançant tècniques de neuroimatge han suggerit una relació entre la VP i determinades característiques del "cablejat" cerebral, tals com el diàmetre de les vies nervioses, la integritat de les beines de mielina, el grau de mielinització, el nombre de canals iònics i l'eficiència de les sinapsis (Ríos-Lago & Periañez, 2010). Donat que els tests neuropsicològics que mesuren la VP requereixen que els subjectes executin ràpidament tasques simples que integren un bon nombre d'operacions cognitives bàsiques, les investigacions de les bases neuronals de la VP s'han centrat en la connectivitat anatòmica del cervell, mitjançant la DTI, com Karbasforoushan i col., que van observar que el dèficit cognitiu en pacients amb esquizofrènia estava mediat per la reducció de la integritat de la matèria blanca i que aquesta relació era més forta per la VP (Karbasforoushan et al., 2015).

Kochunov i altres (Kochunov et al., 2017) van fer un estudi transversal amb 166 pacients i 213 controls amb la finalitat de conèixer si l'alteració de la connectivitat estructural cerebral era responsable de 2 dels dèficits cognitius bàsics de l'esquizofrènia: la reducció de la VP i el deteriorament de la memòria de treball. Van suggerir que la VP contribueix a l'associació entre la microestructura de la matèria blanca i la memòria de treball en l'esquizofrènia, i també en controls sans però de forma menys robusta, i que la deficiència de matèria blanca és regional i específica pels tractes que normalment es relacionen amb el rendiment de la VP.

Recentment, Yang i altres col·laboradors (M. Yang et al., 2020) han realitzat el primer estudi sobre l'associació entre la funció cognitiva i la integritat de la matèria blanca en pacients amb un primer episodi psicòtic que no havien pres mai tractament farmacològic en comparació amb controls sans. Han observat una alteració generalitzada i significativa de la matèria blanca en 5 regions cerebrals (circumvolució cingular, càpsula interna, cos callós, cerebel i tronc cerebral), un deteriorament neurocognitiu generalitzat en els pacients comparat amb els controls i una correlació negativa de la FA al gir cingular esquerra amb l'índex del *Trail Making Test-A* al grup de pacients. Aquestes troballes suggereixen també que la desconnexió de la matèria blanca pot ser una de les causes dels dèficits cognitius en els TEEAP.

### 5.3.3. Part A del *Trail Making Test*

El *Trail Maing Test* (TMT) és un dels tests neuropsicològics més populars i s'inclou en la majoria de bateries neuropsicològiques. Originalment era part de l'*Army Individual Test Battery* (1944) i posteriorment es va incorporar a la *Halstead Reitan Battery* (Reitan & Wolfson, 1985). El TMT consta de dos parts. La part A del TMT consisteix a connectar, mitjançant línies i de forma consecutiva, 25 nombres distribuïts a l'atzar en un full de paper. El TMT-A s'inclou en la MCCB i s'utilitza per mesurar la VP. La part B és una tasca similar, a excepció que la persona ha d'alternar nombres i lletres. Sembla que el TMT-B reflecteix processos d'ordre superior com la flexibilitat cognitiva. La puntuació de cada part representa la quantitat de temps necessari per completar la tasca. Puntuacions altes indiquen un rendiment cognitiu pitjor.

Hi ha diversos factors que s'associen al deteriorament cognitiu en l'esquizofrènia, com l'edat, el gènere, els anys d'educació, els anys de duració de la malaltia, l'edat d'inici del trastorn i els símptomes negatius. Laere i col·laboradors (Laere et al., 2018) van fer una metaanàlisi sobre la VP cognitiu i la flexibilitat cognitiva de pacients amb esquizofrènia (mesurades amb TMT-A i B respectivament) i la contribució de factors sociodemogràfics

al rendiment cognitiu. Van concloure que la funció cognitiva dels pacients amb esquizofrènia mesurats per TMT-A i B estava deteriorada en comparació amb els controls sans, i que els factors com ara l'abús de substàncies, anys d'educació, anys de duració de la malaltia i l'estat clínic dels pacients amb el rendiment cognitiu mostraven una associació però amb un efecte petit i no significatiu en les puntuacions.

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Cinta Gas Prades

# II. HIPÒTESIS

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Com s'ha descrit en la introducció, disposàvem d'evidències prèvies de la relació entre el gen *DDR1* i l'esquizofrènia així com de la seva participació en la mielinització.

A partir d'aquestes evidències es va formular la hipòtesi general següent:

- Les variants del locus del gen *DDR1* confereixen susceptibilitat per presentar un TEEAP en associació amb variacions en la microestructura de la matèria blanca cerebral i els dèficits neurocognitius com la VP.

I amb aquesta hipòtesi general es van plantejar les hipòtesis específiques següents:

1. Els estudis d'expressió de *Ddr1* realitzats en models animals i l'estudi de *DDR1* en càncer ens poden proporcionar detalls de la funció de *DDR1* útils per entendre el seu paper en la mielinització.
2. L'associació entre variants de tipus SNP de *DDR1* i esquizofrènia trobada en la mostra de pacients i controls reclutada des de l'HU Institut Pere Mata també es trobarà en una mostra més àmplia de població espanyola.
3. L'associació del gen *DDR1* amb els TEEAPs és mediada per variacions en la microestructura de la mielina observables per l'anàlisi de neuroimatge per DTI.
4. Les variants del gen *DDR1* associades a TEEAPs també es troben associades a dèficits en la VP, tant en pacients amb un TEEAP establert com en pacients en primeres fases de la psicosi i en controls sans.

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# III. OBJECTIUS

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Per contrastar les hipòtesis plantejades, es van proposar els objectius següents:

1) ARTICLE 1:
    a. Fer una revisió bibliogràfica sobre l'expressió gènica i proteica de *DDR1* en SNC, tant en humans com en models animals i en els diversos tipus de cèl·lules, i descriure la relació de *DDR1* amb malalties del SNC.

2) ARTICLE 2:
    a. Replicar l'associació entre els SNPs rs1264323 i rs2267641 del gen *DDR1* amb el TEEAP en una mostra de casos i controls representativa de l'Estat espanyol.
    b. Determinar la influència dels SNPs rs1264323 i rs2267641 de *DDR1* en la VP en una mostra de pacients amb diagnòstic de TEEAP establert.
    c. Explorar, mitjançant la FA, la relació entre la microestructura de la matèria blanca cerebral, la VP i el genotip *DDR1* en una mostra de pacients amb diagnòstic de TEEAP establert seleccionats d'acord amb el genotip rs1264323.

3) ARTICLE 3:
    a. Replicar el resultat de l'associació de les variants rs1264323 i rs2267641 del *DDR1* amb la VP mesurada amb el TMT-A en dues mostres de pacients en primeres fases de la psicosi i en controls sans.

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# IV. RESULTATS

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**ARTICLE 1:**

***Expression of DDR1 in the CNS and in myelinating oligodendrocytes.***

Vilella, E., Gas, C., Garcia-Ruiz, B., & Rivera, F. J. (2019).

*Biochimica et Biophysica Acta - Molecular Cell Research*, *1866*(11), 0–1. https://doi.org/10.1016/j.bbamcr.2019.04.010

**ARTICLE 2:**

***Discoidin domain receptor 1 gene variants are associated with decreased white matter fractional anisotropy and decreased processing speed in schizophrenia.***

Gas, C., Canales-Rodríguez, E. J., Radua, J., Abasolo, N., Cortés, M. J., Salvadó, E., Muntané, G., Alemán-Gómez, Y., Julià, T., Marsal, S., Sanjuan, J., Guitart, M., Costas, J., Martorell, L., Pomarol-Clotet, E., & Vilella, E. (2019).

*Journal of Psychiatric Research*, *110* (December 2018), 74–82. https://doi.org/10.1016/j.jpsychires.2018.12.021

**ARTICLE 3:**

***Association of DDR1 variants with processing speed in subjects at the early phase of psychosis compared to healthy controls.***

Gas, C., Ayesa R., Vázquez-Bourgon J., Crespo-Facorro, B., Labad, J., Martorell, L., Muntané, G., Sanchez-Gustau, V., Vilella, E.

Article en preparació.

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BBA - Molecular Cell Research 1866 (2019) 118483

Contents lists available at ScienceDirect

BBA - Molecular Cell Research

journal homepage: www.elsevier.com/locate/bbamcr

# Expression of DDR1 in the CNS and in myelinating oligodendrocytes

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ARTICLE INFO

*Keywords:*
Brain
CNS
DDR1
Myelin
Oligodendrocyte

ABSTRACT

Discoidin domain receptor 1 (DDR1) is a tyrosine kinase receptor that is activated by fibrillar collagens. Here, we review the expression and role of DDR1 in the central nervous system (CNS). In a murine model, *DDR1* is expressed in oligodendrocytes in the developing brain and during remyelination. In human adult brain tissue, DDR1 is detected in a similar pattern as other classical myelin proteins such as myelin basic protein (MBP). Up to 50 transcripts of *DDR1* have been detected in human tissues, of which 5 isoforms have been identified. In the human brain, all 5 isoforms are detectable, but *DDR1*b is the most highly expressed, and *DDR1*c is coexpressed with myelin genes. *DDR1* sequence variants have been associated with psychiatric disorders, and upregulation of this gene occurs in gliomas. Moreover, mutations in *DDR1* have been found in tumors of Schwann cells, which are the myelinating cells of the peripheral nervous system. All these data suggest that DDR1 plays a role in myelination and is relevant to neuropsychiatric diseases.

## 1. Introduction

Discoidin domain receptor 1 (DDR1) is a pleiotropic protein that is present in several tissues and is involved in several diseases [1], including cancer [2]. Cell type-specific *DDR1* expression is not well described, as most data on *DDR1* expression are derived from tissue homogenates. Since we first described the expression of DDR1 in human oligodendrocytes (OLs) [3], new data on the presence of *DDR1* in these cells have been presented. Here, we aimed to present information on *DDR1* expression during the generation of mature myelinating OLs from oligodendrocyte precursor cells (OPCs) and to discuss its role during this progression. However, *DDR1* is expressed as at least 3 isoforms with a complex pattern that is difficult to interpret. Additionally, we provide information that suggests the involvement of DDR1 in the pathogenesis of some neuropsychiatric diseases.

## 2. Expression of DDR1

### 2.1. DDR1 and DDR1 isoforms

*DDR1* was first identified in human cDNA libraries as a tyrosine kinase protein by several research groups and received the following names: DDR, EDDR1, TRKE, CAK and RTK6 [4–10]. Later, *DDR1* was identified as a unique gene and was given the consensus name of *DDR1* due to the discoidin domain in the extracellular region. Together with DDR2, these proteins comprise the family of tyrosine kinase discoidin domain receptors and are uniquely activated by fibrillar collagens [1]. The *DDR1* gene was mapped to mouse chromosome 17 and human chromosome 6p21.3 [7,8]. Northern blots and *in situ* hybridization have shown that *DDR1* is mainly expressed in epithelial or epithelial-like cells [10,11] and that its expression levels in the brain are among the

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https://doi.org/10.1016/j.bbamcr.2019.04.010
Received 14 January 2019; Received in revised form 29 April 2019; Accepted 30 April 2019
Available online 18 May 2019

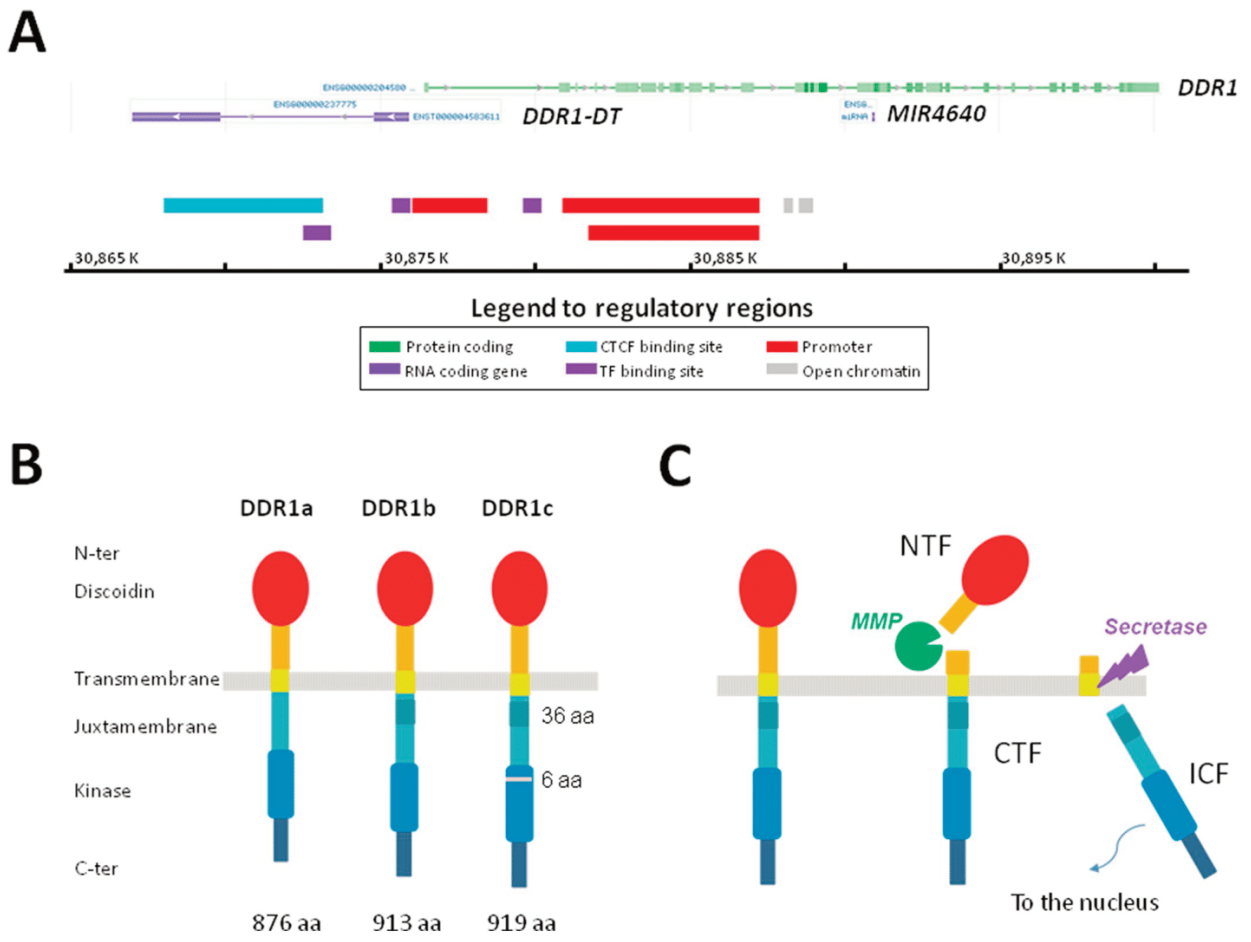



**Fig. 1.** Human *DDR1* gene structure and primary receptor isoforms.
A. Structure of human *DDR1* and the neighboring genes *DDR1-DT* and *MIR4640* according to Ensembl (Chromosome 6. GRCh38. p12). *DDR1-DT* and *MIR4640* are RNA coding genes.
B. Schematic diagram of the primary 3 *DDR1* isoforms.
C. Schematic diagram of DDR1 cleavage by extracellular matrix metalloproteinases at the extracellular region and by a secretase in the transmembrane or juxtamembrane region. Note that cleavage by a secretase has not been experimentally demonstrated. NTF: N-terminal fragment; CTF: C-terminal fragment; ICF: Intracellular fragment.

highest [4,6,10–12]. The prediction of the primary protein structure identified an extracellular domain, a transmembrane domain, a juxtamembrane domain and an intracellular domain with a catalytic kinase domain [5,13]. The extracellular region near the transmembrane domain contains a furin sequence [14] where the receptor can be cleaved by membrane-type matrix metalloproteinases (Fig. 1, panel C) [15]. The human *DDR1* gene contains 17 exons and was described by Playford and colleagues. [16]. Early on, two isoforms with different expression patterns in mouse embryos and adult brains were described [9], and two isoforms resulting from exon skipping during neurogenesis were recently identified by RNA-seq [17]. Alves and colleagues described a third *DDR1* isoform in a cDNA library isolated from embryonic brain tissue [18], and the same author later described two more isoforms present in cancer cells [19]. The protein length and structure of the 3 most relevant isoforms are presented in Fig. 1 (panel B).

Current genomic databases (*i.e.*, Ensembl, www.ensembl.org) display an extensive list of *DDR1* transcripts (Ensembl, annotations for more than 50 transcripts of human *DDR1*), of which only some code for a protein, and the most abundant transcripts correspond to isoforms *DDR1*a, *DDR1*b and *DDR1*c (also named 1, 2 and 3) (Fig. 1, panel B). More information about *DDR1* isoform expression is provided in the subsequent sections.

### 2.2. Trafficking of DDR1 mRNA

Using *in situ* hybridization with a *DDR1* riboprobe in human brain tissue slices, Roig and colleagues obtained a staining pattern that showed mRNA in axon fibers similar to the pattern previously found for the classical myelin protein, myelin basic protein (MBP) [20]. This RNA labeling was in agreement with that obtained with C-terminus DDR1 antibody-based immunochemistry. Moreover, strong coexpression of DDR1 and MBP was also observed [20]. These results suggest that *DDR1* mRNA may be intracellularly transported from the OL soma to the processes, as previously described for MBP. RNA granules transporting mRNAs from the nucleus to the processes for local translation have been described in neurons, OLs [21] and other cell types [22]. This mechanism is possible due to a group of proteins, one of which is hnRNP A2/B1, which recognizes a sequence in RNA known as the hnRNP A2 response element (A2RE) [21]. By *in silico* analysis, Roig and colleagues screened the *DDR1* sequence for an A2RE element and found

one inside exon 14, particularly, in isoforms a, b, c and e. Through *in vitro* experiments using the oligodendroglial cell line HOG1, the authors silenced hnRNP A2/B1, which led to a decrease (45%) in the amount of hnRNP A2/B1 mRNA and protein; this was accompanied by a decrease (40%) in DDR1 protein in OL processes [23]. Interestingly, decreases in hnRNP A2/B1 expression were associated with a decrease in *DDR1*c mRNA and a concomitant increase in *DDR1*b mRNA, which suggests that, besides its involvement in *DDR1* mRNA transport, hnRNP A2/B1 is involved in the alternative splicing of *DDR1*b and *DDR1*c isoforms. In summary, the *DDR1* A2RE sequence is functionally involved in both mRNA transport and alternative splicing.

### 2.3. DDR1 mRNA expression in tissue

The Genotype-Tissue Expression (GTEx, www.getexportal.org) project and BioGPS (http://biogps.org) are public access portals that provide information on gene expression in different tissues. Human *DDR1* expression is detectable in several adult tissues (Fig. 3). Clearly, spinal cord shows the highest levels, followed by other tissues including the brain, while the expression of *DDR2* in the brain is undetectable (data not shown).

#### 2.3.1. DDR1 expression in brain tissue

Early studies on *DDR1* expression showed that the gene is more highly expressed in the brain than in other tissues [6,9,10]. Detailed *in situ* hybridization with Ddr1 riboprobes in mouse embryos specifically detected expression in the brain during neurogenesis [3,4,11]. Bhatt also observed Ddr1 expression in mouse secondary areas of neurogenesis [24]. In the postnatal period, Ddr1 is highly expressed in OLs and peaks at postnatal day 15 [3]. Bhatt and colleagues also found Ddr1 expression in the cerebellum of adult mice [24]. Expression of *DDR1* in the adult cerebellum may occur through a different transcript than expression in the spinal cord or other brain areas, according to GTEx data on transcript expression. After observing that *Ddr1* expression in mice during neurodevelopment parallels that of classical myelin proteins such as MBP, Franco-Pons and colleagues tested whether *Ddr1* expression varied in an experimental mouse model of demyelination and remyelination by oral administration of the toxicant drug cuprizone. By *in situ* hybridization, they found that during remyelination after experimental myelin injury, *Ddr1* is first upregulated in fornix OLs (where OPCs are activated) and later in the corpus callosum and external capsule OLs (where OLs reestablish myelin sheaths) [25]. In the same experiment, these authors found a 2-fold increase in *Ddr1* mRNA peak expression, measured by RT-qPCR, in the corpus callosum [25], which confirms the *in situ* hybridization results. All these mRNA analysis-based data demonstrate that *DDR1* transcript expression is dependent on the cell type and on the stage of cell and tissue differentiation.

Recent experiments with 6 to 8-month-old *DDR1* KO mice generated using the LacZ/Neo3 cassette (which substituted exons 1–3) showed high expression of the inserted ß-galactosidase gene in brain tissue (and in the heart and skin but not in the aorta), indirectly demonstrating that the *DDR1* regulatory system is enhanced in the adult mouse brain [26].

According to GTEx data, 3 transcripts, 2 corresponding to *DDR1*b and 1 corresponding to *DDR1*a, are the most represented in all tissues, including the brain (Fig. 4, panel A), while the expression of the *DDR1*c isoform is very low in nerve tissue. GTEx data also show that exons at the 5′ end of the gene are almost exclusively present in brain tissue (data not shown). Roig and colleagues measured DDR1 expression by qRT-PCR in human dorsolateral prefrontal and occipital cortical tissue and found detectable expression of all 5 protein-coding transcripts (*DDR1*a, b, c, d and e). *DDR1*b was the most abundant, with mRNA levels 200-fold higher than the levels of *DDR1*a mRNA [20], and *DDR1*c expression levels were approximately 2-fold higher than *DDR1*a expression levels (Fig. 4, panel B). Unfortunately, data regarding tissue-specific isoform expression are scarce in public databases.

### 2.4. DDR1 protein in brain tissue

#### 2.4.1. Endothelial cells

Expression of *DDR1* mRNA in human brain capillary endothelial cells was detected by *in situ* hybridization and colocalization by immunostaining using an endothelial cell marker (antibody against the Von Willebrand protein). Interestingly, in endothelial cells, DDR1 could only be detected by an N-terminus DDR1 antibody that recognizes the extracellular domain near the N-terminus of the receptor (Fig. 5, panels A, B and C) [20]. In the murine model, *DDR1* expression in endothelial cells was undetectable [3,25,27]. These data together suggest the possibility that *DDR1* expression in human brain capillaries, as documented by Roig and colleagues, may not be restricted to endothelial cells, as perivascular cells may contribute to these observations.

#### 2.4.2. OLs and myelin

The presence of *DDR1* in myelinating OLs was detected by *in situ* hybridization and immunohistochemistry in murine [3] as well as in human brain tissue [20]. The DDR1 protein expression pattern in the human brain is very similar to that of the classical myelin protein MBP [20]. Notably, DDR1 in myelin was detected with a C-terminus DDR1 antibody, while DDR1 in the soma of OLs was detected using an N-terminus DDR1 antibody [20]. Positive immunostaining with a C-terminus DDR1 antibody was also observed inside the nucleus of OLs [23] (Fig. 5, panels B, C and D). Shedding of DDR1 at the extracellular domain produces a soluble ectodomain fragment plus two intracellular C-terminal fragments (CTFs) of 62 and 58 kDa, which have been described in transformed cell lines [14,28]. The extracellular cleavage is generated by membrane-type metalloproteinases (MT-MMP) [15]. The detection of the CTFs prompted the authors to hypothesize that the CTFs undergo a second proteolysis by another membrane-anchored protease, which results in an intracellular terminal fragment (ICF) that may elicit intracellular functions including translocation to the nucleus, where it regulates the transcription of target genes [15,28]. For instance, this mechanism was described for MBP [29] and other tyrosine kinases such as Erb4, which is first cleaved by the MT-MMP ADAM17 protease and then subsequently cleaved by a ɣ-secretase [30]. We propose two possible hypotheses for the respective CTF and ICF functions in OLs. On the one hand, since we detect DDR1 immunoreactivity in myelin fibers only with the C-terminus DDR1 antibody, one explanation could be that, in myelin, the CTF anchored at the plasma membrane exerts an adhesion function. Actually, DDR1 in epithelial cells is an important stabilizer of E-cadherin-mediated cell-cell adhesion [31,32]. Therefore, the DDR1 CTF could stabilize axon-OL membrane adhesion or OL-OL membrane adhesion in myelin. On the other hand, since we observed DDR1 C-terminus immunoreactivity inside the nucleus of OLs *in vivo* and *in vitro*, we hypothesize that, at least in OLs, the ICF is generated by the action of a secretase or a similar protease that cleaves the CTF and that subsequently, the ICF is then transported to the nucleus where it exerts a regulatory role (Fig. 1, panel C). Similarly, for Erb4, the ICF is translocated to the nucleus, where it activates the transcription of certain genes [30]. DDR1 is also expressed in Schwann cells, which are the cells responsible for myelin sheath synthesis in the peripheral nervous system [33]. More detailed information about DDR1 expression in OLs can be found in Section 3 of this review.

#### 2.4.3. Astrocytes

Sakuma and colleagues identified a transcript in a cDNA library of rat astrocytes irradiated *in vitro*. Northern blot and cloning studies indicated the presence of at least two *DDR1* mRNA transcripts [34]. Using double immunochemistry with an N-terminus DDR1 antibody and a GFAP antibody, Roig and colleagues labeled cell bodies that were compatible with astrocytes in human brain cortical slices (Fig. 5, panel C). Recently, upregulation of *DDR1*, together with other proteins of the extracellular matrix, such as collagen alpha-1(IV) chain (COL4A1), COL4A2 and platelet-derived growth factor subunit A (PDGFA), has

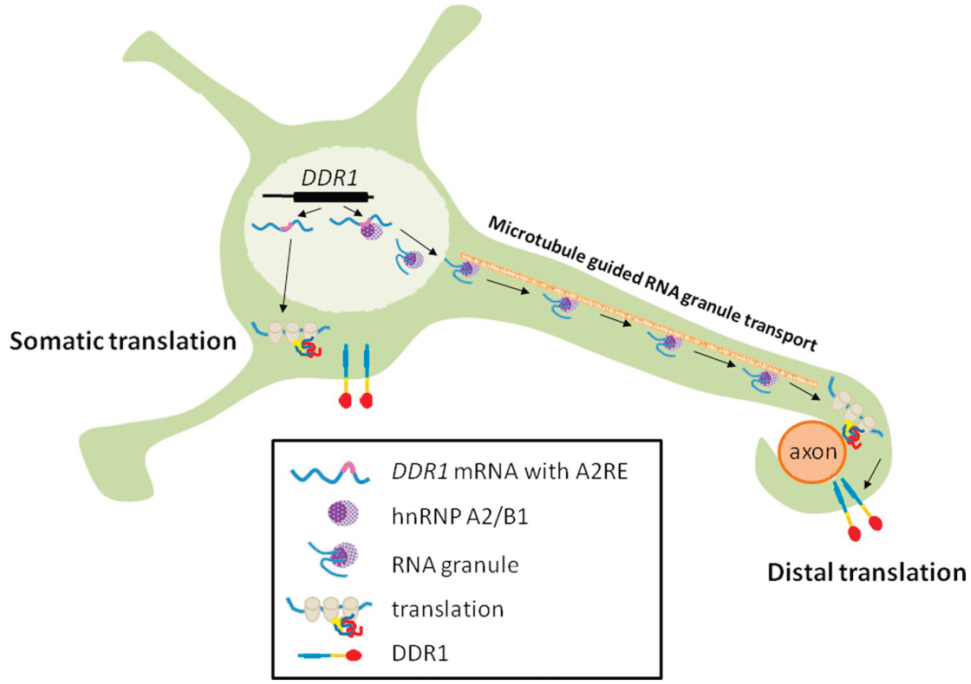



**Fig. 2.** Intracellular transport of *DDR1* mRNA in OLs.
hnRNP A2/B1 binds to the A2RE sequence in *DDR1* mRNA, and together with other proteins, forms an RNA granule to transport the mRNA from the nucleus to the distal ends of OL processes. Translation of *DDR1* occurs at two intracellular sites: 1) in the somatic endoplasmic reticulum and 2) locally and under specific regulation in the processes that unsheathe axons. The insert corresponds to an *in situ* hybridization image using a *DDR1* riboprobe in human brain cortical tissue [20].

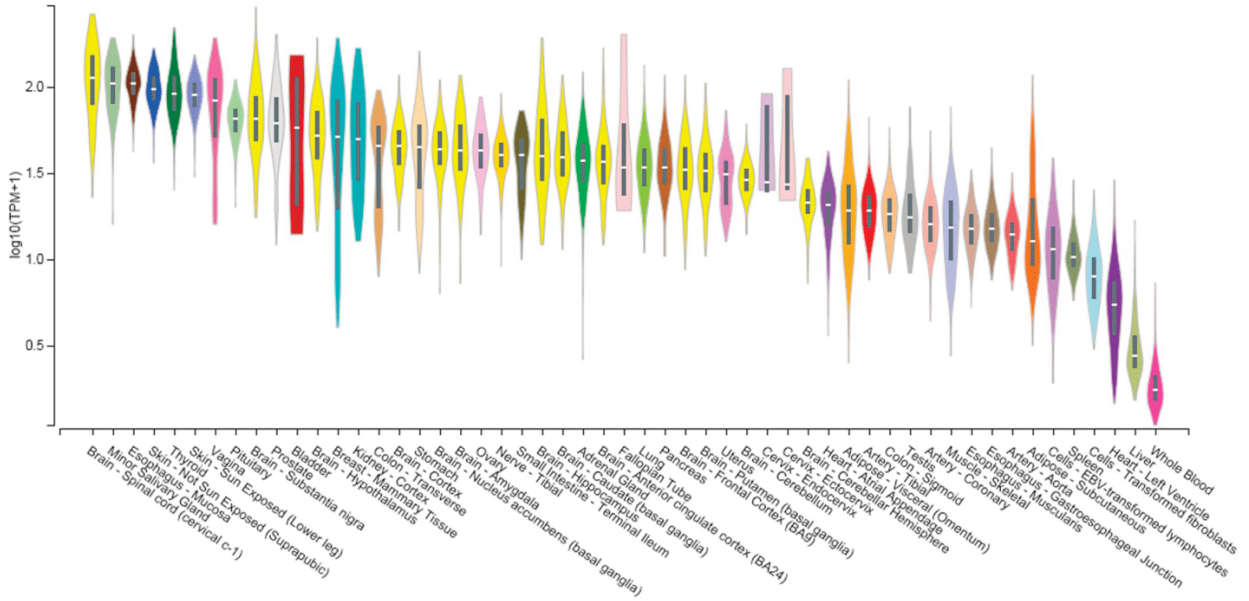



**Fig. 3.** *DDR1* expression in human tissue.
Violin graphs represent the expression levels of *DDR1* in descending order in several human tissues. Nerve tissues are represented in yellow. The data were obtained from the GTEx Portal on 01/04/19. Details on the number of samples used per tissue and sample characteristics can be found at www.getexportal.org.TPM: transcripts per million.

been described in astrocyte and glioblastoma cell lines [35]. Together, these observations suggest that *DDR1* expression in astrocytes is upregulated under activation circumstances.

*2.4.4. Microglia*

Collagen activates brain microglia through DDR1 in an integrin-independent manner [36] in a mouse model. Moreover, Hebron and colleagues, in a pilot study, found higher DDR1 and DDR2

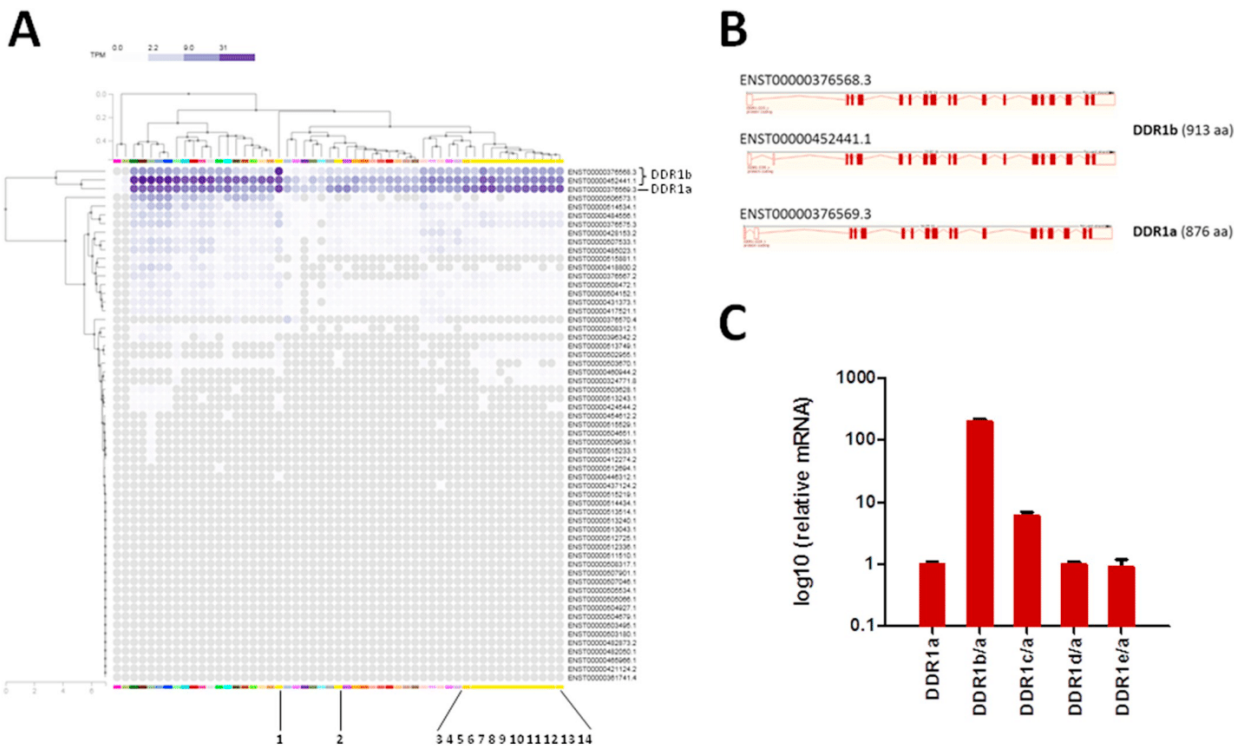



**Fig. 4.** Human brain *DDR1* transcript expression.
A. Heatmap diagram representing the median expression levels (as number of transcripts per million) of each *DDR1* transcript in descending order (rows) from several human tissues (columns). The tissues and transcripts are ordered based on hierarchical clustering. Nerve tissues are represented in yellow. 1: spinal cord; 2: cerebellar hemisphere; 3: tibial nerve; 4: cerebellum; 5: substantia nigra; 6: hypothalamus; 7: putamen; 8: frontal cortex BA9; 9: anterior cingulate cortex BA24; 10: hippocampus; 11: caudate (basal ganglia); 12: cortex; 13: nucleus accumbens (basal ganglia); 14: amygdala. The data were obtained from the GTEx Portal on 01/04/19. Details on the number of samples used per tissue and sample characteristics can be found at www.getexportal.org.TPM: transcripts per million.
B. The 3 most highly expressed transcripts from panel A correspond to *DDR1*b (2 transcripts) and *DDR1*a (1 transcript).
C. qRT-PCR of the *DDR1* isoforms in human brain cortical tissue expressed as the relative amount of mRNA with respect to *DDR1*a. Data were obtained from the author's database [53].

immunoreactivity in brain tissue slices from subjects with Alzheimer's disease and Parkinson's disease than in healthy controls. Although they did not identify the cells in which DDR1 was present, the results suggest a role of DDR1 in microglia. For instance, they obtained results suggesting that DDRs reduce clearance of neurotoxicant products, such as ß-amyloid peptide and α-synuclein, and also induce TREM2 signaling, increasing the microglial cell number [37]. However, scarce data are available regarding the expression of DDR1 in human microglia.

### 2.4.5. Brain-derived cell lines expressing DDR1

The human oligodendroglial cell lines MO3.13 and HOG16 can be cultured *in vitro* in specific medium and conditions to induce differentiation into cells with a more mature myelinating phenotype [38], and under these conditions (transition from the immature to the mature phenotype), *DDR1* expression is upregulated [25]. Human glioma cells and glioma cell lines such as G140 and U87-MG also express *DDR1* [35,39] and the differential isoforms *DDR1*a and *DDR1*b, and autophosphorylation of these proteins modulates cell proliferation and invasion [39]. The PC12 cell line, with a neuron-like phenotype, expresses moderate *DDR1* levels, but the protein is not activated by collagen [40].

## 2.5. DDR1 sequence variants affect expression in nerve tissue

Expression quantitative trait loci (eQTLs) are genomic loci that explain all or a fraction of variation in expression levels of mRNAs. Here, we present single nucleotide polymorphisms (SNPs) that are eQTLs for *DDR1* in nerve tissue. Data from public databases such as GETex show that multiple local SNPs in the *DDR1* locus affect its expression. Focusing on tissues with available data, 3 clear regions are differentiable (arbitrarily named a, b and c): one 5′ region upstream from the *DDR1*, a second region centered on the gene locus and a third one located 3′ downstream from the gene (Fig. 6, panel A). SNPs in region a are relevant for thyroid, skeletal muscle and tibial artery *DDR1* expression. However, region b is more important for nerve, lung and transformed fibroblast *DDR1* expression. Region b includes two genes that code for long noncoding RNAs (LINC00243 and LINC02570) (Fig. 6, panel A). In addition, region b contains the *DDR1* divergent transcript gene (*DDR1-DT*, formerly named *DDR1-AS1*) and the promoter for *DDR1* (Fig. 1, panel A). *DDR1-DT* codes for an RNA that hybridizes with intron 9 of *DDR1* and is highly expressed in the testis and moderately expressed in brain and other tissues. Regarding the influence of eQTLs on specific transcripts or isoforms, the C allele for rs2267641, located inside the *DDR1* A2RE, was found to be associated with higher levels of *DDR1*c mRNA and lower levels of *DDR1*b mRNA than the common allele in whole human dorsolateral prefrontal brain tissue [23]. Here, we show that minor alleles at rs9394020 located inside LINC00243, rs2844654 located inside *DDR1-DT* and rs1264323 in the promoter region of *DDR1* also demonstrate an inverse association with *DDR1*b and c expression levels in human brain tissue (Fig. 6, panel B). Nerve cell type eQTLs for isoform transcripts are not yet available in public databases.

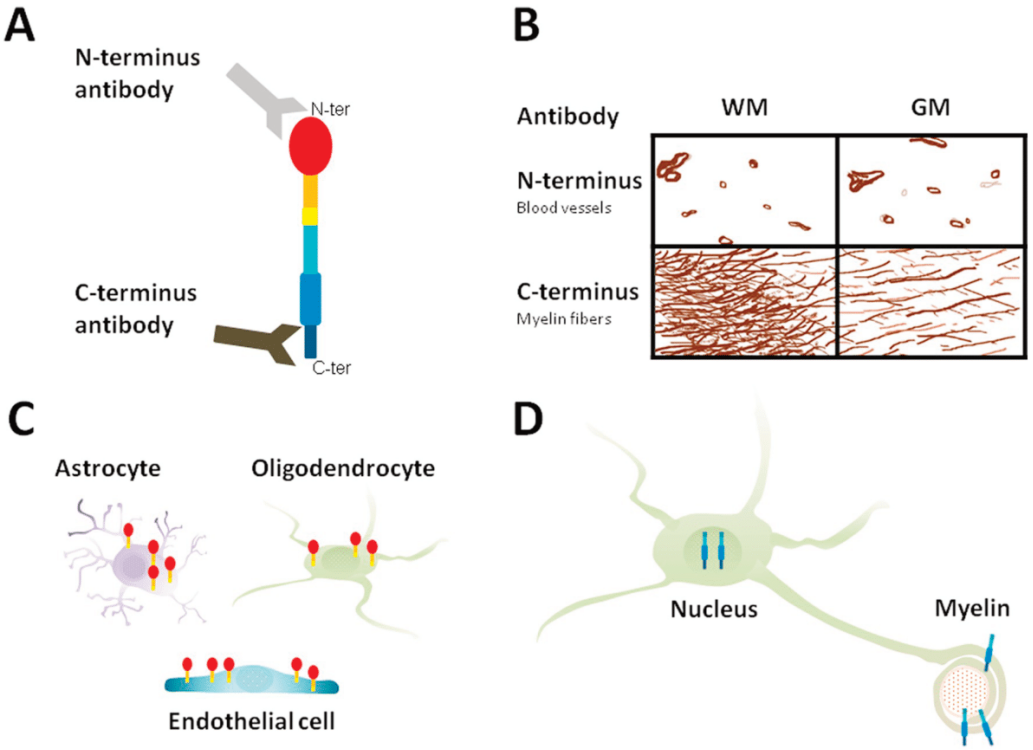



**Fig. 5.** DDR1 protein detection in CNS cells.
A. Schematic drawing of the 2 types of antibodies used to detect DDR1 by immunochemistry in human CNS cells.
B. Schematic drawing of DDR1 immunoreactivity in with matter (WM) and gray matter (GM) of human brain cortical tissue according to Roig and colleagues [20]. The N-terminus antibody labels blood vessels (endothelial cells), and the C-terminus antibody labels myelin fibers.
C. Schematic drawing of CNS cells (astrocytes, OLs and endothelial cells) that show somatic DDR1 immunostaining with an N-terminus antibody.
D. Schematic drawing showing OL DDR1 immunostaining using the C-terminus antibody.

## 3. Expression of *DDR1* in OLs

### 3.1. *DDR1* in OPCs

Early data of *in situ* hybridization using Ddr1 probes in the embryo and postnatal mouse brain did not result in labeling of OPCs. Instead, the labeling pattern was compatible with that of mature and myelinating OLs [3,4,11]. Data from an RNA-seq database on mouse nerve cells show that expression of Ddr1 in OPCs is moderate [27] (Fig. 7, panel A).

### 3.2. *DDR1* in newly formed oligodendrocytes (NFOLs)

*In vivo* and *in vitro* data suggest that *DDR1* expression is upregulated during the transition from OPCs to OLs. Franco-Pons and colleagues used *in situ* hybridization and immunohistochemistry to demonstrate that Ddr1 OL expression is upregulated during the remyelination of damaged myelin sheaths after cuprizone exposure in mice. Cells expressing Ddr1 (Ddr1 + ) were not OPCs or other glial cells; rather, they were myelin-forming OLs [25]. More recent work based on single-cell RNA-seq confirmed that Ddr1 expression increases 3-fold during the transition of OPCs to NFOLs [27] (Fig. 7, panel A). Moreover, in NFOLs, Ddr1 is the fourth-ranked gene in the list of the top 20 membrane receptors expressed [27]. A subsequent study that followed the same methodology and that was able to identify 12 stages of oligodendrogenic progression showed the peak of Ddr1 expression in the window comprising the late stage of NFOLs and the first stage of myelin-forming OLs (MyOLs) [41] (Fig. 7, panel B).

The regulation of oligodendrogenic progression is well orchestrated by several types of epigenetic mechanisms, such as DNA methylation and microRNA interactions [42]. Indeed, miR-199a-5p was recently identified as one of the main microRNAs that is upregulated during the differentiation of OPCs to OLs, and an approximate 9-fold increase in the first stage of differentiation was concomitant with the expression of the OL biomarker galactocerebrosidase (GalC). This increase was maintained in the second stage, where 2′, 3′-cyclic nucleotide 3′-phosphodiesterase (CNPase) begins to be expressed [43]. *DDR1* has 4 sites that bind miR-199a-5p at the 3′ UTR [43]; therefore, miR-199a-5p likely regulates *DDR1* expression during OPC differentiation, but detailed molecular data on the regulatory function of miR-199a-5p in OLs are not available. However, experimental data on miR-199a-5p in cancer cells and endothelial cells show that increasing the miR-199a-5p concentration decreases the amount of DDR1. In these experiments, increasing miR-199a-5p caused downregulation of *DDR1* and decreased cell proliferation [44]. These contradictory data and the increases in miR-199a-5p and DDR1 concentrations in differentiating OLs may indicate that either miR-199a-5p can differentially regulate *DDR1* expression in different cell types (this is unlikely because the microRNA functional mechanism involves silencing target mRNA) or that miR-199a-5p in OLs downregulates *DDR1* in a narrow window during the differentiation process. The maximum increase in the miR-199a-5p concentration occurs in the early stages of OPC differentiation into OLs [43] when DDR1 expression peaks, according to data from Zhang and colleagues [27], which suggests that miR-199a-5p may fine-tune *DDR1* expression. Furthermore, we cannot discount the possibility that miR-199a-5p regulates *DDR1* expression in an isoform-dependent manner.

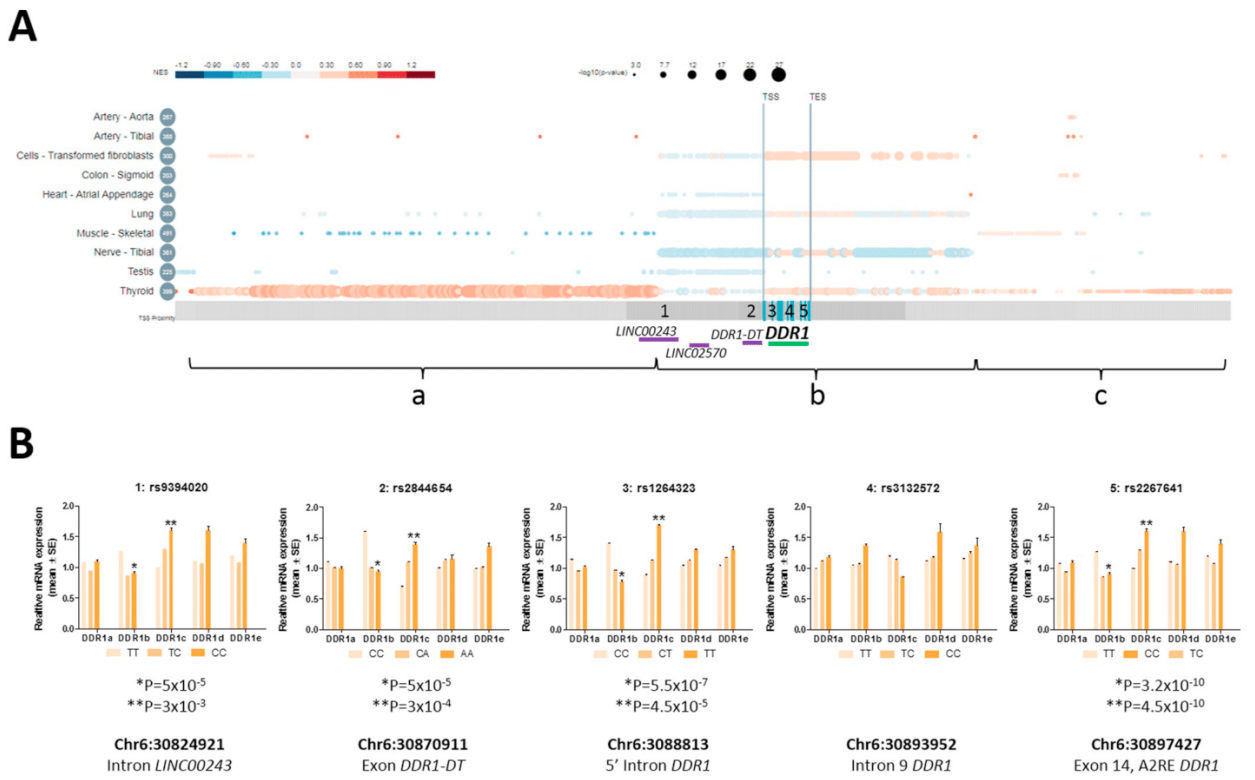



**Fig. 6.** Human brain *DDR1* eQTLs.
A. SNPs at the *DDR1* locus showing negative (blue) or positive (brown) associations with *DDR1* mRNA expression in several human tissues. The *DDR1* locus and 230 kb upstream and 180 kb downstream are shown. The data were obtained from the GTEx Portal on 01/04/19. Details on the number of samples used per tissue and sample characteristics can be found at www.getexportal.org.
B. Influence of several SNPs spread around and inside *DDR1* on *DDR1*a, b and c isoform expression in the human brain cortex. mRNA expression levels of each isoform were measured by RT-qPCR using TaqMan (Applied Biosystems, Madrid, Spain) reagents, and RNA was isolated from fresh brain tissue using TRIzol. Data from the author's group are shown (from [53] and unpublished data). Relative units of mRNA levels are expressed as the mean ± standard error. *P* values correspond to the ANCOVA analysis using a SNP as an independent variable and sex, age, RNA quality and brain pH as covariables. The chromosomal position of each SNP corresponds to what is shown in the Ensemble database (GRch38.p12). The linkage disequilibrium of the SNPs measured in the 1000 Genomes Data resource was below 0.4. The highest was 0.36 (between rs1264323-rs2267641), while the lowest was 0.002 (between rs9394020-rs2844654). Therefore, SNPs were analyzed individually.

### *3.3. DDR1 in MyOLs*

Using *in situ* hybridization, Western blot and immunohistochemistry, Franco-Pons and colleagues were the first to report the expression of Ddr1 in MyOLs in the mouse brain during neurodevelopment [3]. *In situ* hybridization images of Ddr1 in the adult mouse brain are available in the Allen Brain Atlas data portal (http://mouse.brain-map.org). Recent data using single-cell RNA-seq confirmed that Ddr1 is expressed in MyOLs [27,41]. However, data on DDR1 protein expression in the mouse brain are scarce.

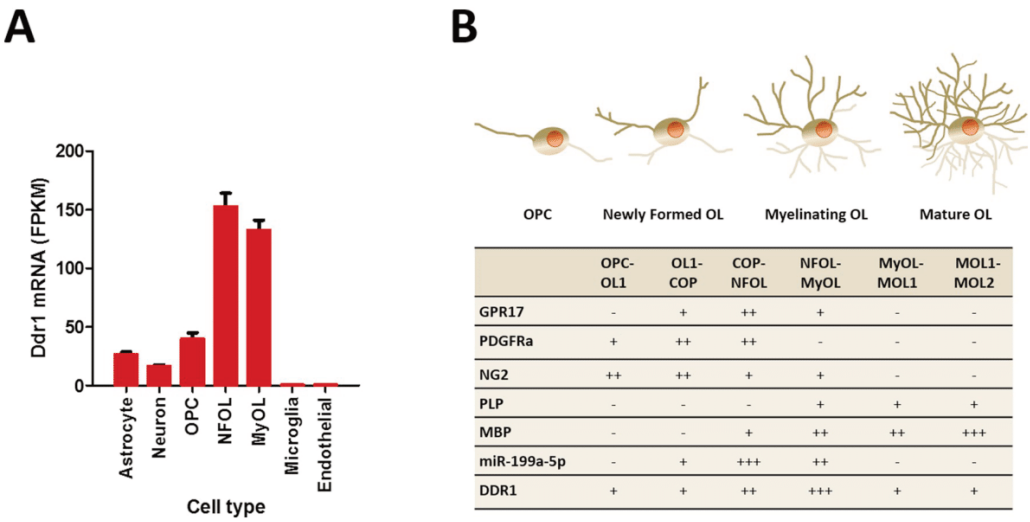
*DDR1* transcript expression in the human brain is available in public portals and in the work of Roig and colleagues [20]. Immunohistochemistry images of brain cortical slices revealed that DDR1 is a structural component of myelin [20] (Fig. 5, panel B). The presence of DDR1 immunoreactivity in myelin clearly differentiates DDR1 expression between the mouse and human brain.

Coexpression analysis also confirmed that *DDR1* expression correlates with the expression of other classical myelin genes; for instance, in mouse NFOLs, Ddr1 expression is increased together with the expression of the receptors semaphorin 4D (Sema4d) and Erb-B2 receptor tyrosine kinase 3 (Erbb3) [27], both of which are important myelin receptors [45,46]. Marques and colleagues found that the 2 transcripts that are expressed in the second stage of NFOLs were myelin-associated oligodendrocyte basic protein (Mobp) and Ddr1 [41]. MOBP is known as a structural myelin protein [47]. Interestingly, Roig and colleagues found that *DDR1*b expression in the human brain did not correlate with the expression of OL proteins, such as oligodendrocyte transcription factor 2 (OLIG2) and myelin-associated glycoprotein (MAG), but that the expression of *DDR1*c did correlate with expression of these other proteins [23]. Altogether, these data suggest that an important increase in *DDR1* (all isoforms) occurs when OPCs begin to proliferate, migrate and differentiate. At this stage, collagen-activated DDR1 may promote cell proliferation and motility, and isoform *DDR1*b probably orchestrates this function. However, when OPCs finally give rise to myelinating OLs, *DDR1*b is downregulated, *DDR1*c is upregulated, and the mRNA is transported to the processes where local DDR1 protein synthesis occurs (see Figs. 2, 5 and 7). This DDR1 synthesized in the OL processes may form part of the myelin sheath, which contributes to the stabilization of membrane-membrane junctions such as axon-OL or OL-OL junctions (as explained in Section 2.4.2).

## 4. DDR1 and central nervous system (CNS) diseases

### *4.1. DDR1 mutations in nervous system cancers*

Sequence variants and copy number variants affecting *DDR1* have been described as somatic cancer mutations. Data from the COSMIC data base (https://cancer.sanger.ac.uk/cosmic) show that up to 777




| | OPC-OL1 | OL1-COP | COP-NFOL | NFOL-MyOL | MyOL-MOL1 | MOL1-MOL2 |
|---|---|---|---|---|---|---|
| GPR17 | - | + | ++ | + | - | - |
| PDGFRa | + | ++ | ++ | - | - | - |
| NG2 | ++ | ++ | + | + | - | - |
| PLP | - | - | - | + | + | + |
| MBP | - | - | + | ++ | ++ | +++ |
| miR-199a-5p | - | + | +++ | ++ | - | - |
| DDR1 | + | + | ++ | +++ | + | + |

**Fig. 7.** Expression of DDR1 in the maturation of OPCs to mature OLs (MOLs).
A. Relative expression of Ddr1 mRNA in CNS-isolated mouse cells. Data are from https://web.stanford.edu/group/barres_lab/brain_rnaseq.html.
B. Relative expression of some mRNAs that are expressed throughout the stages of differentiation in the oligodendroglial linage from OPCs to MOLs. + + + peak of gene expression; + + high gene expression; + presence of gene expression; − absence of gene expression. Data were obtained from published results [27,41,43].

somatic mutations have been identified in *DDR1* (accessed 03/25/2019), and of these, only 5 were identified in CNS cancer tissue from gliomas. Gliomas are defined as cancers of glial cells, but the majority have an astrocyte-like phenotype. Two mutations affect the kinase domain (p. Q830*, c.2488C > T and p R649W, c.1945C > T) and one affects the transmembrane domain (p. R440W, c.1318C > T). The remaining 2 mutations were synonymous substitutions. This relatively low frequency of CNS *DDR1* mutations contrasts with the *DDR1* mutations found in schwannomas. Schwannomas are generally benign tumors of the peripheral myelin (produced by Schwann cells), which can be located in either the cranium or the spine. In an exhaustive study performed to identify genes carrying mutations in sporadic schwannoma, Agnihotri and colleagues found that 14/125 (11%) cases were carriers of *DDR1* mutations; these were also exclusive events that were not seen in healthy controls. Of these, four were point mutations in the kinase domain, and two were point mutations at the discoidin domain. Interestingly, they found a recurrent ($n = 4$) hotspot mutation in the discoidin domain (p.R183H) [48].

### 4.2. Expression of DDR1 in CNS cancer cells

*DDR1* is upregulated in human pediatric and adult brain tumors [1,49]. Little is known about how DDR1 functions in brain cancer, but isoform-dependent functions have been described; for instance, *DDR1*a, but not *DDR1*b, was found to be involved in cell invasion and adhesion in gliomas and could activate matrix metalloproteinase 2 (MMP-2) [39]. These results suggest that DDR1 cooperates with the proteolytic machinery to facilitate tumor invasiveness [35].

### 4.3. Neuropsychiatric diseases

A genetic association of *DDR1* sequence variants with schizophrenia has been described [50–52]. One relevant SNP in this association is rs2267641, located inside the *DDR1* A2RE, which modifies the *DDR1*b/*DDR1*c ratio [23] but shows a complex pattern of risk together with rs1264323 [51]. Roig and colleagues analyzed the expression of *DDR1* mRNA isoforms in human brain tissue and compared data between psychiatric patients (schizophrenia and bipolar diagnosis) and healthy controls. They found that *DDR1*c was significantly increased in dorsolateral prefrontal and occipital cortical brain tissue [53]. Interestingly, Gas and colleagues found that *DDR1* genetic variation is associated with cognitive processing speed and myelin integrity in schizophrenia patients [51]. Additionally, in a genome-wide association study of neuroticism (a personality trait frequently present in patients diagnosed with schizophrenia), an SNP in the *DDR1* locus was found to be associated with the trait [54].

*DDR1* mutations have not been associated with myelin diseases such as multiple sclerosis or leukodystrophies. A few copy number variants (CNVs) have been identified in subjects with developmental delay; one subject with 3 copies of the gene was also diagnosed with autism (www.gencards.org, www.decipher.sanger.ac.uk), but no cause-effect studies have provided conclusive data.

Data showing that shRNA knockdown of DDRs results in degradation of toxic proteins in *in vivo* and *in vitro* models of neurodegeneration [37], together with the evidence that nilotinib (a selective DDR inhibitor) promotes brain autophagy of neurotoxicant products without neuroinflammation, prompted researchers to examine the potential of tyrosine-kinase inhibitors, such as nilotinib, as a new therapy for neurodegenerative diseases [55,56].

## 5. Conclusion and future perspectives

DDR1 is in the right place at the right time to potentially play a role in myelination. As with other myelin proteins, the robustness of myelination prevents a single element from being indispensable; therefore, *DDR1* gene variants have no major impact on myelin-forming cells. Nevertheless, deeper and more sophisticated recent experiments have provided details about the specific role of DDR1 during developmental myelination, and eventually, in myelin repair.

Future studies focusing on isoform expression in specific tissues and cell types will help to elucidate the complexity of *DDR1* expression and functions in the brain.

Given the potentially relevant role of DDR1 in myelination, inducing the upregulation or downregulation of its expression may be the basis of a future therapy for myelin-based diseases, including multiple sclerosis, schizophrenia, bipolar disorder and even Alzheimer's disease.

## Funding sources

This work was supported by the Spanish National Institute of Health

"Instituto de Salud Carlos III" [grant number PI15-00852 (E.V.)] and FEDER; the Brain and Behavior Research Foundation, USA [NARSAD grant (E.V.)]; Chilean Comisión Nacional de Investigación Científica y Tecnológica (CONICYT) FONDECYT Program [Regular Grant number 1161787 (F.J.R.)]; and Chilean CONICYT PCI Program [Grant number REDES170233 (F.J.R.)].

## Author's contribution

Elisabet Vilella and Franciso J Rivera contributed to all the following aspects:

1. Substantial contribution to the review: design, data acquisition, synthesis of data and interpretation.
2. Drafting the article for intellectual content.
3. Agreement to be accountable for all aspects of the work related to the accuracy or integrity of any part of the work.
4. Approval of the final version.

Cinta Gas and Beatriz Garcia contributed to all the following aspects:

1. Substantial contribution to the review: data acquisition, synthesis of data and interpretation.
2. Reviewing the article for intellectual content.
3. Agreement to be accountable for all aspects of the work related to the accuracy or integrity of any part of the work.
4. Approval of the final version.

## Transparency Document

The Transparency document associated with this article can be found, in the online version.

## Declaration of Competing Interest

The authors declare no conflict of interest.

## References

[1] B. Leitinger, Discoidin domain receptor functions in physiological and pathological conditions, Int. Rev. Cell Mol. Biol. 310 (2014) 39–87.
[2] R.R. Valiathan, M. Marco, B. Leitinger, C.G. Kleer, R. Fridman, Discoidin domain receptor tyrosine kinases: new players in cancer progression, Cancer Metastasis Rev. 31 (2012) 295–321.
[3] N. Franco-Pons, et al., Expression of discoidin domain receptor 1 during mouse brain development follows the progress of myelination, Neuroscience 140 (2006) 463–475.
[4] M.P. Sanchez, P. Tapley, S.S. Saini, B.I.N. He, D. Pulidot, Multiple tyrosine protein kinases in rat hippocampal neurons : Isolation of Ptk-3 , a receptor expressed in proliferative zones of the developing brain, Proc. Natl. Acad. Sci. U. S. A. 91 (1994) 1819–1823.
[5] J.D. Johnson, J.C. Edman, W.J. Rutter, A receptor tyrosine kinase found in breast carcinoma cells has an extracellular discoidin I-like domain, Proc. Natl. Acad. Sci. U. S. A. 90 (1993) 5677–5681.
[6] E. Di Marco, N. Cutuli, L. Guerra, R. Cancedda, M. De Luca, Molecular Cloning of trlzE , a Novel trk-related Putative Mosine Kinase Receptor Isolated from Normal Human Keratinocytes and Widely Expressed by Normal Human Tissues *, J. Biol. Chem. 268 (1993) 24290–24295.
[7] A. Valent, et al., Assignment of the NTRK4 (trkE) gene to chromosome 6p21, Hum. Genet. 98 (1996) 12–15.
[8] S. Edelhoff, D.A. Sweetser, C.M. Disteche, Mapping of the NEP Receptor Tyrosine Kinase Gene to Human Chromosome 6p21 . 3 and Mouse Chromosome 17C, Genomics 3 (1995) 309–311.
[9] J.L. Perez, et al., Identification and chromosomal mapping of a receptor tyrosine kinase with a putative phospholipid binding sequence in its ectodomain, Oncogene 9 (1994) 211–219.
[10] S. Laval, et al., Isolation and characterization of an epithelial-specific receptor tyrosine kinase from an ovarian cancer cell line, Cell growth & differentiation: the molecular biology journal of the American Association for Cancer Research 5 (1994) 1173–1183.
[11] M. Zerlin, M.A. Julius, M. Goldfarb, NEP: a novel receptor-like tyrosine kinase expressed in proliferating neuroepithelia, Oncogene 8 (1993) 2731–2739.
[12] J.L. Perez, S.Q. Jing, T.W. Wong, Identification of two isoforms of the Cak receptor kinase that are coexpressed in breast tumor cell lines, Oncogene 12 (1996) 1469–1477.
[13] W. Vogel, Discoidin domain receptors: structural relations and functional implications, FASEB journal: official publication of the Federation of American Societies for Experimental Biology 13 (Suppl) (1999) S77–S82.
[14] W.F. Vogel, Ligand-induced shedding of discoidin domain receptor 1, FEBS Lett. 514 (2002) 175–180.
[15] H.-L. Fu, et al., Shedding of Discoidin Domain Receptor 1 by Membrane-type Matrix Metalloproteinases, J. Biol. Chem. 288 (2013) 12114–12129.
[16] M.P. Playford, et al., The genomic structure of discoidin receptor tyrosine kinase, Genome Res. 6 (1996) 620–627.
[17] J. Yu, et al., Transcriptomic profile analysis of mouse neural tube development by RNA-Seq, IUBMB Life 69 (2017) 706–719.
[18] F. Alves, et al., Distinct structural characteristics of discoidin I subfamily receptor tyrosine kinases and complementary expression in human cancer, Oncogene 10 (1995) 609–618.
[19] F. Alves, et al., Identification of two novel, kinase-deficient variants of discoidin domain receptor 1: differential expression in human colon cancer cell lines, FASEB journal: official publication of the Federation of American Societies for Experimental Biology 15 (2001) 1321–1323.
[20] B. Roig, et al., Expression of the tyrosine kinase discoidin domain receptor 1 (DDR1) in human central nervous system myelin, Brain Res. 1336 (2010) 22–29.
[21] J.H. Carson, E. Barbarese, Systems analysis of RNA trafficking in neural cells, Biology of the cell / under the auspices of the European Cell Biology Organization 97 (2005) 51–62.
[22] N. Neriec, P. Percipalle, Sorting mRNA Molecules for Cytoplasmic Transport and Localization, Front. Genet. 9 (1–9) (2018).
[23] B. Roig, S. Moyano, L. Martorell, J. Costas, E. Vilella, The Discoidin domain receptor 1 gene has a functional A2RE sequence, J. Neurochem. 120 (2012) 408–418.
[24] R.S. Bhatt, T. Tomoda, Y. Fang, M.E. Hatten, Discoidin domain receptor 1 functions in axon extension of cerebellar granule neurons, Genes Dev. 14 (2000) 2216–2228.
[25] N. Franco-Pons, et al., Discoidin domain receptor 1, a tyrosine kinase receptor, is upregulated in an experimental model of remyelination and during oligodendrocyte differentiation in vitro, Journal of molecular neuroscience: MN 38 (2009) 2–11.
[26] J.R. Tonniges, et al., Collagen Fibril Ultrastructure in Mice Lacking Discoidin Domain Receptor 1. Microscopy and microanalysis : the official journal of Microscopy Society of America, Microbeam Analysis Society, Microscopical Society of Canada 22 (2016) 599–611.
[27] Y. Zhang, et al., An RNA-Sequencing Transcriptome and Splicing Database of Glia, Neurons, and Vascular Cells of the Cerebral Cortex, J. Neurosci. 34 (2014) 11929–11947.
[28] B.E. Slack, M.S. Siniaia, J.K. Blusztajn, Collagen Type I Selectively Activates Ectodomain Shedding of the Discoidin Domain Receptor 1 : Involvement of Src Tyrosine Kinase, J. Cell. Biochem. 684 (2006) 672–684.
[29] L. Pedraza, Nuclear transport of myelin basic protein, J. Neurosci. Res. 50 (1997) 258–264.
[30] S. Higashiyama, D. Nanba, H. Nakayama, H. Inoue, S. Fukuda, JB Ectodomain shedding and remnant peptide signalling of EGFRs and their ligands, J. Biochem. 150 (2011) 15–22.
[31] H. Chen, et al., DDR1 promotes E-cadherin stability via inhibition of integrin- E-cadherin endocytosis, Nature Publishing Group, 2016, pp. 1–15, https://doi.org/10.1038/srep36336.
[32] C. Hidalgo-Carcedo, et al., Collective cell migration requires suppression of actomyosin at cell-cell contacts mediated by DDR1 and the cell polarity regulators Par3 and Par6, Nat. Cell Biol. 13 (2011) 49–58.
[33] M. Varela-Rey, et al., S-adenosylmethionine levels regulate the schwann cell DNA methylome, Neuron 81 (2014) 1024–1039.
[34] S. Sakuma, H. Saya, A. Ijichi, P.J. Tofilon, Radiation induction of the receptor tyrosine kinase gene Ptk-3 in normal rat astrocytes, Radiat. Res. 143 (1995) 1–7.
[35] B. Vastrad, C. Vastrad, A. Godavarthi, R. Chandrashekar, Molecular mechanisms underlying gliomas and glioblastoma pathogenesis revealed by bioinformatics analysis of microarray data, Med. Oncol. 34 (1–30) (2017).
[36] M.-C. Seo, et al., Discoidin domain receptor 1 mediates collagen-induced inflammatory activation of microglia in culture, J. Neurosci. Res. 86 (2008) 1087–1095.
[37] M. Hebron, et al., Discoidin domain receptor inhibition reduces neuropathology and attenuates inflammation in neurodegeneration models, J. Neuroimmunol. 311 (1–9) (2017).
[38] M. Buntinx, et al., Characterization of three human oligodendroglial cell lines as a model to study oligodendrocyte injury: morphology and oligodendrocyte-specific gene expression, J. Neurocytol. 32 (2003) 25–38.
[39] R. Ram, et al., Discoidin domain receptor-1a ( DDR1a ) promotes glioma cell invasion and adhesion in association with matrix metalloproteinase-2, J Neuro-Oncology 76 (2006) 239–248, https://doi.org/10.1007/s11060-005-6874-1.
[40] E.D. Foehr, et al., Discoidin domain receptor 1 (DDR1) signaling in PC12 cells: activation of juxtamembrane domains in PDGFR/DDR/TrkA chimeric receptors, FASEB journal: official publication of the Federation of American Societies for Experimental Biology 14 (2000) 973–981.
[41] S. Marques, et al., Oligodendrocyte heterogeneity in the mouse juvenile and adult central nervous system, Science (New York, NY) 352 (2016) 1326–1329.
[42] B. Emery, Q.R. Lu, Transcriptional and Epigenetic Regulation of Oligodendrocyte Development and Myelination in the Central Nervous System, Cold Spring Harb. Perspect. Biol. 7 (1–21) (2015).
[43] B.S. Letzen, et al., MicroRNA expression profiling of oligodendrocyte differentiation from human embryonic stem cells, PLoS ONE 5 (2010).

[44] S. Oh, M. Seo, J. Choi, C. Joo, S.K. Lee, MiR-199a / b-5p Inhibits Lymphangiogenesis by Targeting Discoidin Domain Receptor 1 in Corneal Injury, Mol. Cell 41 (2018) 93–102.
[45] Natalie A. Wheeler, B. Fuss, Extracellular Cues Influencing Oligodendrocyte Differentiation and (Re)myelination, Exp. Neurol. 283 (2016) 512–530.
[46] K.-A. Nave, H.B. Werner, Myelination of the Nervous System: Mechanisms and Functions, Annu. Rev. Cell Dev. Biol. 30 (2014) 503–533.
[47] P. Montague, A.S. McCallion, R.W. Davies, I.R. Griffiths, Myelin-associated oligodendrocytic basic protein: a family of abundant CNS myelin proteins in search of a function, Dev. Neurosci. 28 (2006) 479–487.
[48] S. Agnihotri, et al., The genomic landscape of schwannoma, Nat. Genet. 48 (2016) 1339–1348.
[49] R.R. Valiathan, M. Marco, et al., Discoidin domain receptor tyrosine kinases: new players in cancer progression, Cancer Metastasis Rev. 31 (2013) 295–321.
[50] B. Roig, et al., The discoidin domain receptor 1 as a novel susceptibility gene for schizophrenia, Mol. Psychiatry 12 (2007) 833–841.
[51] C. Gas, et al., Discoidin domain receptor 1 gene variants are associated with decreased white matter fractional anisotropy and decreased processing speed in schizophrenia, J. Psychiatr. Res. 110 (2018) 74–82.
[52] J. Benkovits, et al., Investigation of CNTF, COMT, DDR1, DISC1, DRD2, DRD3, and DTNBP1 candidate genes in schizophrenia: Results from the Hungarian SCHIZOBANK Consortium, Neuropsychopharmacologia Hungarica 18 (2016) 181–187.
[53] B. Roig, N. Abasolo, S. Moyano, L. Martorell, E. Vilella, Increased expression of the spliced DDR1c isoform in brain tissues from schizophrenia patients, J. Psychiatr. Res. 46 (2012) 825–827.
[54] S.E. Kim, et al., Meta-analysis of genome-wide SNP- A nd pathway-based associations for facets of neuroticism, J. Hum. Genet. 62 (2017) 903–909.
[55] A.J. Fowler, et al., Multikinase Abl/DDR/Src Inhibition Produces Optimal Effects for Tyrosine Kinase Inhibition in Neurodegeneration, Drugs in R&D (2019), https://doi.org/10.1007/s40268-019-0266-z.
[56] F.L. Pagan, et al., Pharmacokinetics and pharmacodynamics of a single dose Nilotinib in individuals with Parkinson's disease, Pharmacol. Res. Perspect. 7 (2019) e00470.

Journal of Psychiatric Research 110 (2019) 74–82

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

# Discoidin domain receptor 1 gene variants are associated with decreased white matter fractional anisotropy and decreased processing speed in schizophrenia

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ARTICLE INFO

*Keywords:*
DDR1
Cognition
Imaging
Genetics
Myelin

ABSTRACT

*DDR1* has been linked to schizophrenia (SZ) and myelination. Here, we tested whether *DDR1* variants in people at risk for SZ influence white matter (WM) structural variations and cognitive processing speed (PS). First, following a case-control design *(Study 1)*, SZ patients (N = 1193) and controls (N = 1839) were genotyped for rs1264323 and rs2267641 at *DDR1*, and the frequencies were compared. We replicated the association between *DDR1* and SZ (rs1264323, adjusted P = 0.015). Carriers of the rs1264323AA combined with the rs2267641AC or CC genotype are at risk to develop SZ compared to the other genotype combinations. Second, SZ patients (*Study 2*, N = 194) underwent an evaluation of PS using the Trail Making Test (TMT) and *DDR1* genotyping. To compare PS between *DDR1* genotype groups, we conducted an analysis of covariance (including rs1264323 as a covariate) and found that SZ patients with the rs2267641CC genotype had decreased PS compared to patients with the AA and AC genotypes. Third, 54 patients (*Study 3*) from Study 2 were selected based on rs1264323 genotype to undergo reevaluation, including a DTI-MRI brain scan. To test for associations between PS, WM microstructure and *DDR1* genotype, we first localized those WM regions where fractional anisotropy (FA) was correlated with PS and tested whether FA showed differences between the rs1264323 genotypes. SZ patients with the rs1264323AA genotype showed decreased FA in WM regions associated with decreased PS. We

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https://doi.org/10.1016/j.jpsychires.2018.12.021
Received 29 August 2018; Received in revised form 4 December 2018; Accepted 21 December 2018

conclude that *DDR1* variants may confer a risk of SZ through WM microstructural alterations leading to cognitive dysfunction.

## 1. Introduction

Traditionally, schizophrenia (SZ) was thought to be associated with neuronal dysfunction; however, the current hypothesis that myelin and, specifically, oligodendrocytes are also involved in the development of SZ is gaining traction (Ren et al., 2013; Roussos and Haroutunian, 2014). In this regard, after screening the discoidin domain receptor 1 (*DDR1*) locus in DNA from 100 patients diagnosed with SZ, we identified an association of several genetic variants with the disease (Roig et al., 2007). The haplotype encompassing rs1049623, rs2267641 and rs2239518 was associated with SZ after adjusting for multiple testing (Roig et al., 2007).

DDR1 is a membrane-anchored tyrosine kinase receptor whose unique ligand identified to date is collagen (Leitinger, 2014; Ullrich and Schlessinger, 1990; Vogel, 1999). The *DDR1* gene is located at 6p21.3, near the major histocompatibility complex (MHC) region. This chromosomal region has been associated with SZ (Ripke et al., 2013) but most GWAS arrays used in SZ studies did not contain rare variants at the DDR1 locus such as rs2267641. Alternative splicing of *DDR1* produces at least 5 isoforms, known as *DDR1*a to *DDR1*e (Alves et al., 2001). Isoforms *DDR1*a and *DDR1*b are the most abundant in several tissues, including blood (Leitinger, 2014). Detailed analysis of DDR1 protein in the adult human brain revealed that its expression pattern parallels that of the MBP, a classic white matter (WM) protein (Bàrbara Roig et al., 2010). DDR1c isoform expression is highly correlated with the myelin genes *MAG* and *OLIG2* in the human brain (Barbar Roig et al., 2012b). In rodents, high oligodendrocyte expression of *DDR1* parallels developmental myelination (Franco-Pons et al., 2006) and remyelination after experimental demyelination (Franco-Pons et al., 2009). SNP rs2267641, located in a heterogeneous nuclear ribonucleoprotein A2 response element (A2RE) sequence in *DDR1* exon 14, influences alternative splicing and the concentrations of the isoforms *DDR1*b and *DDR1*c (Barbara Roig et al., 2012b). In the same study, SNP rs1264323, which is in linkage disequilibrium (LD) with rs1049623, was also found to influence the expression of isoforms *DDR1*b and *DDR1*c (Barbara Roig et al., 2012b). Moreover, the abundance of the *DDR1c* isoform was significantly elevated in brain dorsolateral prefrontal cortex (DLPFC) tissue from patients with SZ compared to controls (Bàrbara Roig et al., 2012a).

Diffusion tensor imaging (DTI) has made it possible to investigate microstructural WM abnormalities in vivo (Garin-Muga and Borro, 2014). On the basis of DTI data, several studies reported abnormal WM microstructure in patients with chronic and first-episode psychosis (Andreasen et al., 2011; Bora et al., 2011; Pomarol-Clotet et al., 2010; Tamnes and Agartz, 2016) and even in those who were naïve to antipsychotic drugs (Alvarado-Alanis et al., 2015; Zeng et al., 2016; Zhang et al., 2016). Differential expression levels of myelin-related genes, such as *NRG1*, *ERBB4*, *DISC1*, *RTN4R*, *OLIG2*, *CNP* and *MAG*, in brain tissue from subjects with SZ also revealed molecular WM abnormalities, matching the results found by DTI (Roussos and Haroutunian, 2014; Takahashi et al., 2011; Voineskos, 2015). The abnormal expression of myelin-related genes in SZ was most pronounced in the DLPFC, hippocampus, superior temporal cortex and cingulate gyrus (Höistad et al., 2009; Katsel et al., 2005). Only a few reports have demonstrated a relationship among gene variants, WM tract integrity, and cognitive performance. For instance, genetic variability at *MAG*, *OLIG2,* and *CNP* influenced cognitive performance in a manner mediated by the integrity of WM fiber tracts in patients with SZ (Voineskos et al., 2013); more recently, Poletti et al. showed the influence of the *COMT* Val$^{158}$Met polymorphism on the association between cognitive function and WM microstructure (Poletti et al., 2016). Our present hypothesis is that SNP variants in the *DDR1* locus confer susceptibility to SZ in association with WM microstructure variation and neurocognitive deficits such as processing speed (PS) (Karbasforoushan et al., 2015). To test this hypothesis, we designed 3 different but interrelated studies to achieve three main aims: in Study 1, we aimed to replicate the association between *DDR1* variants and SZ; in Study 2, we aimed to determine whether these *DDR1* variants influence PS; and in Study 3, we assessed whether there is a link between WM microstructure, PS and *DDR1* genotype.

**Table 1**
Sociodemographic, clinical and neuropsychological characteristics of study participants.

| | Study 1 (case-control) | | Study 2 (neurocognition) | Study 3 (neuroimaging) |
|---|---|---|---|---|
| | Control N = 1839 | Schizophrenia N = 1193 | Schizophrenia N = 194 | Schizophrenia N = 54 |
| **Sex** (% men/% women) | 62.2/37.8 | 71.4/28.6 | 66.5/33.5 | 53.7/46.3 |
| **Age** (mean ± SD for men/women) | 51.4 ± 10.0/52.6 ± 9.9 | 47.4 ± 13.0/53.7 ± 15.0 | 34.0 ± 9.7/38.0 ± 11.1 | 32.6 ± 6.8/36.0 ± 9.0 |
| **Years of education** (mean ± SD) | na | na | 10.6 ± 3.1 | 9.9 ± 2.5 |
| **Duration of illness** (years, mean ± SD) | na | na | 10.1 ± 10.2 | 8.1 ± 8.5 |
| **Antipsychotic dose** (CPZ equivalents in mg/day) | na | na | 314.4 ± 188.6 | 373.4 ± 226.8 |
| **Psychotic disorder diagnosis** (%) | | | | |
| Psychotic disorder not otherwise specified | na | na | 18.0 | 3.7 |
| Paranoid schizophrenia | na | na | 45.9 | 50.0 |
| Residual schizophrenia | na | na | 28.4 | 24.1 |
| Undifferentiated schizophrenia | na | na | 6.2 | 20.4 |
| Schizophreniform disorder | na | na | 1.5 | 1.9 |
| **PANSS** (score) | | | | |
| Positive | na | na | 23.1 ± 6.8 | 22.3 ± 7.3 |
| Negative | na | na | 17.3 ± 6.7 | 17.6 ± 7.2 |
| General | na | na | 38.7 ± 7.5 | 38.4 ± 7.3 |
| **TMT-A direct scores** (mean ± SD) | na | na | 56.0 ± 29.5 | 56.8 ± 37.5 |

TMT: Trail Making Test, Direct scores expressed as time (sec).

## 2. Materials and methods

### 2.1. Subjects

#### 2.1.1. Study 1. case-control sample

The cases involved in this study (N = 1193) included patients diagnosed with SZ according to DSM-IV criteria recruited from different hospitals across several regions in Spain. Healthy controls (N = 1839) were recruited from the same regions as the patients (Julià et al., 2014). For further details see Table 1 and Supplementary Material and Methods.

#### 2.1.2. Study 2. neurocognition sample

We recruited 194 unrelated participants who were diagnosed as having SZ spectrum disorders according to the DSM-IV criteria. The Trail Making Test part A (TMT-A), administered as previously described (Martorell et al., 2007), was used as a measure of processing speed (Nuechterlein et al., 2004; Varjacic et al., 2018). The TMT-A scores (in seconds) are shown throughout the article, and higher values indicate lower PS. Further information on inclusion and exclusion criteria is provided in Supplementary Material and Methods.

#### 2.1.3. Study 3. neuroimaging sample

Based on rs1264323 genotype, we selected 54 patients with a diagnosis of SZ from the Study 2 sample distributed as follows: 23 subjects with the rs1264323 GG allele, and 21 with the GA and 10 with the AA genotypes. The group with the rare homozygous AA genotype was limited to the 10 patients available. All patients were enrolled in a quantitative neuroimaging study based on DTI to assess whether the relationship between microscopic variations in WM could underlie the relationship between *DDR1* genotype and neurocognition. Further information can be found in Supplementary Material and Methods.

The authors assert that all procedures contributing to this work complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Declaration of Helsinki of 1975, as revised in 2008. The study protocol and informed consent document were approved by the Hospital Universitari de Sant Joan (Reus, Spain) ethics committee. Informed consent of all the participants was obtained after the nature of the procedures had been fully explained.

### 2.2. Genotyping

DNA isolated from peripheral blood was used for SNP genotyping with TaqMan technology (genotyping details are available in Supplementary Material and Methods). SNPs rs1264323 and rs2267641, which influence *DDR1* isoform expression in the brain (Barbara Roig et al., 2012) and are associated with SZ (Roig et al., 2007), were genotyped. Moreover, rs3135388 (a proxy of HLA-DRB*1501 that has consistently been associated with multiple sclerosis (Cox et al., 2012)) and rs9268895 (near HLA-DRB9 and has been associated with SZ (Ripke et al., 2013)) were genotyped to exclude false locus associations.

### 2.3. Neuroimaging

Each subject in Study 3 underwent an MRI scanning session using a 1.5-T GE Signa scanner (General Electric Medical Systems). DTI data collection and fractional anisotropy (FA) image analysis protocols are described in Supplementary Material and Methods. To assess whether there was a link among *DDR1* genotype, PS and WM microscopic variation, we first localized those WM regions where FA correlated with PS, after which we checked whether FA in these regions showed differences between groups with different *DDR1* rs1264323 genotypes.

### 2.4. Statistical analysis

#### 2.4.1. Study 1. case-control

Genotype frequencies in patients and controls were compared using Pearson's chi-square test. P-values adjusted using Bonferroni correction (2 SNPs analyzed simultaneously) were also calculated. Allele estimates, genotype association, and analysis of epistasis between SNPs were conducted using the software PLINK v1.07. We also evaluated the association between the SNP rs1264323 genotype and SZ using logistic regression, stratifying the sample by rs2267641C allele presence. The degree of association was represented as the odds ratio (OR) with the corresponding 95% confidence interval (CI). These analyses were conducted using SPSS Statistics Package, v22.0 (IBM Corp., New York, NY, USA).

#### 2.4.2. Study 2. neurocognition

Categorical variables were reported as frequencies and percentages. Continuous variables were presented as the mean ± SD. We explored the normality of the distribution of continuous variables using the Kolmogorov-Smirnov test. TMT-A scores are shown in Figures and Tables, however, the normalized log-transformed variable was used in all statistical analyses. Parametric correlation coefficients were calculated to assess the associations between PS, symptoms (positive and negative scale scores and the general PANSS score) and other clinical variables (sex, age, years of education, duration of illness and antipsychotic dose). Student's *t*-tests were used to compare continuous variables stratified by sex. To compare PS between *DDR1* genotype groups, we conducted analysis of covariance (ANCOVA). *DDR1* genotypes were grouped following the dominant, recessive and codominant models and the groupings with the most statistically significant results are shown for clarity. We included as covariates the variables that correlated with cognitive function in the univariate and bivariate analyses (Supplementary Table 1). In addition, a bootstrap method (Dwivedi et al., 2017) was used because of the small size of the group homozygous for the minor allele. To assess whether *DDR1* genotype was associated with PS changes over time (the period between assessment for Study 2 and reassessment for Study 3), we conducted an ANOVA with repeated measures and appropriate covariables. These analyses were conducted using SPSS.

#### 2.4.3. Study 3. neuroimaging

Whole-brain voxel-based statistical analyses were carried out using a general linear model by means of the Statistical Parametric Mapping (SPM12) software package (Wellcome Trust Centre for Neuroimaging, London, UK). The statistical model and contrasts of interest were designed to find regions where the FA values were positively or negatively correlated with PS based on TMT-A scores, the cognitive variable that was significantly associated with *DDR1* genotypes. Covariates were included to adjust for age and sex. Before the statistical analysis, normalized images were spatially filtered with a Gaussian kernel of FWHM = 2.5 mm. The statistical analysis was restricted to all voxels in WM (threshold: FA > 0.2). Regions were reported as significant at $p < 0.05$, fully corrected for multiple comparisons at the cluster level via the topological familywise error (FWE) approach implemented in SPM12 (based on random field theory) using a cluster-forming height threshold of $p < 0.001$ and a spatial extent threshold of $k > 40$ voxels. The anatomical locations of significant regions were determined with reference to the structural atlases integrated into MRIcron software, including the Automated Anatomical Labeling (AAL) structural atlas, the Johns Hopkins University (JHU) DTI-based white-matter atlas and the NatBrainLab tractography atlas. Finally, the average value of FA for all voxels in each significant cluster was extracted and further analyzed to check whether there were differences in FA between distinct genetic groups, as well as to ensure that the correlation between FA and PS was not due to potential confounding factors (age, sex, years of education, disease duration, PANSS score, or medication).

## 3. Results

### 3.1. Study 1. case-control replication study

A description of the study participants is shown in Table 1. Genotype frequencies, shown in Table 2, differed between cases and controls for rs1264323 (adjusted P = 0.015). Interestingly, a significant interaction between the SNPs rs1264323 and rs2267641 was observed (OR = 1.58, P = 0.00152). That is, carriers of one or two rs2267641C alleles who have an rs1264323 GA genotype are protected against the development of SZ (OR = 0.56; 95% CI = 0.40–0.77, P < 0.001) compared to rs1264323AA homozygous subjects. Therefore, an elevated risk of SZ is associated with rs1264323AA and one or two C alleles at rs2267641. In the present study, 8.3% of patients had the *DDR1* risk genotypes, compared to 5.2% of controls (Table 2). Together, these results demonstrate that the genetic association between *DDR1* and SZ is mediated by an interaction between rs1264323 and rs2267641.

One of the most replicated chromosomal regions associated with SZ is 6p21.3, near the MHC, which includes the human leukocyte antigen (HLA) genes (Corvin and Morris, 2014). To assess whether the observed associations between *DDR1* SNPs and SZ were due to or influenced by HLA genes, we assessed LD between *DDR1* SNPs (rs1264323 and rs2267641) and HLA-DRB*1501 (rs313538 associated with multiple sclerosis) and HLA-DRB9 (rs9268895, which has been associated with SZ). All LDs were low ($r^2$ < 0.04) (data not shown). Therefore, we assumed that the association between *DDR1* and SZ was independent of HLA genes.

### 3.2. Study 2. DDR1 and rs2267641 and TMT-A scores

Participants' general characteristics are summarized in Table 1. TMT-A scores, according to the model showing the most statistically significant differences, are shown in Table 3. In Model 1, subjects homozygous for the rs2267641C allele had elevated TMT-A scores (P = 0.001). Similarly, in Model 2, only subjects from AA-CC genotype group had significantly increased TMT-A scores (P = 0.009). Thus, patients with schizophrenia with the rs2267641CC genotype have elevated TMT-A scores that can be read as a sign of decreased PS and suggested a recessive effect of the C allele.

### 3.3. Study 3. DDR1 rs1264323, WM FA, and PS

Patient features, that were similar to those of Study 2, are summarized in Table 1. At a corrected p-value < 0.05, no significant regions of positive correlation between FA and TMT-A were found in the whole-brain analysis. By contrast, the analysis showed two clusters where FA was negatively correlated with TMT-A scores. One of these areas (cluster 1: corrected p-value = 0.006, cluster-size = 66 voxels, peak MNI coordinate (9,4,30), T-score = 4.59) was located in the body of the corpus callosum, reaching the margin of the right cingulum bundle. The second significant area (cluster 2: corrected p-value = 0.009, cluster-size = 61 voxels, peak MNI coordinate (32,-68,33), T-score = 4.96) was centered in a WM region in the right hemisphere close to the middle occipital gyrus, reaching the posterior segment of the arcuate fasciculus. For more details about the anatomical locations, see Fig. 1.

After the average FA value was computed for all voxels in both clusters, the ROI-based analysis revealed that the relationship between FA and PS remained significant (p = 0.007 and p < 0.001 for clusters 1 and 2) for a linear regression of PS by FA with the covariates of age, PANSS score and years of education, thus showing that the correlation between FA and PS was not due to any of the potential confounding factors that we investigated. Note that we had previously shown that these covariates (and not others) were independently associated with PS and that, although PS was not normally distributed (Shapiro-Wilk test p < 0.001), the residuals of the regression were normally distributed (Shapiro-Wilk test p = 0.581 and p = 0.964 for clusters 1 and 2).

Interestingly, we found that individuals with the genotype rs1264323AA showed lower FA in these clusters than individuals carrying the G allele (t-tests: p = 0.015 and p = 0.009 for clusters 1 and 2, respectively) (Fig. 1, panel D). FA in the second cluster showed a relationship with medication (p = 0.027), but medication was not found to be a confounding factor in a regression of FA by polymorphism covarying by medication (p = 0.015 and p = 0.007 for clusters 1 and 2). Thus, in these WM regions, individuals with the genotype rs1264323AA showed decreased FA; and decreased FA was associated with increased TMT-A scores (decreased PS). Moreover, we explored the involvement of the rs1264323 genotype in the differences in TMT-A scores between the first and second assessments, which on average were 6 years apart. The interaction between time and the rs1264323A allele was significantly associated (P = 0.029) with worsening of PS over time (Fig. 2, panels A and B). Together, these results showed that rs1264323 was associated with changes in FA in brain regions involved in PS in patients with SZ.

## 4. Discussion

### 4.1. Study 1

Here, we further demonstrated the association between *DDR1* and SZ in a case-control design using a Spanish sample. Moreover, we showed an interaction between rs1264323 and rs2267641 for the first time, producing a complex association with SZ. The data suggested that SZ was associated with the rs2267641C allele only in rs1264323A

**Table 2**
Genotype distribution (%) and multinomial logistic regression to assess the association between *DDR1* rs1264323 and rs2267641 and schizophrenia in patients and controls from Study 1 sample.

| | Controls N = 1839 | Patients N = 1193 | Adjusted P[c] | |
|---|---|---|---|---|
| **SNP** | | | | |
| **rs1264323** | | | | |
| GG | 47.2 | 49.3 | 0.015 | |
| GA | 44.2 | 39.7 | | |
| AA | 8.7 | 11.0 | | |
| **rs2267641** | | | | |
| AA | 74.1 | 73.3 | ns | |
| AC | 24.4 | 24.9 | | |
| CC | 1.5 | 1.9 | | |
| **Combined genotype**[a] | | | **Effect** | |
| GG-AA | 47.2 | 49.3 | Neutral | |
| GA-AA | 23.4 | 21.3 | Neutral | |
| AA-AA | 3.4 | 2.8 | Neutral | |
| GG-AC | 0 | 0 | NA | |
| **GA-AC** | **20.7** | **18.3** | **Protective** | |
| **AA-AC** | **3.7** | **6.4** | **Risk** | |
| GG-CC | 0 | 0 | NA | |
| GA-CC | 0 | 0 | NA | |
| **AA-CC** | **1.5** | **1.9** | **Risk** | |
| **MLRA** | | | **OR (95%CI)** | **P** |
| **GG-AA/GA-AA**[b] | 95.4 | 96.2 | 1.2 (0.79–1.89) | **ns** |
| **AA-AA** | 4.6 | 3.8 | | |
| **GA-AC**[b] | 79.9 | 68.9 | 0.56 (0.40–0.77) | $4 \times 10^{-4}$ |
| **AA-AC/AA-CC** | 20.1 | 31.1 | | |

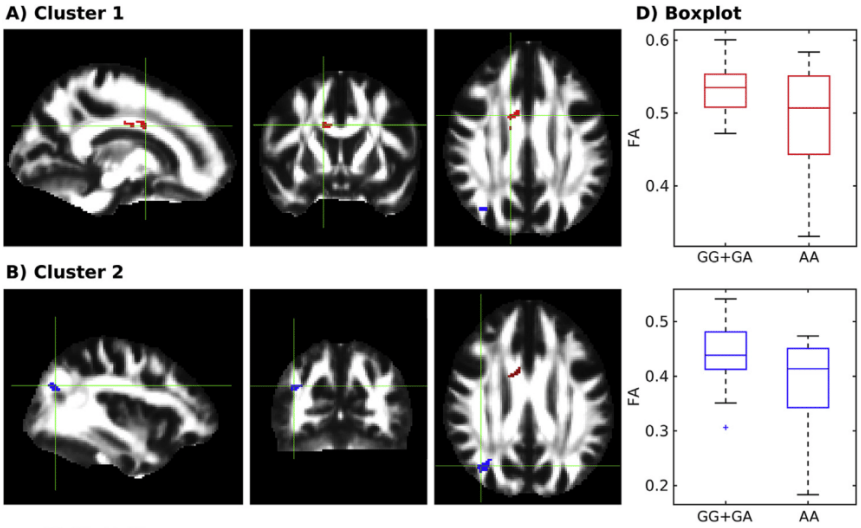
[a] rs1264323-rs2267641 combined genotype: rs1264323 GG, GA, AA; rs2267641 AA, AC, CC.
[b] Reference group in the multinomial logistic regression analysis (MLRA).
[c] Bonferroni correction.

**Table 3**
Analysis of covariance to compare mean TMT-A scores between carriers and non-carriers of the rs2267641 C allele in Study 2 sample.

| Model 1[a] | Genotype rs2267641 | | | | P value | P value[c] |
|---|---|---|---|---|---|---|
| | AA + AC N = 190 | | CC N = 4 | | | |
| TMT-A, mean ± SD | 49.4 ± 1.5 | | 66.7 ± 1.2 | | 0.086 | 0.001 |
| **Model 2[b]** | **Genotype rs1264323-rs2267641** | | | | | |
| | **GG-AA GA-AA AA-AA** N = 145 | **GA-AC** N = 34 | **AA-AC** N = 11 | **AA-CC** N = 4 | **P value** | **P value[c]** |
| TMT-A, mean ± SD | 494 ± 1.5 | 49.4 ± 1.6 | 36.6 ± 1.3 | 66.7 ± .21 | 0.061[d] | 0.009[d] |

[a] The covariates included in the analysis (based on the bivariate analysis shown in Supplementary Table 1) were SNP rs1264323 (GG + GA vs AA), duration of illness, years of education, age at testing, gender, antipsychotic dose and PANSS Negative score.
[b] The covariates included in the analysis (based on the bivariate analysis shown in Supplementary Table 1) were duration of illness, years of education, age at testing, gender, antipsychotic dose and PANSS Negative score.
[c] ANCOVA using bootstrapping.
[d] Comparison AA-AC vs AA-CC.

homozygotes. We previously (Roig et al., 2007) identified the SNP rs1049623, which is in high LD with rs1264323 (examined in the present article), as being associated with SZ (OR = 1.44, 95% CI = 1.15–1.79, adjusted P = 0.0016). It is important to note that rs2267641 has not been included in most GWAS panels; therefore, genotype data on this SNP are scarce. Interestingly, rs2267641 is a functional SNP that has been implicated in the alternative splicing of *DDR1*b and *DDR1*c isoforms, and subjects with the rs2267641CC genotype had lower levels of *DDR1*b mRNA and higher levels of *DDR1*c mRNA in their brain tissue than subjects who were homozygous for the major allele (Barbara Roig et al., 2012b). Further, the levels of the *DDR1*c isoform were increased in patients with SZ compared with controls (Bàrbara Roig et al., 2012a). The epistatic interaction between rs1264323 and rs2267641 regarding the association with SZ, as observed in the present study, could involve differential isoform expression. Neither SNP causes an amino acid change, but both are involved in gene expression: rs2267641 because it alters the binding affinity of the A2RE mRNA sequence for the protein hnRNP A2 (Barbara Roig et al., 2012b), and rs1264323 that is included in the eQTL database (GTEx, http://www.gtexportal.org) for its differential expression in human tibial nerve ($P = 6.9 \times 10^{-5}$, n = 369) and other tissues, probably because of its position in the putative promoter region. Although we assumed that the association between *DDR1* and SZ was independent of HLA genes, HLA is a complex chromosomal region, and we cannot rule out the possibility that other variants linked to *DDR1* might influence the association that we have found. We must take into

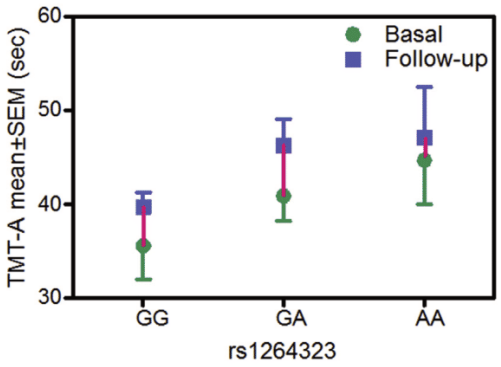



C) Statistics

| | cluster-level $p_{FWE-corr}$ | cluster-level $k$ | peak-level $T$ | peak-level mm | peak-level mm | peak-level mm | white matter regions |
|---|---|---|---|---|---|---|---|
| cluster 1 | 0.006 | 66 | 4.59 | 9 | 4 | 30 | Body of corpus callosum (R), cingulum bundle (R) |
| cluster 2 | 0.009 | 61 | 4.96 | 32 | -68 | 33 | White matter close to the middle occipital gyrus (R), posterior segment of arcuate fasciculus (R) |

**Fig. 1.** Brain regions showing a significant correlation between processing speed (PS, TMT-A scores) and fractional anisotropy (FA) in patients with schizophrenia from Study 3. Panels A), B), and C) depict the anatomical locations and statistical results of the correlation analyses. Panel D) shows the intergroup comparisons between patients who were categorized by the presence of the rs1264323G allele.

A




B **Analysis of covariance with repeated measures to compare TMT-A direct scores between baseline and follow-up[a] according to rs1264232 genotype in Study 3 sample**

| | Variables | P value |
|---|---|---|
| **Between subjects effects[b]** | rs1264323 | 0.884 |
| **Within subjects effects[b]** | Time | 0.054 |
| | Time x rs1264323 | 0.029 |

[a]Mean time (years): 6.27±1.3.
[b]Covariates used: age, years of education, duration of illness, medication and negative symptoms.

**Fig. 2.** The time and rs1264323 effect on processing speed (PS, TMT-A scores) comparing baseline and follow-up measures in patients from Study 3. Panel A) shows a graph representing mean TMT-A scores (time, in seconds) according to rs1264323 genotype group at baseline and follow-up time points. Panel B) depicts the results from the analysis of covariance with repeated measures that compares TMT-A scores between baseline and follow-up according to rs1264323 genotype.

account that although the highest association with SZ ever found for a SNP is for rs9268895 near HLA DRB9 (Ripke et al., 2013), a significant risk was also observed for other genes not related to the immune system but located nearby (Corvin and Morris, 2014). Moreover, Bergen et al. (2012), using a Swedish sample, found a significant association between SZ and both SNPs at *LINCO00243*, which codes for a long mRNA and is located 50 kb upstream of *DDR1*.

### 4.2. Study 2

Through this study, we demonstrated a significant relationship between homozygosity for the rare rs2267641C allele and decreased PS in patients with SZ. There are no published studies on the relationship between *DDR1* and cognitive function. We know that the rs2267641C allele is associated with decreased abundance of the *DDR1*b isoform and increased abundance of the *DDR1*c isoform in whole brain tissue showing a genotype dose-dependent relationship (Supplementary Fig. 1, panel D) (Barbara Roig et al., 2012b), but further investigation is needed to elucidate the exact role of *DDR1* isoforms in brain physiology. However, these results are consistent with several published studies reporting that patients with abnormalities in oligodendrocyte genes show an increased severity of cognitive dysfunction. One example is a paper that reported the effects of genetic variants in oligodendrocyte genes (*CNP*, *MAG,* and *OLIG2*) on cognitive function and the involvement of myelin tract integrity (Voineskos et al., 2013).

### 4.3. Study 3

We found two clusters where FA was significantly correlated with PS. Notably, in these clusters patients with the genotype rs1264323AA showed lower FA than patients carrying the G allele. This result suggested that the G allele at rs1264323 may be protective, as it is associated with higher FA and thus with less damaged WM. This result is in line with the results of Study 1, in which we found that the G allele at rs1264323 is protective against SZ in subjects carrying the rs2267641C allele. *DDR1* is present in myelin (Bàrbara Roig et al., 2010); however, no detailed data exist about differential expression of *DDR1* across brain regions. A number of previous studies have found reduced FA in SZ (Kelly et al., 2018; Pomarol-Clotet et al., 2010), as well as correlations with symptomatology, sensory function, and cognition (Hoptman, 2010). Genetic susceptibility to reduced FA in healthy subjects has been found. For instance, four independent studies have reported that genetic variation in the *NRG1-ERBB4* complex, involved in axon guidance and myelination, is associated with reduced FA in WM, mainly affecting tracts from the frontal and temporal lobes (Konrad et al., 2009; McIntosh et al., 2008; Nickl-Jockschat et al., 2014; Winterer et al., 2008). Additionally, the rs1018381T allele of the *DTNBP1* gene was associated with differential FA compared to the A allele (Nickl-Jockschat et al., 2012). Different SNPs in *NTRK3*, related to oligodendrocyte and myelin development, were correlated with FA in several regions including the corpus callosum and the inferior longitudinal fasciculus (Braskie et al., 2013).

In SZ patients, an association appeared to exist between rs2710126, located inside *CNTNAP*, a protein involved in neuronal synchronization and brain connectivity, and FA in the uncinate fasciculus (Clemm von Hohenberg et al., 2013). A SNP of the *GRM3* gene was found to be correlated with FA in tracts from the cortico-cerebellar-thalamic-cortical circuit of patients with SZ (Mounce et al., 2014). Finally, a recent report showed that the *COMT* Val$^{158}$Met polymorphism moderates the association between WM microstructure and cognitive performance (Poletti et al., 2016).

The underlying neural mechanisms for the interindividual variability in PS remain unknown. It has been proposed that this variability may be due to differences in the physiological properties of the white matter in association fibers and tracts supporting interhemispheric transmission (Kochunov et al., 2017; Penke et al., 2010), such as the differences found in our study. For example, a mediation analysis carried out (Kochunov et al., 2017) using DTI data from 166 patients with schizophrenia found a significant association pathway from FA to PS to working memory. The strongest association was observed for the body of the corpus callosum, which contains interhemispheric motor and sensory fibers. Strong correlations were also observed for a number of association fibers including the cingulum bundle and the superior longitudinal fasciculus that contains the arcuate fasciculus. In two previous studies, the integrity of these tracts, as measured by DTI, was significantly associated with PS in healthy older people (Kerchner et al., 2012; Penke et al., 2010). PS and FA associations in the body of the corpus callosum have been found in other studies examining sickle cell anemia (Stotesbury et al., 2018), multiple sclerosis (Genova et al., 2013), and normal aging (Salami et al., 2012). Similar associations in the cingulum bundle have been reported in early-course schizophrenia (Seitz et al., 2016), normal aging (Salami et al., 2012) and adults with coronary artery disease (Santiago et al., 2015), the latter which also found a significant association in the inferior fronto-occipital fasciculus.

Data are scarce regarding the impact of genes on WM microstructure and PS. On the one hand, a number of neuroimaging studies in patients with SZ found that FA is strongly associated with PS (Karbasforoushan et al., 2015; Roalf et al., 2015; Zeng et al., 2016). On the other hand, a recent exploratory analysis provided preliminary data suggesting that *KCNQ1* may contribute to the correlated risks of diminished PS, diminished FA and SZ (Bruce et al., 2017).

All these previous studies highlighted the point that SZ is a very complex disorder involving multiple genes. The disruption of these genes is associated with local WM changes, which in turn, are related to different symptoms, as well as to sensorial and cognitive malfunction. In this context, our Study 3 provided new information about the involvement of *DDR1* in SZ and its relation to WM microstructure and PS.

Although we observed that DDR1 is present in myelin (Franco-Pons et al., 2009, 2006; B Roig et al., 2010 and speculated that it can modulate WM microstructure, DDR1 is present in activated leukocytes (Hachehouche et al., 2010; Kamohara et al., 2001) and therefore an involvement through brain tissue inflammation cannot be ruled out.

### 4.4. Strengths and limitations

One of the strengths of the present study is that we showed the association between *DDR1* and SZ through 3 different study designs: first, a case-control association analysis; second, a neuropsychological assessment in a cohort of SZ patients; and finally, a DTI neuroimaging study in a sample of SZ patients grouped according to *DDR1* genotype. Another strong point is the capacity to control for many confounding variables, such as the presence of psychotic symptoms, drug abuse, pharmacotherapy, and education. However, there is an important limitation regarding the sample size of the homozygous rare allele groups for both SNPs in Study 3. Future studies with larger sample size to allow detection the relationship between DDR1 variants and PS are required. Also new studies involving more SNPs in white matter genes and even polygenic risk scores to explore their influence in processing speed are worth conducting. FA, sensitive to changes in various microstructure parameters including axon diameter, degree of myelination, membrane permeability, fiber density, and orientation heterogeneity, is the most widely used metric to study WM in vivo. However, a potential limitation of this metric, apart from that we used a 1.5T platform to collect DTI scans, is that it is not specific to any of these parameters. Therefore, it is not possible to identify the particular aspect of the microstructure that is responsible for the FA changes (Beaulieu, 2002). For this reason, future studies should be conducted to explore more advanced neuroimaging techniques based on multiple MRI features (Canales-Rodríguez et al., 2014), allowing the individual characterization of these microstructural parameters (Daducci et al., 2015) by using MRI scanners with higher magnetic fields and stronger diffusion gradients (Jones et al., 2018).

## 5. Conclusions

First, we replicated the association of *DDR1* with SZ in an independent Spanish sample and demonstrated that a SNP-SNP interaction within *DDR1* played a role in the association with the disease. Second, we observed that SZ subjects with the rs2267641CC genotype had decreased PS scores. Third, SZ subjects with the rs1264323AA genotype showed decreased FA in WM regions in association with decreased PS. We conclude that *DDR1* variants may confer a risk of SZ through WM microstructural alterations leading to cognitive dysfunction.

## Acknowledgements

This work was supported by the Spanish 'Instituto de Salud Carlos III' from the Ministry of Economy, Industry and Competitivity and FEDER (project grants to [EV] #SAF2007-60086, #PI12/02111 and [JR] # PI14/00292; and contract grants Miguel Servet #CPII16/00018 to [EP-C] and #MS14/00041 to [JR]) and Generalitat de Catalunya Agency 'AGAUR' (research grant to [EV] #2017-SGR-444 and to [EP-C] #2017-SGR-1271). Nerea Abasolo was the recipient of a predoctoral fellowship from the Universitat Rovira i Virgili. The Authors have declared that there are no conflicts of interest in relation to the subject of this study.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2018.12.021.

## References

Alvarado-Alanis, P., León-Ortiz, P., Reyes-Madrigal, F., Favila, R., Rodríguez-Mayoral, O., Nicolini, H., Azcárraga, M., Graff-Guerrero, A., Rowland, L.M., de la Fuente-Sandoval, C., 2015. Abnormal white matter integrity in antipsychotic-naïve first-episode psychosis patients assessed by a DTI principal component analysis. Schizophr. Res. 162, 14–21.

Alves, F., Saupe, S., Ledwon, M., Schaub, F., Hiddemann, W., Vogel, W.F., 2001. Identification of two novel, kinase-deficient variants of discoidin domain receptor 1: differential expression in human colon cancer cell lines. Faseb. J.: Off. Publ. Fed. Am. Soc. Exper. Biol. 15, 1321–1323.

Andreasen, N.C., Nopoulos, P., Magnotta, V., Pierson, R., Ziebell, S., Ho, B.-C., 2011. Progressive brain change in schizophrenia: a prospective longitudinal study of first-episode schizophrenia. Biol. Psychiatry 70, 672–679.

Beaulieu, C., 2002. The basis of anisotropic water diffusion in the nervous system - a technical review. NMR Biomed. 15, 435–455. https://doi.org/10.1002/nbm.782.

Bergen, S.E., O'Dushlaine, C.T., Ripke, S., Lee, P.H., Ruderfer, D.M., Akterin, S., Moran, J.L., Chambert, K.D., Handsaker, R.E., Backlund, L., Ösby, U., McCarroll, S., Landen, M., Scolnick, E.M., Magnusson, P.K.E., Lichtenstein, P., Hultman, C.M., Purcell, S.M., Sklar, P., Sullivan, P.F., 2012. Genome-wide association study in a Swedish population yields support for greater CNV and MHC involvement in schizophrenia compared with bipolar disorder. Mol. Psychiatr. 17, 880–886. https://doi.org/10.1038/mp.2012.73.

Bora, E., Fornito, A., Radua, J., Walterfang, M., Seal, M., Wood, S.J., Yücel, M., Velakoulis, D., Pantelis, C., 2011. Neuroanatomical abnormalities in schizophrenia: a multimodal voxelwise meta-analysis and meta-regression analysis. Schizophr. Res. 127, 46–57. https://doi.org/10.1016/j.schres.2010.12.020.

Braskie, M.N., Kohannim, O., Jahanshad, N., Chiang, M.-C., Barysheva, M., Toga, A.W., Ringman, J.M., Montgomery, G.W., McMahon, K.L., de Zubicaray, G.I., Martin, N.G., Wright, M.J., Thompson, P.M., 2013. Relation between variants in the neurotrophin receptor gene, NTRK3, and white matter integrity in healthy young adults. Neuroimage 82, 146–153. https://doi.org/10.1016/j.neuroimage.2013.05.095.

Bruce, H.A., Kochunov, P., Paciga, S.A., Hyde, C.L., Chen, X., Xie, Z., Zhang, B., Xi, H.S., O'Donnell, P., Whelan, C., Schubert, C.R., Bellon, A., Ament, S.A., Shukla, D.K., Du, X., Rowland, L.M., O'Neill, H., Hong, L.E., 2017. Potassium channel gene associations with joint processing speed and white matter impairments in schizophrenia. Gene Brain Behav. 16, 515–521. https://doi.org/10.1111/gbb.12372.

Canales-Rodríguez, E.J., Pomarol-Clotet, E., Radua, J., Sarró, S., Alonso-Lana, S., Del Mar Bonnín, C., Goikolea, J.M., Maristany, T., García-Álvarez, R., Vieta, E., McKenna, P., Salvador, R., 2014. Structural abnormalities in bipolar euthymia: a multicontrast molecular diffusion imaging study. Biol. Psychiatry 76, 239–248. https://doi.org/10.1016/j.biopsych.2013.09.027.

Clemm von Hohenberg, C., Wigand, M.C., Kubicki, M., Leicht, G., Giegling, I., Karch, S., Hartmann, A.M., Konte, B., Friedl, M., Ballinger, T., Eckbo, R., Bouix, S., Jäger, L., Shenton, M.E., Rujescu, D., Mulert, C., 2013. CNTNAP2 polymorphisms and structural brain connectivity: a diffusion-tensor imaging study. J. Psychiatr. Res. 47, 1349–1356. https://doi.org/10.1016/j.jpsychires.2013.07.002.

Corvin, A., Morris, D.W., 2014. Genome-wide association studies: findings at the major histocompatibility complex locus in psychosis. Biol. Psychiatry 75, 276–283. https://doi.org/10.1016/j.biopsych.2013.09.018.

Cox, M.B., Ban, M., Bowden, N.A., Baker, A., Scott, R.J., Lechner-Scott, J., 2012. Potential association of vitamin D receptor polymorphism Taq1 with multiple sclerosis. Mult. Scler. 18, 16–22. https://doi.org/10.1177/1352458511415562.

Daducci, A., Canales-Rodríguez, E.J., Zhang, H., Dyrby, T.B., Alexander, D.C., Thiran, J.-P., 2015. Accelerated microstructure imaging via convex optimization (AMICO) from diffusion MRI data. Neuroimage 105, 32–44. https://doi.org/10.1016/J.NEUROIMAGE.2014.10.026.

Dwivedi, A.K., Mallawaarachchi, I., Alvarado, L.A., 2017. Analysis of small sample size studies using nonparametric bootstrap test with pooled resampling method. Statistics in Medicine. https://doi.org/10.1002/sim.7263.

Franco-Pons, N., Tomas, J., Roig, B., Auladell, C., Martorell, L., Vilella, E., 2009. Discoidin domain receptor 1, a tyrosine kinase receptor, is upregulated in an experimental model of remyelination and during oligodendrocyte differentiation in vitro. J. Mol. Neurosci.: MN 38, 2–11. https://doi.org/10.1007/s12031-008-9151-x.

Franco-Pons, N., Virgos, C., Vogel, W.F., Ureña, J.M., Soriano, E., del Rio, J.A., Vilella, E., 2006. Expression of discoidin domain receptor 1 during mouse brain development follows the progress of myelination. Neuroscience 140, 463–475. https://doi.org/10.1016/j.neuroscience.2006.02.033.

Garin-Muga, A., Borro, D., 2014. Review and challenges of brain analysis through DTI measurements. Stud. Health Technol. Inf. 207, 27–36.

Genova, H.M., DeLuca, J., Chiaravalloti, N., Wylie, G., 2013. The relationship between executive functioning, processing speed, and white matter integrity in multiple sclerosis. J. Clin. Exp. Neuropsychol. 35, 631–641. https://doi.org/10.1080/13803395.2013.806649.

Hachehouche, L.N., Chetoui, N., Aoudjit, F., 2010. Implication of discoidin domain receptor 1 in T cell migration in three-dimensional collagen. Mol. Immunol. 47, 1866–1869. https://doi.org/10.1016/j.molimm.2010.02.023.

Höistad, M., Segal, D., Takahashi, N., Sakurai, T., Buxbaum, J.D., Hof, P.R., 2009. Linking white and grey matter in schizophrenia: oligodendrocyte and neuron pathology in the prefrontal cortex. Front. Neuroanat. 3, 9. https://doi.org/10.3389/neuro.05.009.2009.

Hoptman, J.M., 2010. Clinical correlates of MRI white matter abnormalities in schizophrenia. Prilozi 31, 115–133.

Jones, D.K., Alexander, D.C., Bowtell, R., Cercignani, M., Dell'Acqua, F., McHugh, D.J., Miller, K.L., Palombo, M., Parker, G.J.M., Rudrapatna, U.S., Tax, C.M.W., 2018.

Microstructural imaging of the human brain with a 'super-scanner': 10 key advantages of ultra-strong gradients for diffusion MRI. Neuroimage 182, 8–38. https://doi.org/10.1016/j.neuroimage.2018.05.047.
Julià, A., Domènech, E., Chaparro, M., García-Sánchez, V., Gomollón, F., Panés, J., Mañosa, M., Barreiro-De Acosta, M., Gutiérrez, A., Garcia-Planella, E., Aguas, M., Muñoz, F., Esteve, M., Mendoza, J.L., Vera, M., Márquez, L., Tortosa, R., López-Lasanta, M., Alonso, A., Gelpí, J.L., García-Montero, A.C., Bertranpetit, J., Absher, D., Myers, R.M., Gisbert, J.P., Marsal, S., 2014. A genome-wide association study identifies a novel locus at 6q22.1 associated with ulcerative colitis. Hum. Mol. Genet. 23, 6927–6934. https://doi.org/10.1093/hmg/ddu398.
Kamohara, H., Yamashiro, S., Galligan, C., Yoshimura, T., 2001. Discoidin domain receptor 1 isoform-a (DDR1a) promotes migration of leukocytes in three- dimensional collagen lattices. Faseb. J.: Off. Publ. Fed. Am. Soc. Exp. Biol. 15, 2724–2726. https://doi.org/10.1096/fj.01.
Karbasforoushan, H., Duffy, B., Blackford, J.U., Woodward, N.D., 2015. Processing speed impairment in schizophrenia is mediated by white matter integrity. Psychol. Med. 45, 109–120.
Katsel, P., Davis, K., Haroutunian, V., 2005. Variations in myelin and oligodendrocyte-related gene expression across multiple brain regions in schizophrenia: a gene ontology study. Schizophr. Res. 79, 157–173. https://doi.org/10.1016/j.schres.2005.06.007.
Kelly, S., Jahanshad, N., Zalesky, A., Kochunov, P., Agartz, I., Alloza, C., Andreassen, O.A., Arango, C., Banaj, N., Bouix, S., Bousman, C.A., Brouwer, R.M., Bruggemann, J., Bustillo, J., Cahn, W., Calhoun, V., Cannon, D., Carr, V., Catts, S., Chen, J., Chen, J.X., Chen, X., Chiapponi, C., Cho, K.K., Ciullo, V., Corvin, A.S., Crespo-Facorro, B., Cropley, V., De Rossi, P., Diaz-Caneja, C.M., Dickie, E.W., Ehrlich, S., Fan, F.M., Faskowitz, J., Fatouros-Bergman, H., Flyckt, L., Ford, J.M., Fouche, J.P., Fukunaga, M., Gill, M., Glahn, D.C., Gollub, R., Goudzwaard, E.D., Guo, H., Gur, R.E., Gur, R.C., Gurholt, T.P., Hashimoto, R., Hatton, S.N., Henskens, F.A., Hibar, D.P., Hickie, I.B., Hong, L.E., Horacek, J., Howells, F.M., Hulshoff Pol, H.E., Hyde, C.L., Isaev, D., Jablensky, A., Jansen, P.R., Janssen, J., Jönsson, E.G., Jung, L.A., Kahn, R.S., Kikinis, Z., Liu, K., Klauser, P., Knöchel, C., Kubicki, M., Lagopoulos, J., Langen, C., Lawrie, S., Lenroot, R.K., Lim, K.O., Lopez-Jaramillo, C., Lyall, A., Magnotta, V., Mandl, R.C.W., Mathalon, D.H., McCarley, R.W., McCarthy-Jones, S., McDonald, C., McEwen, S., McIntosh, A., Melicher, T., Mesholam-Gately, R.I., Michie, P.T., Mowry, B., Mueller, B.A., Newell, D.T., O'Donnell, P., Oertel-Knöchel, V., Oestreich, L., Paciga, S.A., Pantelis, C., Pasternak, O., Pearlson, G., Pellicano, G.R., Pereira, A., Pineda Zapata, J., Piras, F., Potkin, S.G., Preda, A., Rasser, P.E., Roalf, D.R., Roiz, R., Roos, A., Rotenberg, D., Satterthwaite, T.D., Savadjiev, P., Schall, U., Scott, R.J., Seal, M.L., Seidman, L.J., Shannon Weickert, C., Whelan, C.D., Shenton, M.E., Kwon, J.S., Spalletta, G., Spaniel, F., Sprooten, E., Stäblein, M., Stein, D.J., Sundram, S., Tan, Y., Tan, S., Tang, S., Temmingh, H.S., Westlye, L.T., Tønnesen, S., Tordesillas-Gutierrez, D., Doan, N.T., Vaidya, J., Van Haren, N.E.M., Vargas, C.D., Vecchio, D., Velakoulis, D., Voineskos, A., Voyvodic, J.Q., Wang, Z., Wan, P., Wei, D., Weickert, T.W., Whalley, H., White, T., Whitford, T.J., Wojcik, J.D., Xiang, H., Xie, Z., Yamamori, H., Yang, F., Yao, N., Zhang, G., Zhao, J., Van Erp, T.G.M., Turner, J., Thompson, P.M., Donohoe, G., 2018. Widespread white matter microstructural differences in schizophrenia across 4322 individuals: results from the ENIGMA Schizophrenia DTI Working Group. Mol. Psychiatr. 23, 1261–1269. https://doi.org/10.1038/mp.2017.170.
Kerchner, G.A., Racine, C.A., Hale, S., Wilheim, R., Laluz, V., Miller, B.L., Kramer, J.H., 2012. Cognitive processing speed in older adults: relationship with white matter integrity. PLoS One 7, e50425. https://doi.org/10.1371/journal.pone.0050425.
Kochunov, P., Coyle, T.R., Rowland, L.M., Jahanshad, N., Thompson, P.M., Kelly, S., Du, X., Sampath, H., Bruce, H., Chiappelli, J., Ryan, M., Fisseha, F., Savransky, A., Adhikari, B., Chen, S., Paciga, S.A., Whelan, C.D., Xie, Z., Hyde, C.L., Chen, X., Schubert, C.R., O'Donnell, P., Hong, L.E., 2017. Association of white matter with core cognitive deficits in patients with schizophrenia. JAMA psychiatry 74, 958–966. https://doi.org/10.1001/jamapsychiatry.2017.2228.
Konrad, A., Vucurevic, G., Musso, F., Stoeter, P., Dahmen, N., Winterer, G., 2009. ErbB4 genotype predicts left frontotemporal structural connectivity in human brain. Neuropsychopharmacology 34, 641–650. https://doi.org/10.1038/npp.2008.112.
Leitinger, B., 2014. Discoidin domain receptor functions in physiological and pathological conditions. In: International Review of Cell and Molecular Biology, pp. 39–87. https://doi.org/10.1016/B978-0-12-800180-6.00002-5.
Martorell, L., Valero, J., Mulet, B., Gutierrez-Zotes, A., Cortes, M.J., Jariod, M., Perez, M., Labad, A., Vilella, E., 2007. M129V variation in the prion protein gene and psychotic disorders: relationship to neuropsychological and psychopathological measures. J. Psychiatr. Res. 41, 885–892. https://doi.org/10.1016/j.jpsychires.2006.07.003.
McIntosh, A.M., Moorhead, T.W.J., Job, D., Lymer, G.K.S., Muñoz Maniega, S., McKirdy, J., Sussmann, J.E.D., Baig, B.J., Bastin, M.E., Porteous, D., Evans, K.L., Johnstone, E.C., Lawrie, S.M., Hall, J., 2008. The effects of a neuregulin 1 variant on white matter density and integrity. Mol. Psychiatr. 13, 1054–1059. https://doi.org/10.1038/sj.mp.4002103.
Mounce, J., Luo, L., Caprihan, A., Liu, J., Perrone-Bizzozero, N.I., Calhoun, V.D., 2014. Association of GRM3 polymorphism with white matter integrity in schizophrenia. Schizophr. Res. 155, 8–14. https://doi.org/10.1016/j.schres.2014.03.003.
Nickl-Jockschat, T., Stöcker, T., Krug, A., Markov, V., Huang, R., Schneider, F., Habel, U., Eickhoff, S.B., Zerres, K., Nöthen, M.M., Treutlein, J., Rietschel, M., Shah, N.J., Kircher, T., 2014. A Neuregulin-1 schizophrenia susceptibility variant causes perihippocampal fiber tract anomalies in healthy young subjects. Brain and Behavior 4, 215–226. https://doi.org/10.1002/brb3.203.
Nickl-Jockschat, T., Stöcker, T., Markov, V., Krug, A., Huang, R., Schneider, F., Habel, U., Zerres, K., Nöthen, M.M., Treutlein, J., Rietschel, M., Shah, N.J., Kircher, T., 2012. The impact of a Dysbindin schizophrenia susceptibility variant on fiber tract integrity in healthy individuals: a TBSS-based diffusion tensor imaging study. Neuroimage 60, 847–853. https://doi.org/10.1016/j.neuroimage.2011.10.012.
Nuechterlein, K.H., Barch, D.M., Gold, J.M., Goldberg, T.E., Green, M.F., Heaton, R.K., 2004. Identification of separable cognitive factors in schizophrenia. Schizophr. Res. 72, 29–39. https://doi.org/10.1016/j.schres.2004.09.007.
Penke, L., Munoz Maniega, S., Murray, C., Gow, A.J., Hernandez, M.C.V., Clayden, J.D., Starr, J.M., Wardlaw, J.M., Bastin, M.E., Deary, I.J., 2010. A general factor of brain white matter integrity predicts information processing speed in healthy older people. J. Neurosci.: the official journal of the Society for Neuroscience 30, 7569–7574. https://doi.org/10.1523/JNEUROSCI.1553-10.2010.
Poletti, S., Mazza, E., Bollettini, I., Falini, A., Smeraldi, E., Cavallaro, R., Benedetti, F., 2016. The COMT Val158Met polymorphism moderates the association between cognitive functions and white matter microstructure in schizophrenia. Psychiatr. Genet. 26, 193–202. https://doi.org/10.1097/YPG.0000000000000130.
Pomarol-Clotet, E., Canales-Rodríguez, E., Salvador, R., Sarró, S., Gomar, J., Vila, F., Ortiz-Gil, J., Iturria-Medina, Y., Capdevila, A., Mckenna, P., 2010. Medial prefrontal cortex pathology in schizophrenia as revealed by convergent findings from multimodal imaging. Mol. Psychiatr. 15, 823–830. https://doi.org/10.1038/mp.2009.146.
Ren, Y., Wang, H., Xiao, L., 2013. Improving myelin/oligodendrocyte-related dysfunction: a new mechanism of antipsychotics in the treatment of schizophrenia? Int. J. Neuropsychopharmacol. 16, 691–700. https://doi.org/10.1017/S1461145712001095.
Ripke, S., O'Dushlaine, C., Chambert, K., Moran, J.L., Kähler, A.K., Akterin, S., Bergen, S.E., Collins, A.L., Crowley, J.J., Fromer, M., 2013. Genome-wide association analysis identifies 13 new risk loci for schizophrenia. Nat. Genet [WWW Document]. https://doi.org/10.1038/ng.2742.
Roalf, D.R., Gur, R.E., Verma, R., Parker, W.A., Quarmley, M., Ruparel, K., Gur, R.C., 2015. White matter microstructure in schizophrenia: associations to neurocognition and clinical symptomatology. Schizophr. Res. 161, 42–49.
Roig, B., Abasolo, N., Moyano, S., Martorell, L., Vilella, E., 2012a. Increased expression of the spliced DDR1c isoform in brain tissues from schizophrenia patients. J. Psychiatr. Res. 46, 825–827.
Roig, B., Franco-Pons, N., Martorell, L., Tomas, J., Vogel, W.F., Vilella, E., 2010a. Expression of the tyrosine kinase discoidin domain receptor 1 (DDR1) in human central nervous system myelin. Brain Res. 1336, 22–29. https://doi.org/10.1016/j.brainres.2010.03.099.
Roig, B., Moyano, S., Martorell, L., Costas, J., Vilella, E., 2012b. The discoidin domain receptor 1 gene has a functional A2RE sequence. J. Neurochem. 120, 408–418.
Roig, B., Virgos, C., Franco, N., Martorell, L., Valero, J., Costas, J., Carracedo, A., Labad, A., Vilella, E., 2007. The discoidin domain receptor 1 as a novel susceptibility gene for schizophrenia. Mol. Psychiatr. 12, 833–841. https://doi.org/10.1038/sj.mp.4001995.
Roussos, P., Haroutunian, V., 2014. Schizophrenia: susceptibility genes and oligodendroglial and myelin related abnormalities. Front. Cell. Neurosci. 8, 5. https://doi.org/10.3389/fncel.2014.00005.
Salami, A., Eriksson, J., Nilsson, L.-G., Nyberg, L., 2012. Age-related white matter microstructural differences partly mediate age-related decline in processing speed but not cognition. Biochim. Biophys. Acta 1822, 408–415. https://doi.org/10.1016/j.bbadis.2011.09.001.
Santiago, C., Herrmann, N., Swardfager, W., Saleem, M., Oh, P.I., Black, S.E., Lanctot, K.L., 2015. White matter microstructural integrity is associated with executive function and processing speed in older adults with coronary artery disease. Am. J. Geriatr. Psychiatry: Off. J. Am. Assoc. Geriatric Psychiatry 23, 754–763. https://doi.org/10.1016/j.jagp.2014.09.008.
Seitz, J., Zuo, J.X., Lyall, A.E., Makris, N., Kikinis, Z., Bouix, S., Pasternak, O., Fredman, E., Duskin, J., Goldstein, J.M., Petryshen, T.L., Mesholam-Gately, R.I., Wojcik, J., McCarley, R.W., Seidman, L.J., Shenton, M.E., Koerte, I.K., Kubicki, M., 2016. Tractography analysis of 5 white matter bundles and their clinical and cognitive correlates in early-course schizophrenia. Schizophr. Bull. 42, 762–771. https://doi.org/10.1093/schbul/sbv171.
Stotesbury, H., Kirkham, F.J., Kolbel, M., Balfour, P., Clayden, J.D., Sahota, S., Sakaria, S., Saunders, D.E., Howard, J., Kesse-Adu, R., Inusa, B., Pelidis, M., Chakravorty, S., Rees, D.C., Awogbade, M., Wilkey, O., Layton, M., Clark, C.A., Kawadler, J.M., 2018. White matter integrity and processing speed in sickle cell anemia. Neurology 90, e2042–e2050. https://doi.org/10.1212/WNL.0000000000005644.
Takahashi, N., Sakurai, T., Davis, K.L., Buxbaum, J.D., 2011. Linking oligodendrocyte and myelin dysfunction to neurocircuitry abnormalities in schizophrenia. Prog. Neurobiol. 93, 13–24. https://doi.org/10.1016/j.pneurobio.2010.09.004.
Tamnes, C.K., Agartz, I., 2016. White matter microstructure in early-onset schizophrenia: a systematic review of diffusion tensor imaging studies. J. Am. Acad. Child Adolesc. Psychiatr. 55, 269–279. https://doi.org/10.1016/j.jaac.2016.01.004.
Ullrich, A., Schlessinger, J., 1990. Signal transduction by receptors with tyrosine kinase activity. Cell 61, 203–212.
Varjacic, A., Mantini, D., Demeyere, N., Gillebert, C.R., 2018. Author ' s Accepted Manuscript Neural signatures of Trail Making Test performance : evidence from lesion-mapping and neuroimaging studies. Neuropsychologia. https://doi.org/10.1016/j.neuropsychologia.2018.03.031.
Vogel, W., 1999. Discoidin domain receptors: structural relations and functional implications. Faseb. J.: Off. Publ. Fed. Am. Soc. Exp. Biol. 13 (Suppl. l), S77–S82.
Voineskos, A.N., 2015. Genetic underpinnings of white matter "connectivity": heritability, risk, and heterogeneity in schizophrenia. Schizophr. Res. 161, 50–60.
Voineskos, A.N., Felsky, D., Kovacevic, N., Tiwari, A.K., Zai, C., Chakravarty, M.M., Lobaugh, N.J., Shenton, M.E., Rajji, T.K., Miranda, D., Pollock, B.G., Mulsant, B.H., McIntosh, A.R., Kennedy, J.L., 2013. Oligodendrocyte genes, white matter tract integrity, and cognition in schizophrenia. Cerebr. Cortex 23, 2044–2057. https://doi.org/10.1093/cercor/bhs188.
Winterer, G., Konrad, A., Vucurevic, G., Musso, F., Stoeter, P., Dahmen, N., 2008.

Association of 5′ end neuregulin-1 ( NRG1 ) gene variation with subcortical medial frontal microstructure in humans. Neuroimage 40, 712–718. https://doi.org/10.1016/j.neuroimage.2007.12.041.

Zeng, B., Ardekani, B.A., Tang, Y., Zhang, T., Zhao, S., Cui, H., Fan, X., Zhuo, K., Li, C., Xu, Y., Goff, D.C., Wang, J., 2016. Abnormal white matter microstructure in drug-naive first episode schizophrenia patients before and after eight weeks of antipsychotic treatment. Schizophr. Res. 172, 1–8. https://doi.org/10.1016/j.schres.2016.01.051.

Zhang, X.Y., Fan, F.-M., Chen, D.-C., Tan, Y.-L., Tan, S.-P., Hu, K., Salas, R., Kosten, T.R., Zunta-Soares, G., Soares, J.C., 2016. Extensive white matter abnormalities and clinical symptoms in drug-naive patients with first-episode schizophrenia: a voxel-based diffusion tensor imaging study. J. Clin. Psychiatr. 77, 205–211.

**MATERIAL SUPLEMENTARI DE L'ARTICLE 2:**

**Supplementary Materials and methods**

**Subjects**

Study 1. Case-control sample

The cases involved in this study (N=1193) included patients diagnosed with schizophrenia according to DSM-IV criteria and recruited from different hospitals across several regions in Spain Spain: 275 from Valencia (East), 435 from Santiago de Compostela (Northwest), 217 from Sabadell and 266 from Sant Boi de Llobregat (Northeast). Healthy controls (N=1839) were recruited from 13 blood donor centers in the same regions as the cases[1]. The sampling inclusion criteria were being of Caucasian origin, unrelated, aged above 18 years, and, for controls, free of psychiatric illness. None of the participants were from the discovery sample[2] region.

Study 2. Neurocognition sample

Using convenience sampling, we recruited participants from the acute hospitalization unit of the Hospital Universitari Institut Pere Mata (Reus, Spain) with the following inclusion criteria: Caucasian men and women aged 18-65 who were diagnosed as having schizophrenia spectrum disorders using a semi-structured interview, the Schedules for Clinical Assessment in Neuropsychiatry (SCAN), according to the DSM-IV criteria. The exclusion criteria were the following: present severe neurocognitive impairment, intellectual disability or disabling psychosis, psychosis due to drug abuse, evidence of organic disease or concomitant trauma and/or medical criteria that would discourage participation. Participants were assessed when the referring psychiatrist considered them clinically stable before clinical discharge. All participants completed a study protocol consisting of symptom and neurocognitive evaluations and blood sampling for genotypic analysis. Symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS), Spanish version[3]. A neuropsychological battery to measure key cognitive domains such as working memory (the Stroop Color-Word Test and the Wisconsin Card Sorting Test [WCST]), attention/vigilance (the Continuous Performance Test CPT), processing speed (the Trail Making Test, Part A [TMT-A]) and executive function (the TMT-B) was used as previously described[4]. Note that direct scores on neuropsychological evaluations were used throughout the article. General intellectual function was estimated using the Vocabulary subtest of the Wechsler Adult Intelligence Scale-Third Edition[5]. Sex, age, years of education, age of onset, duration of illness, handedness, drug abuse and medication (as antipsychotic dose converted into chlorpromazine equivalents)[6] were among the other variables collected for the study. From this sample, we selected 194 unrelated participants to complete the neuropsychological battery and be genotyped for *DDR1* to assess whether *DDR1* genotypic variants are associated with psychotic symptoms and neurocognitive functions in

schizophrenia. In the present study *DDR1* genotypes and TMT-A scores were used to test the working hypothesis.

Study 3. Neuroimaging sample

From Study 2 sample we searched patients to conduct the neuroimaging study to explore whether *DDR1* SNPs are associated to white matter microstructure alterations in SZ patients. Although rs2267641 is associated to SZ(2) and has functional consequences affecting isoform splicing and expression[7], the risk allele is very rare (rs2267641CC genotype f<4%)**.** Instead, we used rs1246323 because it has been linked to SZ also previously[2] and in the present Study 1 sample. Thus, according to rs1264323 genotype, we selected a group of SZ patients from the Study 2 sample a diagnosis of SZ (confirmed again using the SCAN and according to DSM-IV) as inclusion criteria. Exclusion criteria included left-handedness, age outside the range of 18-55 years, history of brain trauma or neurologic disease, and alcohol/substance abuse or dependence within the 12 months immediately before assessment. We end up with a group of 54 SZ patients distributed as follows: 23 subjects with the rs1264323 GG allele, 21 with GA and 10 with AA genotype. The group with the rare homozygous AA genotype was limited to the 10 patients available. All 54 selected patients were enrolled in a quantitative neuroimaging study based on DTI in order to assess whether the relationship between microscopic variations in white matter could underlie the relationship between *DDR1* genotype and neurocognition. Concomitantly, patients underwent a new neuropsychological and symptom evaluation using exactly the same protocol as for Study 2. At this time, all patients were being treated at community mental health centers; none of them were hospitalized. For this group of patients, we have evaluations carried out at two time points separated by an average of 6 years, the first when they were recruited during their hospitalization in an acute psychiatric unit and the second when they were recontacted at the community mental health centers.

All three studies were carried out with approval of the Ethics Committee, and all subjects provided voluntary written informed consent.

**Genotyping**

Rationale of SNPs included in the present study

In our previous report, we found that rs1049623 was the SNP most strongly associated with *DDR1* and schizophrenia[2]. However, rs1049623, located inside an intron, is in total linkage disequilibrium (LD) with rs1264323 ($r^2$=1, according to 1000 Genomes data), located in the promoter region. We decided to genotype rs1264323 instead because of its potential influence on gene regulation. The SNP rs2267641 was also included because of its functional impact on the alternative splicing and expression of *DDR1* isoforms[7].

rs3135388, a proxy of HLA-DRB*1501 that has been consistently associated with multiple sclerosis as an 'inflammatory disease'[8], and rs9268895, an SNP near HLA-DRB9, that has been

associated with schizophrenia[9] , were also genotyped to explore whether association of DDR1 with schizophrenia is due to this highly disease-linked SNPs.

Genotyping

We used two TaqMan SNP genotyping assays to detect genetic variations of the *DDR1* SNPs rs1264323 and rs2267641, rs3135388 (HLA-DRB*1501) and rs9268895 (near HLA-DRB9) respectively (Life Technologies, Madrid, Spain). Detailed information on the sequences of SNPs used is publicly available (http://www.ncbi.nlm.nih.gov/SNP/). Polymorphisms were assessed using an allelic discrimination method on an ABI PRISM 7900HT Fast Real-Time PCR System (Life Technologies, Madrid, Spain). PCR was performed following the standard protocol with a 5 µl final reaction volume in a 384-well plate. As a template, we used 20 ng of genomic DNA. The cycling program conditions were 1 cycle at 50ºC for 2 min, 1 cycle at 95ºC for 10 min, 40 cycles of 95ºC for 15 s and 60ºC for 1 min. The software SDS, version 2.4 (Life Technologies, Madrid, Spain), was used to automatically assign the allele calls. Allele calling failed in less than 0.1% of the samples. DNA samples of known genotypes were included in all plates as internal positive controls; 80% of the case participants were included in a previous study from our research group that involved assessment of population substructure via analysis of a set of 32 highly polymorphic SNPs[10]. We also calculated the allele and genotype frequencies for each *DDR1* SNP and compared the frequencies between samples from different regions to ensure that they were not different from each other. In the present study, a Hardy–Weinberg equilibrium test was used to assess independence between the alleles inherited from the parents (data not shown). Hardy–Weinberg equilibrium and LD were calculated using Haploview v4.1.

**Neuroimaging**

Image acquisition

Each subject underwent a single MRI scanning session using a 1.5-Tesla GE Signa scanner (General Electric Medical Systems) located at the Centre del Diagnòstic per la Imatge – Hospital Universitari Joan XXIII (Tarragona, Spain). DTI data were collected using a dual spin-echo echo-planar pulse sequence along 25 equidistant gradient directions on one sphere in q-space. The sequence parameters were as follows: repetition and echo times of 12000 and 92.9 milliseconds, respectively; b value=1000 s/mm$^2$; field of view=256×256 mm$^2$; number of contiguous axial slices=40; slice thickness=3 mm; in-plane resolution=1.05×1.05 mm$^2$; flip angle=90º. One T2 b0 image with no diffusion weighting (b value=0 s/mm$^2$) was also obtained from each subject. An automatic quality-control workflow was implemented to correct possible acquisition artifacts.

DTI image processing

Following Canales-Rodriguez, et al.[11], we applied the normalized correlation between successive slices to detect slicewise intensity-related abnormalities, with diffusion volumes containing one or more artifacts being excluded [12,13]. Next, eddy current and head motion correction were performed using the FMRIB Software Library (FSL)[14]. Finally, the diffusion gradient vectors were properly reoriented using the resulting affine transformations[15]. Fractional anisotropy (FA) images were obtained from the resulting diffusion tensors[16], which were estimated from the corrected images using the '*dtifit*' tool in FSL. After skull removal, images were normalized with the symmetric normalization (SyN) algorithm, a high-resolution diffeomorphic nonlinear registration method[17]. To assess whether there was a link among *DDR1* genotype, processing speed and white matter microscopic variation, we first localized those white matter regions where FA was correlated with processing speed, after which we checked whether FA in these regions showed differences between different *DDR1* rs1264323 genotypes.

**References**

1. Julià A, Domènech E, Chaparro M, et al. A genome-wide association study identifies a novel locus at 6q22.1 associated with ulcerative colitis. Human molecular genetics. 2014 Dec 20;23(25):6927–34.

2. Roig B, Virgos C, Franco N, et al. The discoidin domain receptor 1 as a novel susceptibility gene for schizophrenia. Molecular psychiatry. 2007 Sep;12(9):833–41.

3. Peralta V, Cuesta MJ. Psychometric properties of the positive and negative syndrome scale (PANSS) in schizophrenia. Psychiatry research. Psychiatric Unit, Virgen del Camino Hospital, Pamplona, Spain.; 1994 Jul;53(1):31–40.

4. Martorell L, Valero J, Mulet B, et al. M129V variation in the prion protein gene and psychotic disorders: relationship to neuropsychological and psychopathological measures. Journal of psychiatric research. Departament de Formacio i Investigacio, Hospital Psiquiatric Universitari Institut Pere Mata, Reus, Spain. lourdes.martorell@urv.cat; 2007 Nov;41(10):885–92.

5. Wechsler D. WAIS-III: Wechsler adult intelligence scale. San Antonio, TX: The Psychological Corporation. 1997.

6. Alan F. Schatzberg MD, Jonathan O. et al. Manual of Clinical Psychopharmacology. Seventh Edition. ISBN 978-1.

7. Roig B, Moyano S, Martorell L, et al. The discoidin domain receptor 1 gene has a

functional A2RE sequence. Journal of neurochemistry. 2012 Feb;120(3):408–18.

8. Cox MB, Ban M, Bowden NA, et al. Potential association of vitamin D receptor polymorphism Taq1 with multiple sclerosis. Multiple sclerosis (Houndmills, Basingstoke, England). 2012 Jan;18(1):16–22.

9. Ripke S, O'Dushlaine C, Chambert K, et al. Genome-wide association analysis identifies 13 new risk loci for schizophrenia. Nature genetics. Nature Publishing Group; 2013 Oct;45(10):1150–9.

10. Vilella E, Costas J, Sanjuan J, et al. Association of schizophrenia with DTNBP1 but not with DAO, DAOA, NRG1 and RGS4 nor their genetic interaction. Journal of psychiatric research. 2008 Mar;42(4):278–88.

11. Canales-Rodriguez EJ, Pomarol-Clotet E, Radua J, et al. Structural abnormalities in bipolar euthymia: A multicontrast molecular diffusion imaging study. Biological Psychiatry. 2014 Aug;76(3):239–48.

12. Cohen-Adad J, Descoteaux M, Wald LL. Quality assessment of high angular resolution diffusion imaging data using bootstrap on Q-ball reconstruction. Journal of magnetic resonance imaging : JMRI. 2011 May;33(5):1194–208.

13. Liu Z, Wang Y, Gerig G, et al. Quality control of diffusion weighted images. In: Liu BJ, Boonn WW, editors. Proceedings of SPIE--the International Society for Optical Engineering. 2010. p. 76280J.

14. Smith SM, Jenkinson M, Woolrich MW, et al. Advances in functional and structural MR image analysis and implementation as FSL. NeuroImage. 2004 Jan;23 Suppl 1:S208-19.

15. Leemans A, Jones DK. The B-matrix must be rotated when correcting for subject motion in DTI data. Magnetic resonance in medicine. 2009 Jun;61(6):1336–49.

16. Basser PJ, Pierpaoli C. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. 1996. Journal of magnetic resonance (San Diego, Calif : 1997). 2011 Dec;213(2):560–70.

17. Avants BB, Epstein CL, Grossman M, Gee JC. Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain. Medical image analysis. 2008Feb;12(1):26–41.

# Association of DDR1 variants with processing speed in subjects at the early phase of psychosis compared to healthy controls

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ARTICLE INFO

*Keywords:*
*DDR1*
early-phase psychosis
processing speed
cognition

ABSTRACT

Recent evidence supports that *DDR1* participates in myelination and that variants are associated with decreased cognitive processing speed (PS) in schizophrenia (SZ). Here, we explore whether *DDR1* single nucleotide polymorphism (SNP) variants are associated with PS in subjects at the early phase of psychosis (EPP), a diagnosis often preceding SZ. Two EPP-independent samples (n=75 and n=312, respectively) were compared to respective healthy controls (HCs; n=57 and n=160, respectively) using Trail Making Test part A to evaluate PS; *DDR1* SNPs rs1264323 and rs2267641 were genotyped. SZ-risk rs1264323AA-rs2267641AC/CC combined genotypes were associated with increased PS in EPP patients but not in HCs, suggesting that *DDR1* SNP variants have a direct association with PS in the early phases but an indirect association as the disease progresses.

## 1. Introduction

Schizophrenia (SZ) is a highly heritable psychiatric disorder with positive and negative symptoms as well as cognitive deficits. Decreased processing speed (PS) is one of the most replicatable cognitive deficits in people with SZ (Sheffield et al., 2018). Moreover, premorbid cognitive deficits, including PS, have been described as a risk factor for the development of a psychotic disorder (Bolt et al., 2019).

Successful genome-wide approaches have demonstrated that a considerable proportion of the heritability of SZ is attributable to the aggregate effect of common genetic variants, mainly single-nucleotide polymorphisms (SNPs). The chromosome region with the highest genome-wide association is the 6p21.33 major histocompatibility complex (MHC) region, and complement component 4 (C4) *A* and *B* genes have been identified as relevant in this region. Nevertheless, the presence of other relevant genes in this region cannot be excluded. The discoidin domain receptor 1 (*DDR1*) gene is also located at 6p21.33, and *DDR1* SNP variants have been found to be associated with SZ (Benkovits et al., 2016; Gas et al., 2019; Roig et al., 2007). *DDR1* is expressed in oligodendrocytes and plays a role in myelination (Vilella et al., 2019). We previously reported that *DDR1* rs1264323, an SNP associated with SZ in case-control designs, is associated with fractional anisotropy (FA) of some white matter areas correlating with PS in SZ patients. Specifically, the major allele (rs1264323G) was found to be associated with higher FA values, which in turn were associated with increased PS. Conversely, carriers of the minor rs1264323A allele showed lower FA, and lower FA was associated with decreased PS. In the same sample, SZ patients who were carriers of the homozygous genotype CC of the functional SNP rs2267641 (Roig et al., 2012) exhibited a significantly decreased PS (Gas et al., 2019). Notably, the rs1264323A allele was detected to be in linkage disequilibrium with the rs2267641C allele. Nonetheless, no study of *DDR1* gene variants and PS has been conducted in psychotic patients at the early phase, a time when early interventions are critical to preventing disease progression (Fusar-Poli et al., 2017).

In the present study, we aimed to determine whether *DDR1* SNP variants are associated with PS in subjects with early-phase psychosis (EPP) compared to healthy controls (HCs). Our main hypothesis was that *DDR1* rs1264323 and rs2267641 SZ-risk genotypes are associated with decreased PS in subjects with EPP compared to HCs, as previously described for SZ.

## 2. Material and methods

### *2.1 Subjects*

*Reus sample*

We included 75 EPP outpatients attending Early Psychosis Program (HPU Institut Pere Mata, Reus, Spain). The patients were diagnosed according to DSM-IV criteria. The exclusion criteria were a history of brain injury or illness, intellectual disability, non-Caucasian, DSM-IV diagnosis of drug dependence (except nicotine dependence) and a scalar score of less than 6 in the WAIS-III Vocabulary subtest (Lezak, 1997). We included an HC group of 57 subjects who were nongenetic relatives or friends of the patients and screened to rule out past or current history of psychiatric disorder. This sample (patients and HCs) was selected from a dataset used in previous studies (Montalvo et al., 2014).

*Santander sample*

We included 312 EPP patients who attended Epidemiological and Longitudinal Intervention Programme of First Episode Psychosis at the University Hospital Marqués de Valdecilla (Santander, Spain) (Crespo-Facorro et al., 2006). The patients were diagnosed according to DSM-IV criteria, and the exclusion criteria were the same as above plus the presence of an affective psychosis diagnosis (Pelayo-Terán et al., 2008). In addition, 160 HC individuals screened to exclude a personal or family history of mental disease were recruited from the same geographical area (Suárez-Pinilla et al., 2015).

### *2.2 Ethical aspects*

All procedures were in accordance with international standards for research ethics and were approved by the local institutional Ethics Committee for clinical research in each case.

*2.3 Genotyping*

For the Reus sample, DNA was isolated from peripheral blood white cells, and TaqMan technology was used for SNP genotyping, as previously described (Stojanovic et al., 2014). For the Santander sample, DNA was extracted from whole peripheral blood cells and genotyped with Genome-wide Human SNP Array 6.0 at Affymetrix Services Laboratory. Standard quality control procedures, phasing and imputation and adjustments for population structure were as previously described (Bramon et al., 2014). Based on our previous publications, we examined *DDR1* rs1264323 and rs2267641 (Gas et al., 2019; Roig et al., 2007; Vilella et al., 2019). In sample 2, we used rs3213644 as a proxy for rs2267641 ($r^2$=1 (Machiela & Chanock, 2015)), but we use 'rs2267641' for clarity herein. Moreover, because we showed that the genetic association between *DDR1* and SZ is mostly represented by interaction between rs1264323 and rs2267641 (Gas et al., 2019), herein, the genotype combinations formed by rs1264323AA-rs2267641AC and rs1264323AA-rs2267641CC (AA-AC/CC) genotypes are termed risk genotypes, and the remaining are referred to as nonrisk genotypes. Notably, the genotype combinations rs1264323GG-rs2267641AC, rs1264323GG-rs2267641CC and rs1264323GA-rs2267641CC were not represented in either the two samples studied or in 1000 Genomes Project (IBS) samples (Supplementary Table S1). Hardy-Weinberg equilibrium was calculated for every SNP using the Michael H. Court calculator (Court M. H., 2012), and the distribution of genotype frequencies for both SNPs (rs1264323 and rs2267641) was consistent with Hardy-Weinberg equilibrium in the patients and controls and in both samples (data not shown).

*2.4 Clinical and psychological assessments*

In the two samples, general intellectual function was evaluated using the Vocabulary subtest of Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) (Wechsler, 1997). PS was assessed using Trail Making Test part A (TMT-A) (Nuechterlein et al., 2004), and the scores (measured as seconds used to perform the task) were used directly. Higher values of TMT-A indicate more time spent in the task and hence a lower PS.

Psychotic symptoms were assessed with Positive and Negative Syndrome Scale (PANSS), Spanish version (Peralta & Cuesta, 1994) in the Reus sample and Brief Psychiatric Rating Scale (Overall & Gorham, 1962), the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983) and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) in the Santander sample.

Pharmacological antipsychotic treatment information was collected and converted to chlorpromazine dose equivalents according to Gardner et al. (Gardner et al., 2010).

*2.5 Statistical analyses*

In both samples, categorical variables are reported as frequencies and percentages and continuous variables as the mean ± SD. We explored the normality of the distribution of continuous variables using the Kolmogorov-Smirnov test. TMT-A followed a normal distribution in the Reus sample; however, TMT-A did not meet normality criteria in the Santander sample, even after log-transformation. Nonparametric correlation coefficients were calculated to assess associations between PS and psychotic symptoms and other variables (age, years of education and antipsychotic dose as chlorpromazine equivalent). The association of PS with sex was evaluated with the Mann-Whitney U test. Univariate and bivariate analysis results are shown in Supplementary Table S2. To compare PS among *DDR1* genotype groups, we used a general linear model (univariate analysis of variance) with variables associated with PS in the previous univariate and bivariate analyses as covariates. *DDR1* genotypes were grouped into two haplotypes (see Material and methods) to analyze the relationship between *DDR1* variants and PS. We used the same covariates in the two samples for consistency, though fewer correlating variables were found in the Reus sample. In addition, a bootstrap method that resamples by replacing a computed value obtained from the observed data a large number of times (10.000 iterations) (Dwivedi et al., 2017) was employed because of the small sample size of carriers of risk genotypes. These analyses were conducted using SPSS Statistics Package v22.0 (IBM Corp., New York, NY, USA), and $p<0.05$ indicated statistical significance.

## 3. Results

Descriptive statistics for the participants are shown in Table 1. In both samples, men were more represented than women, but with a similar proportion in both the patient and control groups and without statistical significance. Age was similar in the patients and HCs in both samples. Although the HCs showed a higher education level than the patients in both samples, it was only statistically significant in the Santander sample. The risk combined genotype group (AA-AC/CC) was detected at higher frequencies in patients compared to HC in both samples, but without reaching statistical significance. In both samples, patients had higher TMT-A scores (decreased PS) than HCs (Table 1). Table 2 shows the results of the general linear model used to test variables associated with PS. In both samples, patients with EPP and carrying combined risk genotypes (AA-AC/CC) had lower TMT-A scores (faster PS) than nonrisk genotype carriers, yet the differences were only statistically significant in the Santander sample. This difference was not observed in the HC group in either sample. Interestingly, PS did not differ between EPP patients and HCs carrying the risk genotype combination in either sample. HCs in the risk combined genotype group exhibited a trend toward higher TMT-A scores (decreased PS) than in the nonrisk combined genotype group (Table 2).

## 4. Discussion

In this study, we applied two EPP samples to show that *DDR1* rs1264323 and rs2267641 combined genotypes are associated with PS. The rs1264323AA-rs2267641AC/CC (AA-AC/CC) combined genotypes were associated with decreased TMT-A scores (increased PS) only in EPP patients, and the difference was only statistically significant in the larger Santander sample. We previously found that carriers of rs1264323AA-rs2267641AC/CC were at risk of developing SZ and that carriers of the rs2267641CC genotype had slower PS than other genotype groups (Gas et al., 2019). There may be different explanations for these apparently contradictory results between our two studies, i.e., the association of the *DDR1* SNPs with faster PS in EPP samples and slower PS in SZ samples. For example, the patients in the present study met the inclusion criteria of EPP which implicates that illness duration is < 5 years (Newton et al., 2018). Conversely, patients in the study of Gas and colleagues had a diagnosis of SZ with a mean illness duration of >10 years. In general, PS decreases with age (Cohen et al., 2019) but also with illness progression (Fett et al., 2020; Menkes et al., 2019). Moreover, the findings published earlier (Gas et al., 2019) about the interaction of the *DDR1* rs1264323 variant with a worsening PS over time in SZ patients were based on two neuropsychological evaluations with a mean of 6 years apart and agree with the differences observed between EPP and SZ patients. Indeed, *DDR1* SNP variants may have a positive association with PS in the early illness phases but a negative association as the disease progresses. Several differential disease features between EEP and SZ may also explain these results: (1) the highest prevalence of negative symptoms in SZ (Correll & Schooler, 2020) is negatively associated with PS (Harvey et al., 2006; Rodríguez-Sánchez et al., 2008); (2) EPP includes patients who do not develop SZ and that probably have high cognitive functioning scores (Ayesa-Arriola et al., 2016; Vaskinn et al., 2020); (3) cannabis use in EPP is more frequent and may influence PS (Bogaty et al., 2018); and (4) there are treatment differences, and SZ patients probably take more anxiolytics and antidepressants. The fact that the *DDR1*-PS association was not observed in the HC sample in the present study suggests that it may be more strongly related to disease molecular mechanisms than to age-related mechanisms. In this sense, rs2267641 has been associated with *DDR1* mRNA splicing, intracellular trafficking and expression (Roig et al., 2012). In addition, *DDR1* rs1264323 is classified as an eQTL in nervous tissue (GTEX portal), and *DDR1* is mainly expressed in oligodendrocytes in the central nervous system (CNS) (Franco-Pons et al., 2006; Roig et al., 2010; Vilella et al., 2019). Therefore, it is

plausible that the relative amount of DDR1 and its isoform pattern of expression play a role in myelination, as the principal function of myelin is to increase axon signal transmission, which directly correlates with PS (Tirapu-Ustárroz et al., 2011). In agreement with this hypothesis, a recent article showed that among 90 relevant proteins in the CNS, levels of plasma DDR1 correlated negatively with cognitive ability in three Scottish healthy cohorts of elderly individuals (mean age 76 years) (Harris et al., 2020), and this correlation was not observed in a younger cohort (mean age 58 years). Unfortunately, genotype data were not included in Harris et al.'s article; therefore, the possible effect of *DDR1* SNPs was not assessed. Notably, nilotinib, a potent DDR inhibitor, has been proposed to prevent neurodegeneration (Fowler et al., 2019; Pagan et al., 2019), and in a recent study, the drug was able to restore memory function in a mouse model of Alzheimer's disease (La Barbera et al., 2021).

Some limitations of this study need to be mentioned. First, the two samples are representative of EPP patients of a slightly different age (18-37 years in the Reus sample versus 15-59 years in the Santander sample), even though age was used as a covariate in all analyses. Additionally, affective and nonaffective psychoses were included in the Reus sample, whereas only the latter was considered in the Santander sample. We conducted the same analysis in the Reus sample but excluded patients with affective diagnosis and obtained similar results (data not shown). Second, the sample size is an important limitation regarding the low frequency of minor alleles for both SNPs.

In summary, we report statistically significant associations between combined genotypes of two *DDR1* variants (rs1264323 and rs2267641) and PS in subjects in the early stages of psychosis but not in controls.

Future studies with larger samples are needed to obtain more robust results, and longitudinal studies should be carried out to identify whether *DDR1* SNP variants can predict accelerated cognitive decline in patients with psychosis. Positive results from such studies will help to better understand cognitive deficits in psychosis and to design more specific cognitive therapies to prevent age- and disease-related cognitive decline.

**Table 1. Sociodemographic, clinical and neuropsychological data of the study participants.**

| | Reus sample | | | Santander sample | | |
|---|---|---|---|---|---|---|
| | **Patients** | **Controls** | | **Patients** | **Controls** | |
| | **N=75** | **N=57** | **P** | **N=312** | **N=160** | **P** |
| **Sex** (% male/female) | 65/35 | 60/40 | 0.503[a] | 56/44 | 62/38 | 0.254[a] |
| **Age** (mean ± SD) | 24.8 ± 5.4 | 23.7 ± 4.8 | 0.284[b] | 29.7 ± 9.7 | 29.3 ± 7.8 | 0.580[b] |
| **Years of education** (mean ± SD) | 11.3 ± 2.7 | 13.3 ± 2.8 | <0.001[b] | 10.7 ± 3.4 | 11.1 ± 2.7 | 0.125[b] |
| **TMT-A direct scores**[c] (mean ± SD) | 32.6 ± 9.6 | 24.4 ± 6.4 | <0.001[b] | 43.6 ± 15.8 | 34.5 ± 10.4 | <0.001[b] |
| **Antipsychotic dose** (CPZ equivalents in mg/day) | 371.0 ± 288.7 | - | | 240.0 ± 143.7 | - | |
| ***DDR1* combined genotypes**[d] (%) | | | | | | |
| Risk (AA-AC/CC) | 6.7 | 5.3 | 0.738[a] | 8.0 | 6.9 | 0.748[a] |
| Nonrisk (all other) | 93.3 | 94.7 | | 92.0 | 93.1 | |
| **Psychotic disorder diagnosis** (%) | | | | | | |
| Psychotic disorder not otherwise specified | 54.7 | - | | 6.7 | - | |
| Schizophrenia | 10.7 | - | | 44.9 | - | |
| Schizophreniform disorder | 9.3 | - | | 31.7 | - | |
| Schizoaffective disorder | 12.0 | - | | 2.6 | - | |
| Brief psychotic disorder | 0 | - | | 13.8 | - | |
| Bipolar disorder | 8.0 | - | | na | - | |
| Depressive disorder with psychotic symptoms | 4.0 | - | | na | - | |
| Manic episode with psychotic symptoms | 1.3 | - | | na | - | |
| **Psychotic symptoms**[e] | | | | | | |
| Positive | 10.2 ± 3.6 | - | | 13.4 ± 4.4 | - | |
| Negative | 13.7 ± 5.2 | - | | 6.2 ± 5.8 | - | |
| General | 25.2 ± 6.7 | - | | 60.9 ± 14.1 | - | |

[a]Pearson Chi-Square test.
[b]Mann-Whitney U test.
[c]Trail Making Test A, direct scores expressed as time (sec).
[d]rs3213644 SNP used as a proxy of rs2267641 in Santander sample, as described in Materials and Methods.
[e]Measured with PANSS in Reus sample and with SAPS, SANS and BPRS in Santander sample.

**Table 2. Lineal general model analysis to compare mean TMT-A scores between carriers and noncarriers of the risk combined genotype of *DDR1* in patients and controls in the two samples.**

| | Reus sample | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Patients** | | **Controls** | | **Intragroup P[c]** | | **Intergroup P[c]** | |
| | **Risk N=5** | **Nonrisk N=70** | **Risk N=3** | **Nonrisk N=54** | **Patients Risk vs Nonrisk[a]** | **Controls Risk vs Nonrisk[b]** | **Risk Patients vs controls[b]** | **Nonrisk Patients vs controls[b]** |
| **TMT-A** | 29.4 ± 9.7 | 32.8 ± 9.6 | 24.7 ± 12.0 | 24.3 ± 6.1 | 0.736 | 0.766 | 0.382 | 0.001 |
| | **Santander sample** | | | | | | | |
| | **Patients[a]** | | **Controls[b]** | | **Intragroup P[c]** | | **Intergroup P[c]** | |
| | **Risk N=24** | **Nonrisk N=288** | **Risk N=11** | **Nonrisk N=149** | **Patients Risk vs Nonrisk** | **Controls Risk vs Nonrisk** | **Risk Patients vs controls** | **Nonrisk Patients vs controls** |
| **TMT-A** | 37.1 ± 10.8 | 44.1 ± 16.0 | 39.6 ± 13.2 | 34.2 ± 10.1 | 0.031 | 0.442 | 0.864 | 0.001 |

[a] Covariates included in the analysis (based on the bivariate analysis shown in supplementary material Table 2) were age at testing, sex, years of education and antipsychotic dose.
[b] Covariates included in the analysis (based on the bivariate analysis shown in supplementary material Table 2) were age at testing, sex and years of education.
[C] P value calculated using bootstrapping.

**Author contributions**

EV, JL and BC-F designed and directed the projects. EV and CG conceived and planned the study. RA, JV-B, JL and VS-G were involved in the patient assessment. CG, LM and CG performed the statistical analyses. A.B. B. CG and EV took the lead in writing the manuscript. All authors discussed the results and commented on the manuscript.

**Declaration of competing interest**

The authors declare no conflicts of interest.

**Acknowledgments**

The study was supported by grants from the Spanish Instituto de Salud Carlos III (ISCIII) cofounded by FEDER (PI12-02111 to E. Vilella, PI10-01607 to J Labad, PI14/00639 and PI14/00918 to B Crespo-Facorro), the Fundació ´La Marató de TV3' (092230/092231 to J Labad) and the Cerca Programme/Generalitat de Catalunya. Dr. Ayesa-Arriola is funded by a Miguel Servet contract from the ISCIII (CP18/00003), and Dr. Vázquez-Bourgon is funded by a Research Intensification contract (INT/A20/04) from Fundación Instituto de Investigación Marqués de Valdecilla.

**Appendix A. Supplementary data**

**Supplementary Table S1:** Genotype combinations of *DDR1* variants (rs1264323 and rs2267641) in 1000 Genomes (IBS) samples and the two samples in our study.

**Supplementary Table S2:** Bivariate analysis between TMT-A scores and sociodemographic and clinical variables.

**References**

Andreasen, N. C. (1983). *Scale for the Assessment of Negative Symptoms (SANS)*. Iowa City, Ia: University of Iowa.
Andreasen, N. C. (1984). *Scale for the Assessment of Positive Symptoms (SAPS)*. Iowa City, Ia: University of Iowa.
Ayesa-Arriola, R., Rodríguez-Sánchez, J. M., Suero, E. S., Reeves, L. E., Tabarés-Seisdedos, R., & Crespo-Facorro, B. (2016). Diagnosis and neurocognitive profiles in first-episode non-affective psychosis patients. *European Archives of Psychiatry and Clinical Neuroscience*, *266*(7), 619–628. https://doi.org/10.1007/s00406-015-0667-0
Benkovits, J., Magyarósi, S., Pulay, A., Makkos, Z., Égerházi, A., Balogh, N., Álmos, P., Likó, I., Konzorcium, M. S., Németh, G., Molnár, M. J., Nagy, L., & Réthelyi, J. (2016). Investigation of CNTF, COMT, DDR1, DISC1, DRD2, DRD3, and DTNBP1 candidate genes in schizophrenia: Results from the Hungarian SCHIZOBANK consortium. *Neuropsychopharmacologia Hungarica*, *18*(4), 181–187. https://pubmed.ncbi.nlm.nih.gov/28259861/
Bogaty, S. E. R., Lee, R. S. C., Hickie, I. B., & Hermens, D. F. (2018). Meta-analysis of neurocognition in young psychosis patients with current cannabis use. In *Journal of Psychiatric Research* (Vol. 99, pp. 22–32). Elsevier Ltd. https://doi.org/10.1016/j.jpsychires.2018.01.010
Bolt, L. K., Amminger, G. P., Farhall, J., McGorry, P. D., Nelson, B., Markulev, C., Yuen, H. P., Schäfer, M. R., Mossaheb, N., Schlögelhofer, M., Smesny, S., Hickie, I. B., Berger, G. E., Chen, E. Y. H., de Haan, L., Nieman, D. H., Nordentoft, M., Riecher-Rössler, A., Verma, S., … Allott, K. A. (2019). Neurocognition as a predictor of transition to psychotic disorder and functional outcomes in ultra-high risk participants: Findings from the NEURAPRO randomized clinical trial. *Schizophrenia Research*, *206*, 67–74. https://doi.org/10.1016/j.schres.2018.12.013
Bramon, E., Pirinen, M., Strange, A., Lin, K., Freeman, C., Bellenguez, C., Su, Z., Band, G., Pearson, R., Jankowski, J.,

Langford, C., Deloukas, P., Hunt, S., Gray, E., Dronov, S., Potter, S. C., Tashakkori-Ghanbaria, A., Viswanathan, A. C., Bumpstead, S. J., … Spencer, C. C. A. (2014). A genome-wide association analysis of a broad psychosis phenotype identifies three loci for further investigation. *Biological Psychiatry*, *75*(5), 386–397. https://doi.org/10.1016/j.biopsych.2013.03.033

Cohen, R. A., Marsiske, M. M., & Smith, G. E. (2019). Neuropsychology of aging. In *Handbook of Clinical Neurology* (Vol. 167, pp. 149–180). Elsevier B.V. https://doi.org/10.1016/B978-0-12-804766-8.00010-8

Correll, C. U., & Schooler, N. R. (2020). Negative symptoms in schizophrenia: A review and clinical guide for recognition, assessment, and treatment. In *Neuropsychiatric Disease and Treatment* (Vol. 16, pp. 519–534). Dove Medical Press Ltd. https://doi.org/10.2147/NDT.S225643

Court M. H. (2012). *Court's (2005-2008) online calculator. Tuft University Web site*.

Crespo-Facorro, B., Pérez-Iglesias, R., Ramirez-Bonilla, M. L., Martínez-García, O., Llorca, J., & Vázquez-Barquero, J. L. (2006). A practical clinical trial comparing haloperidol, risperidone, and olanzapine for the acute treatment of first-episode nonaffective psychosis. *Journal of Clinical Psychiatry*, *67*(10), 1511–1521. https://doi.org/10.4088/JCP.v67n1004

Dwivedi, A. K., Mallawaarachchi, I., & Alvarado, L. A. (2017). Analysis of small sample size studies using nonparametric bootstrap test with pooled resampling method. *Statistics in Medicine*. https://doi.org/10.1002/sim.7263

Fett, A. K. J., Velthorst, E., Reichenberg, A., Ruggero, C. J., Callahan, J. L., Fochtmann, L. J., Carlson, G. A., Perlman, G., Bromet, E. J., & Kotov, R. (2020). Long-term Changes in Cognitive Functioning in Individuals with Psychotic Disorders: Findings from the Suffolk County Mental Health Project. *JAMA Psychiatry*, *77*(4), 387–396. https://doi.org/10.1001/jamapsychiatry.2019.3993

Fowler, A. J., Hebron, M., Missner, A. A., Wang, R., Gao, X., Kurd-Misto, B. T., Liu, X., & Moussa, C. E. H. (2019). Multikinase Abl/DDR/Src Inhibition Produces Optimal Effects for Tyrosine Kinase Inhibition in Neurodegeneration. *Drugs in R and D*, *19*(2), 149–166. https://doi.org/10.1007/s40268-019-0266-z

Franco-Pons, N., Virgos, C., Vogel, W. F., Ureña, J. M., Soriano, E., del Rio, J. A., & Vilella, E. (2006). Expression of discoidin domain receptor 1 during mouse brain development follows the progress of myelination. *Neuroscience*, *140*(2), 463–475. https://doi.org/10.1016/j.neuroscience.2006.02.033

Fusar-Poli, P., McGorry, P. D., & Kane, J. M. (2017). Improving outcomes of first-episode psychosis: an overview. *World Psychiatry*, *16*(3), 251–265. https://doi.org/10.1002/wps.20446

Gardner, D. M., Murphy, A. L., O'Donnell, H., Centorrino, F., & Baldessarini, R. J. (2010). International consensus study of antipsychotic dosing. *American Journal of Psychiatry*, *167*(6), 686–693. https://doi.org/10.1176/appi.ajp.2009.09060802

Gas, C., Canales-Rodríguez, E. J., Radua, J., Abasolo, N., Cortés, M. J., Salvadó, E., Muntané, G., Alemán-Gómez, Y., Julià, T., Marsal, S., Sanjuan, J., Guitart, M., Costas, J., Martorell, L., Pomarol-Clotet, E., & Vilella, E. (2019). Discoidin domain receptor 1 gene variants are associated with decreased white matter fractional anisotropy and decreased processing speed in schizophrenia. *Journal of Psychiatric Research*, *110*(December 2018), 74–82. https://doi.org/10.1016/j.jpsychires.2018.12.021

Harris, S. E., Cox, S. R., Bell, S., Marioni, R. E., Prins, B. P., Pattie, A., Corley, J., Muñoz Maniega, S., Valdés Hernández, M., Morris, Z., John, S., Bronson, P. G., Tucker-Drob, E. M., Starr, J. M., Bastin, M. E., Wardlaw, J. M., Butterworth, A. S., & Deary, I. J. (2020). Neurology-related protein biomarkers are associated with cognitive ability and brain volume in older age. *Nature Communications*, *11*(1), 1–12. https://doi.org/10.1038/s41467-019-14161-7

Harvey, P. D., Koren, D., Reichenberg, A., & Bowie, C. R. (2006). Negative symptoms and cognitive deficits: What is the nature of their relationship? *Schizophrenia Bulletin*, *32*(2), 250–258. https://doi.org/10.1093/schbul/sbj011

La Barbera, L., Vedele, F., Nobili, A., Krashia, P., Spoleti, E., Latagliata, E. C., Cutuli, D., Cauzzi, E., Marino, R., Viscomi, M. T., Petrosini, L., Puglisi-Allegra, S., Melone, M., Keller, F., Mercuri, N. B., Conti, F., & D'Amelio, M. (2021). Nilotinib restores memory function by preventing dopaminergic neuron degeneration in a mouse model of Alzheimer's Disease. *Progress in Neurobiology*, 102031. https://doi.org/10.1016/j.pneurobio.2021.102031

Lezak, M. (1997). Neuropsychological assessment. In *NY: OUP*.

Machiela, M. J., & Chanock, S. J. (2015). LDlink: A web-based application for exploring population-specific haplotype structure and linking correlated alleles of possible functional variants. *Bioinformatics*, *31*(21), 3555–3557. https://doi.org/10.1093/bioinformatics/btv402

Menkes, M. W., Armstrong, K., Blackford, J. U., Heckers, S., & Woodward, N. D. (2019). Neuropsychological functioning in early and chronic stages of schizophrenia and psychotic bipolar disorder. *Schizophrenia Research*, *206*, 413–419. https://doi.org/10.1016/j.schres.2018.10.009

Montalvo, I., Gutiérrez-Zotes, A., Creus, M., Monseny, R., Ortega, L., Franch, J., Lawrie, S. M., Reynolds, R. M., Vilella, E., & Labad, J. (2014). Increased prolactin levels are associated with impaired processing speed in subjects with early psychosis. *PLoS ONE*, *9*(2). https://doi.org/10.1371/journal.pone.0089428

Newton, R., Rouleau, A., Nylander, A.-G., Loze, J.-Y., Resemann, H. K., Steeves, S., & Crespo-Facorro, B. (2018). Diverse definitions of the early course of schizophrenia-a targeted literature review. *NPJ Schizophrenia*, *4*(1), 21. https://doi.org/10.1038/s41537-018-0063-7

Nuechterlein, K. H., Barch, D. M., Gold, J. M., Goldberg, T. E., Green, M. F., & Heaton, R. K. (2004). Identification of separable cognitive factors in schizophrenia. *Schizophrenia Research*, *72*(1), 29–39. https://doi.org/10.1016/j.schres.2004.09.007

Overall, J. E., & Gorham, D. R. (1962). The Brief Psychiatric Rating Scale. *Psychological Reports*, *10*(3), 799–812. https://doi.org/10.2466/pr0.1962.10.3.799

Pagan, F. L., Hebron, M. L., Wilmarth, B., Torres-Yaghi, Y., Lawler, A., Mundel, E. E., Yusuf, N., Starr, N. J., Arellano, J., Howard, H. H., Peyton, M., Matar, S., Liu, X., Fowler, A. J., Schwartz, S. L., Ahn, J., & Moussa, C. (2019). Pharmacokinetics and pharmacodynamics of a single dose Nilotinib in individuals with Parkinson's disease. *Pharmacology Research and Perspectives*, *7*(2). https://doi.org/10.1002/prp2.470

Pelayo-Terán, J. M., Pérez-Iglesias, R., Ramírez-Bonilla, M. L., González-Blanch, C., Martínez-García, O., Pardo-García, G., Rodríguez-Sánchez, J. M., Roiz-Santiáñez, R., Tordesillas-Gutiérrez, D., Mata, I., Vázquez-Barquero, J. L., & Crespo-Facorro, B. (2008). Epidemiological factors associated with treated incidence of first-episode non-affective psychosis in Cantabria: Insights from the Clinical Programme on Early Phases of Psychosis. *Early Intervention in Psychiatry*, *2*(3), 178–187. https://doi.org/10.1111/j.1751-7893.2008.00074.x

Peralta, V., & Cuesta, M. J. (1994). Psychometric properties of the positive and negative syndrome scale (PANSS) in schizophrenia. *Psychiatry Research*, *53*(1), 31–40.

Rodríguez-Sánchez, J. M., Crespo-Facorro, B., González-Blanch, C., Pérez-Iglesias, R., Álvarez-Jiménez, M., Martínez, O., & VáZquez-Barquero, J. L. (2008). Cognitive functioning and negative symptoms in first episode schizophrenia: Different patterns of correlates. *Neurotoxicity Research*, *14*(2–3), 227–235. https://doi.org/10.1007/BF03033812

Roig, B., Franco-Pons, N., Martorell, L., Tomas, J., Vogel, W. F., & Vilella, E. (2010). Expression of the tyrosine kinase discoidin domain receptor 1 (DDR1) in human central nervous system myelin. *Brain Research*, *1336*, 22–29. https://doi.org/10.1016/j.brainres.2010.03.099

Roig, B., Moyano, S., Martorell, L., Costas, J., & Vilella, E. (2012). The discoidin domain receptor 1 gene has a functional A2RE sequence. *Journal of Neurochemistry*, *120*(3), 408–418. http://www.ncbi.nlm.nih.gov/pubmed/22077590

Roig, B., Virgos, C., Franco, N., Martorell, L., Valero, J., Costas, J., Carracedo, A., Labad, A., & Vilella, E. (2007). The discoidin domain receptor 1 as a novel susceptibility gene for schizophrenia. *Molecular Psychiatry*, *12*(9), 833–841. https://doi.org/10.1038/sj.mp.4001995

Sheffield, J. M., Karcher, N. R., & Barch, D. M. (2018). Cognitive Deficits in Psychotic Disorders: A Lifespan Perspective. In *Neuropsychology Review* (Vol. 28, Issue 4, pp. 509–533). Springer New York LLC. https://doi.org/10.1007/s11065-018-9388-2

Stojanovic, A., Martorell, L., Montalvo, I., Ortega, L., Monseny, R., Vilella, E., & Labad, J. (2014). Increased serum interleukin-6 levels in early stages of psychosis: Associations with at-risk mental states and the severity of psychotic symptoms. *Psychoneuroendocrinology*, *41*, 23–32. https://doi.org/10.1016/j.psyneuen.2013.12.005

Suárez-Pinilla, P., Roíz-Santiañez, R., Mata, I., Ortiz-García De La Foz, V., Brambilla, P., Fañanas, L., Valle-San Román, N., & Crespo-Facorro, B. (2015). Progressive structural brain changes and nrg1 gene variants in first-episode nonaffective psychosis. *Neuropsychobiology*, *71*(2), 103–111. https://doi.org/10.1159/000370075

Tirapu-Ustárroz, J., Luna-Lario, P., Hernáez-Goñi, P., & García-Suescun, I. (2011). Relation between white matter and cognitive functions. *Revista de Neurologia*, *52*(12), 725–742. https://doi.org/10.33588/rn.5212.2010554

Vaskinn, A., Haatveit, B., Melle, I., Andreassen, O. A., Ueland, T., & Sundet, K. (2020). Cognitive Heterogeneity across Schizophrenia and Bipolar Disorder: A Cluster Analysis of Intellectual Trajectories. *Journal of the International Neuropsychological Society*, *26*(9), 860–872. https://doi.org/10.1017/S1355617720000442

Vilella, E., Gas, C., Garcia-Ruiz, B., & Rivera, F. J. (2019). Expression of DDR1 in the CNS and in myelinating oligodendrocytes. In *Biochimica et Biophysica Acta - Molecular Cell Research* (Vol. 1866, Issue 11). Elsevier B.V. https://doi.org/10.1016/j.bbamcr.2019.04.010

Wechsler, D. (1997). WAIS-III: Wechsler adult intelligence scale. In *San Antonio, TX: The Psychological Corporation*.

## MATERIAL SUPLEMENTARI DE L'ARTICLE 3:

**Supplementary Table S1. Genotype combinations of *DDR1* variants (rs1264323 and rs2267641) in a 1000 Genomes (IBS) sample and the two samples of our study.**

| rs1264323-rs2267641 | 1000 Genomes (IBS) N=107 | Reus sample N=129 | Santander sample N=472 |
|---|---|---|---|
| **GG-AA** | 55.1 | 46.5 | 47.9 |
| **GG-AC** | 0.0 | 0.0 | 0.0 |
| **GG-CC** | 0.0 | 0.0 | 0.0 |
| **GA-AA** | 22.4 | 24.0 | 21.0 |
| **GA-AC** | 15.0 | 19.4 | 21.0 |
| **GA-CC** | 0.0 | 0.0 | 0.0 |
| **AA-AA** | 1.9 | 3.9 | 2.8 |
| **AA-AC** | 2.8 | 4.7 | 4.0 |
| **AA-CC** | 2.8 | 1.6 | 3.4 |
| **P-value**[a] | $4.6x10^{-14}$ | $3.1x10^{-11}$ | $2.4x10^{-64}$ |

[a]Chi-Square test

**Supplementary Table S2. Bivariate analysis between TMT-A scores and sociodemographic and clinical variables.**

| | TMT-A | | | |
|---|---|---|---|---|
| | Reus sample | | Santander sample | |
| | **Patients** | **Controls** | **Patients** | **Controls** |
| **Sex**[a] | 613 | 364.5 | 10402* | 2904 |
| **Age**[b] | -0.07 | 0.09 | 0.21** | 0.18* |
| **Years of education**[b] | -0.05 | -0.34* | -0.21** | -0.22* |
| **Antipsychotic dose**[b,c] | -0.11 | - | -0.17* | - |
| **Psychotic symptoms score**[b,d] | | | | |
| Positive | 0.14 | - | 0.05 | - |
| Negative | 0.18 | - | 0.01 | - |
| General | 0.20 | - | 0.08 | - |

[a] Mann-Whitney U test.

[b] Spearman's rho.

[c] CPZ equivalents in mg/day.

[d] Measured with PANSS in Reus sample and with SAPS, SANS and BPRS in Santander sample.

*P<0.05; **P<0.001.

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Cinta Gas Prades

# V. DISCUSSIÓ

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L'objectiu principal d'aquesta tesi va ser explorar el paper de les variants del gen *DDR1* en la microestructura de la matèria blanca cerebral i en la VP dels TEEAP.

Les principals hipòtesis van sorgir a partir dels coneixements previs de què disposàvem sobre el rol del gen *DDR1* en la mielinització i l'associació amb l'esquizofrènia.

- **Revisió sobre el coneixement del paper de *DDR1* en el SNC**

El primer article va consistir en una revisió bibliogràfica sobre el paper del *DDR1* en el SNC (Vilella et al., 2019). No hi havia en la literatura cap document que recollís el coneixement publicat en revistes indexades i en bases de dades sobre el paper del *DDR1* en el SNC. La revisió es va encarregar al nostre grup de recerca i va formar part d'un volum monogràfic de la revista *BBA-MCR* sobre DDRs. La nostra aportació va ser important per diversos motius: 1) com ja hem comentat, és la primera revisió sistemàtica sobre *DDR1* i SNC; 2) es van aportar de manera ordenada i exhaustiva dades tant en rosegadors com en humans de l'expressió de *DDR1* en els diversos tipus cel·lulars del SNC i informació sobre l'associació entre la variabilitat genètica de *DDR1* i patologies del SNC i perifèric; 3) es va aportar evidència per afirmar que el *DDR1* té un rol rellevant en el procés de la mielinització i s'apuntava que podia tenir un paper important en la fisiopatologia d'algunes malalties neuropsiquiàtriques.

Pel que fa a la l'associació del gen *DDR1* amb malalties del SNC, han sorgit evidències (posteriors a la publicació de l'article) que mutacions de *DDR1* es poden associar a malalties de la mielina com l'EM (Mo et al., 2019). Pel que fa a l'esquizofrènia, ja s'havia reportat una associació genètica de variants de *DDR1* amb aquest trastorn: les primeres evidències pel nostre grup (Roig et al., 2007) i, posteriorment, també per Benkovits et al. (Benkovits et al., 2016), en ambdós estudis concretament amb la variant rs1049623 del gen *DDR1*. Com ja hem apuntat, les variants del *DDR1* estudiades no causen un canvi d'aminoàcids però, o bé poden estar implicades en la regulació de l'expressió del gen, o en desequilibri de lligament (LD, en anglès) amb altres variants funcionals. Aquests resultats concorden amb estudis previs, comentats anteriorment, que mostren l'expressió alterada de gens relacionats amb la mielina en pacients amb TEEAP (Gouvêa-Junqueira et al., 2020; Prata et al., 2013; Roussos & Haroutunian, 2014; Voineskos, 2015).

- **Associació entre les variants del gen *DDR1* i els TEEAP**

Un dels objectius del segon article d'aquesta tesi va ser replicar l'associació entre les variants del gen *DDR1* amb TEEAP en una mostra de casos i controls sans més gran i representativa de la població de l'Estat espanyol. Es va observar una associació entre el SNP rs1264323 de *DDR1* i els TEEAP en un disseny cas-control i es va identificar una

interacció entre els SNPs de *DDR1* rs1264323 i rs2267641: es va observar una combinació genotípica que es mostrava de risc per presentar un TEEAP (rs1264323AA i 1 o 2 al·lels C de rs2267641) i una protectora (rs1264323GA i 1 o 2 al·lels C de rs2267641). Aquests SNPs ja formaven part del llistat de SNPs que mostraven associació a l'estudi previ del nostre grup (Roig et al., 2007), tot i que el que més significativament es va associar era el rs1049623, el mateix SNP de *DDR1* que relacionaven amb l'esquizofrènia Benkovits i col. (Benkovits et al., 2016), com hem comentat. Cal remarcar que rs1264323 i rs1049623 estan en alt LD ($r^2$=1). Aquests resultats van reforçar la hipòtesi de la implicació del *DDR1* en els TEEAP a la vegada que també van evidenciar que l'arquitectura genètica d'aquestes associacions és complexa.

Volem apuntar també que un estudi d'associació de tot el genoma sobre el neuroticisme va trobar una associació d'un SNP en el locus del *DDR1* amb aquest tret (Kim et al., 2017). El neuroticisme és un tret de personalitat caracteritzat per la inestabilitat emocional i la predisposició a experimentar ansietat, por i tristesa, i s'ha assenyalat com un possible factor de risc per a la psicosi (Krabbendam et al., 2002).

- **Influència de *DDR1* sobre la VP en pacients amb TEEAP establert, pacients en primeres fases de la psicosi i controls**

El segon objectiu del segon article d'aquesta tesi (Gas et al., 2019) era analitzar també la influència dels SNPs de *DDR1* en la VP en una mostra de pacients amb diagnòstic de TEEAP establert.

Com hem comentat, l'afectació cognitiva és una alteració nuclear en els TEEAP. Els estudis mostren un cert grau de deteriorament cognitiu abans de l'aparició de la psicosi (Mollon & Reichenberg, 2018). Entre els diveros dominis, la VP és un dels dèficits cognitius més replicats en pacients amb esquizofrènia (Fatouros-Bergman et al., 2014; Schaefer et al., 2013; Sheffield et al., 2018) i és predictora del grau de funcionalitat dels pacients (Bolt et al., 2019; Lahera et al., 2017). Pel que fa a les estructures subjacents de la VP, s'ha observat una relació entre la reducció de la integritat de la matèria blanca cerebral i els dèficits cognitius en pacients amb esquizofrènia, i s'ha assenyalat una associació més forta per la VP (Karbasforoushan et al., 2015; Kochunov et al., 2017).

Segons els resultats del segon article, es va suggerir un efecte recessiu de l'al·lel C de rs2267641, ja que, en estudiar les variants per separat, vam evidenciar que els pacients amb el genotip rs2267641CC presentaven puntuacions directes més grans de TMT-A, cosa que es pot llegir com una disminució de la VP. En la mateixa línia, quan vam analitzar la influència de la combinació genotípica de rs1264323 i rs2267641, només els pacients amb el genotip AA-CC van presentar una disminució de la VP. En el tercer treball

d'aquesta tesi (Gas et al., en preparació) es va aplicar el mateix plantejament, però en dues mostres independents de pacients amb psicosi en les primeres fases i els respectius controls sans. L'objectiu era analitzar si el que s'havia observat en l'esquizofrènia també es detectava en les primeres fases del trastorn, ja que en aquestes primeres fases és clau saber quins dèficits hi ha per poder actuar de forma precoç, i en els controls volíem saber si les variants de risc conformaven també un empitjorament en la VP. El que vàrem observar, en les dues mostres analitzades, va ser una tendència d'associació de la combinació genotípica de risc dels 2 SNPs de *DDR1* (rs1264323 i rs2267641) amb la VP, i es va aconseguir la significació estadística en la mostra més gran. No obstant això, al contrari del que esperàvem obtenir segons el segon article que conforma aquesta tesi (Gas et al., 2019), els pacients amb una combinació genotípica de risc presentaven una VP augmentada respecte dels que eren portadors de la combinació genotípica de no risc. Aquests resultats inicialment ens van semblar contradictoris, per la qual cosa en vam analitzar les possibles raons i vam assenyalar primerament les diferències que hi podien haver entre els subjectes analitzats en els dos estudis, tenint en compte que en l'últim estudi els pacients es trobaven en les primeres fases de la psicosi. Els pacients amb psicosi incipient presenten diverses característiques que poden implicar un rendiment millor en la VP respecte a la mostra amb diagnòstic de TEEAP del segon article (Gas et al., 2019): 1) mitjana d'edat menor (Cohen et al., 2019); 2) menys anys d'evolució del trastorn (Fett et al., 2020; Harvey & Rosenthal, 2018); 3) grup de diagnòstic heterogeni (Peralta et al., 2013) amb inclusió de pacients que no desenvoluparan esquizofrènia (Ayesa-Arriola et al., 2016; Vaskinn et al., 2020); 4) augment del consum de cànnabis (Bogaty et al., 2018; Mandelbaum & de la Monte, 2017); 5) diferències en el tractament (ansiolítics i antidepressius) (Picton et al., 2018; Prado et al., 2018; Saczynski et al., 2015); 6) menys prevalença de simptomatologia negativa que els pacients amb esquizofrènia (Correll & Schooler, 2020).

Hem de ressaltar que en els dos estudis s'han utilitzat les mateixes covariables per a les anàlisis (anys d'educació, edat, gènere, dosi d'antipsicòtics en equivalents de clorpromazina) menys les variables "anys d'evolució de la malaltia" (que no es va incloure en la mostra de psicosi incipient) i la "PANSS negativa" que es va incloure en l'estudi previ però no en l'últim, ja que en les mostres de psicosi incipient no va correlacionar amb el TMT-A cap variable en relació amb la simptomatologia. Per tant, tot indica que, a part de les variables incloses, hi ha d'haver altres variables que expliquin per què en primers episodis la combinació genotípica s'associa amb més VP i, en canvi, en fases més consolidades de la malaltia, ho fa de manera inversa.

Un altre punt que cal tenir en consideració és l'observació, en el segon article (Gas et al., 2019), d'un empitjorament de la VP resultant de la interacció de la variant rs1264323

amb el temps en pacients amb TEEAP. Aquest efecte pot concordar amb els resultats diferents observats en les mostres d'individus amb psicosi en fases inicials i en la mostra dels pacients amb TEEAP amb més anys d'evolució de la malaltia.

Resumint: pot ser que les variants de *DDR1* s'associïn de forma positiva amb la VP en les primeres fases i de forma negativa a mesura que avança el trastorn.

Pel que fa a la influència de les variants de *DDR1* en la VP en controls sans, no hi vam trobar diferències significatives. No disposem d'estudis previs del paper de *DDR1* en el perfil cognitiu de controls sans però pot indicar que els efectes de les variants de risc del gen són diferents en individus sans que en pacients, ja que en aquests últims sembla que actuen de forma conjunta amb factors de risc.

Com ja sabem, amb l'edat hi ha un declivi de la VP (Cohen et al., 2019; Harvey & Rosenthal, 2018). En aquesta direcció, un estudi recent de Harris i col·laboradors (Harris et al., 2020) mostra que els nivells de DDR1 plasmàtics es correlacionen negativament amb la capacitat cognitiva en tres cohorts de persones sanes ancianes (edat mitjana de 76,4 anys), i en canvi no es va observar aquesta correlació en una cohort més jove (edat mitjana de 58 anys). El DDR1 en plasma s'expressa en leucòcits i l'expressió s'associa a inflamació (Vilella et al., 2019). Segons aquest estudi, els nivells més alts de DDR1 en casos amb menys capacitat cognitiva es poden explicar per un estat "inflamatori". També pot ser que els nivells de DDR1 en plasma siguin un mirall dels nivells de DDR1 al cervell i que els casos amb menys capacitat cognitiva també tinguin nivells més alts de DDR1 al cervell. En aquest sentit, el nostre grup va trobar augmentat el nivell del ARNm de *DDR1*c en el cervell de pacients amb esquizofrènia comparat amb controls sans (Roig, Abasolo et al., 2012).

- **Associació entre el genotip *DDR1*, la matèria blanca cerebral i la VP en TEEAP**

El tercer objectiu del segon article d'aquesta tesi (Gas et al., 2019) era explorar la relació entre la microestructura de la matèria blanca cerebral, la VP i el genotip *DDR1* en una mostra amb pacients amb diagnòstic de TEEAP. Es va trobar una relació entre el genotip rs1264323AA i un descens de la FA (que implica una alteració de la integritat dels tractes de mielina) en regions de matèria blanca en associació amb un descens de la VP. També es va observar un empitjorament de la VP en el temps (amb una diferència de 6 anys aproximadament) en els portadors de l'al·lel A de rs1264323. Aquests resultats concordaven amb els previs, en què se suggeria una funció protectora de l'al·lel G d'aquesta variant de *DDR1*, i mostraven que el rs1264323 estava associat a canvis de FA

en regions cerebrals implicades en la VP en pacients amb TEEAP com el cos del cos callós.

La teoria del neurodesenvolupament (Feinberg, 1982; Weinberger, 1987), com hem comentat en la introducció, postulava que alteracions en el desenvolupament prenatal i postnatal del cervell sembla que conferien certa susceptibilitat per desenvolupar la malaltia a l'adolescència juntament amb factors ambientals estressants i genètics. El nostre grup de recerca va descriure la importància de *DDR1* en la mielinització durant el neurodesenvolupament i del model murí (Franco-Pons et al., 2006b). Per tant, podem pensar que les persones portadores de variants del gen *DDR1* poden presentar alteracions a la mielina que els facin més susceptibles a desenvolupar dèficits cognitius com la VP. I que això a la vegada fos un factor de risc que, juntament amb altres, facilités el desenvolupament de la psicosi. D'altra banda, el paper del *DDR1* en la mielinització pot encaixar en el model de la desconnectivitat neuronal, en què els errors en la integració funcional són mediats per alteracions en les connexions anatòmiques (Friston, 2002) que són principalment assolides per axons mielinitzats. Alteracions en els oligodendròcits i la mielina poden portar a canvis en la formació sinàptica i la funció, que a la vegada, pot conduir a una disfunció cognitiva (Takahashi et al., 2011). La VP es mesura mitjançant tasques simples i bàsiques i és un domini estretament relacionat amb la integritat de la mielina (Penke et al., 2010; Ríos-Lago & Periañez, 2010); aquest fet pot explicar per què està més associada amb la variabilitat genètica de DDR1 que altres dominis cognitius, processos que impliquen tasques més complexes i amb els quals no trobem associació (dades no mostrades en aquesta tesi).

Fins ara no disposem d'altres estudis sobre la relació entre *DDR1*, matèria blanca i neurocognició, per la qual cosa aquesta publicació aporta informació rellevant que permet integrar els coneixements previs que teníem sobre *DDR1*. D'altra banda, es necessiten més estudis per confirmar-ho.

- **Fortaleses i limitacions**

Per poder interpretar correctament els resultats dels estudis que conformen aquesta tesi doctoral, cal tenir en compte una sèrie de limitacions.

Primerament, s'ha de considerar la mida mostral dels diversos estudis que podria haver limitat el nostre poder estadístic. Concretament amb relació a la mida de la mostra dels grups homozigots de l'al·lel rar dels 2 SNPs de *DDR1* analitzats. Els SNPs són comuns en la població, però en general han de suportar una pressió selectiva; en conseqüència, associacions entre un SNP i una condició perjudicial com un trastorn generalment tindran un efecte de mida petita. Aquests efectes petits requereixen grans estudis per

proporcionar el poder necessari per declarar una associació estadísticament significativa (Michaelson, 2017). Per intentar reduir aquesta limitació, vam utilitzar l'anàlisi no paramètrica de bootstrap (Dwivedi et al., 2017) que fa un remostreig reemplaçant un valor calculat obtingut a partir de les dades observades un gran nombre de vegades (10.000 iteracions). Aquest mètode és útil en casos com en una mostra petita o quan la distribució teòrica de l'estadística és complicada.

Pel que fa a l'anàlisi de la matèria blanca, a part d'apuntar que les imatges de què disposàvem de RM eren d'1,5T i actualment ja s'utilitzen de 3T o més, hem de tenir en compte que la FA és molt sensible a diversos paràmetres de la microestructura (com el diàmetre axonal, el grau de mielinització, la permeabilitat de la membrana, l'heterogeneïtat de la orientació) però no és específica per a cap d'aquests paràmetres.

Una fortalesa que ja hem comentat en l'apartat 3 d'aquesta discussió és que vam controlar per les variables de confusió (edat, gènere, dosi d'antipsicòtics, anys d'educació, anys d'evolució del trastorn i simptomatologia negativa), i que la dependència de tòxics va ser un criteri exclusió.

Cal assenyalar també, pel que fa a les fortaleses, que hi ha molt poca literatura sobre *DDR1* i esquizofrènia. Amb el nostre treball: 1) vam recollir la informació disponible de *DDR1*; 2) vam replicar l'associació entre esquizofrènia i *DDR1*, i vam mostrar la relació entre *DDR1* i VP tant en pacients amb TEEAP com en primeres fases de la psicosi (cal apuntar la dificultat que comporta aconseguir aquest últim tipus de mostra, donada la baixa prevalença i les dificultats en la participació i seguiment); 3) també vam assenyalar el paper de *DDR1* per conferir un risc d'esquizofrènia a través d'alteracions microestructurals de la matèria blanca que poden conduir a la disfunció cognitiva.

Mitjançant aquesta tesi aportem més dades a la literatura científica per valorar el paper del gen *DDR1* en els TEEAP.

- **Perspectives futures**

Donada la complexitat en l'etiologia dels TEEAP, conèixer possibles variants de susceptibilitat per a la psicosi o aprofundir en l'etiopatogènia identificant gens implicats en la microestructura del tracte de la mielina, pot ajudar a comprendre millor la fisiologia de la psicosi i trobar noves dianes terapèutiques. Per exemple, un dels desafiaments clínics en TEEAP és la resistència als tractaments antipsicòtics. No coneixem les causes de la ineficàcia del tractament però es pot associar a algunes característiques clíniques, com l'inici primerenc del trastorn o els dèficits cognitius més severs (Nucifora et al., 2019), especialment en la VP (Frydecka et al., 2015). Kochunov i altres col·laboradors van testar la hipòtesi que les alteracions de la matèria blanca implicades en el

desenvolupament i la severitat dels dèficits cognitius en l'esquizofrènia s'associen a un risc més gran de resistència al tractament (Kochunov et al., 2019). I van suggerir que s'ha de considerar el desenvolupament d'intervencions orientades a preservar o millorar la integritat de la matèria blanca, ja que és una part dels orígens etiopatològics de la resistència al tractament de l'esquizofrènia (Crocker & Tibbo, 2018; Kochunov et al., 2019). La generació de nous tractaments i teràpies en aquesta direcció poden millorar el processament de la informació i el resultat funcional de la psicosi.

Actualment, l'estratègia terapèutica principal per tractar els TEEAP es basa en l'ús d'antipsicòtics. Tot i l'ús generalitzat, els efectes dels antipsicòtics en les cèl·lules glials, especialment els oligodendròcits, continuen sent poc clars (Gouvêa-Junqueira et al., 2020). Per la qual cosa, és interessant estudiar quins fàrmacs són promielinitzants i en quins pacients són més necessaris. Entre els possibles tractaments nous, encara de forma molt preliminar, s'ha proposat el Nilotinib, un inhibidor potent de DDR, per prevenir la neurodegeneració (Fowler et al., 2019; Pagan et al., 2019). Barbera i altres col·laboradors van reportar que el fàrmac va ser capaç de restaurar la funció de la memòria en un model de ratolí de la malaltia d'Alzheimer (La Barbera et al., 2021). Un altre tractament que cal destacar és el de la rehabilitació cognitiva, amb efectivitat consolidada en pacients amb psicosi establerta (Gómez-Gastiasoro et al., 2019; Wykes et al., 2011) que també amb un paper important per prevenir la transició a la psicosi dels individus amb un estat mental d'alt risc (Glenthøj et al., 2017).

Futures línies d'investigació inclouen analitzar grans cohorts independents, l'anàlisi en pacients antipsicòtic naïf, anàlisis segons el diagnòstic (ja que els TEEAP són un grup amb diagnòstic heterogeni) o segons el gènere (ja que pot implicar un ritme de neurodesenvolupament diferent). Un altre punt que tenir en compte és analitzar la relació de *DDR1* amb altres dominis cognitius i amb la simptomatologia.

També seria interessant fer estudis de seguiment per veure si en un mateix pacient les variants genètiques tenen una influència en la VP diferent en les primeres etapes respecte a l'avançament de la malaltia. Això podria permetre estratificar els pacients ja des de les fases inicials del trastorn per millorar-ne el diagnòstic i aplicar tractaments preventius.

Altres estudis futurs poden consistir a analitzar el paper de *DDR1* en altres patologies mentals greus, com el trastorn bipolar o altres trastorns del neurodesenvolupament, com els trastorns de l'espectre autista o la discapacitat intel·lectual.

Un dels reptes principals de la psiquiatria és identificar biomarcadors que siguin útils per al diagnòstic i per al monitoratge dels pacients. Donat que els TEEAP formen part del que

anomenem malalties complexes amb la implicació de factors genètics i factors ambientals i la interacció entre ambdós tipus de factors, pensar en els estudis epigenètics en sang i en cervell sembla ineludible. En aquest sentit el nostre grup de recerca va fer un estudi de metilació de DDR1 en sang i cervell en TEEAP i va trobar hipermetilació de DDR1, tant en sang com en cervell, i associació de la hipermetiliació amb variables d'estrès i marcadors d'inflamació (Garcia-Ruiz et al., 2020).

Aquesta tesi doctoral és una petita aportació del paper del *DDR1* amb relació a la matèria blanca i la VP en els TEEAP. Calen estudis futurs per aprofundir en aquesta relació.

# VI. CONCLUSIONS

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1) Al cervell de ratolí el *Ddr1* augmenta la seva expressió en la transició des d'OPCs cap a oligodendròcits madurs, i la màxima expressió es troba just abans de convertir-se en oligodendròcits mielinitzants, la qual cosa suggereix que pot tenir un paper important en la diferenciació dels oligodendròcits.

2) Mutacions de *DDR1* en gliomes i schwannomes suggereixen que el *DDR1* està implicat en la proliferació d'aquests tumors.

3) Variants de tipus SNP de *DDR1* (rs1049623, rs2267641 i rs2239518) s'han trobat associades a l'esquizofrènia.

4) La combinació dels SNPs de *DDR1* (rs1264323AA-rs2267641AC/CC) s'ha trobat associada als TEEAP establerts en una mostra cas-control recollida a l'Estat espanyol amb 1.193 casos i 1.839 controls.

5) La variant funcional rs2267641 en la forma genotípica CC s'ha trobat associada a una VP més petita en una mostra de pacients amb diagnòstic de TEEAP establert (n=194).

6) En el subgrup de 54 pacients amb un TEEAP establert que es van avaluar inicialment i reavaluar 6 anys més tard, l'al·lel A del rs1264323 s'ha trobat associat a una disminució de la VP.

7) La combinació genotípica rs1264323AA-rs2267641AC/CC s'ha associat a un augment de la VP en una mostra de pacients en les primeres fases de la psicosi de dues mostres independents (n=75 i n=312, respectivament), tot i que només ha aconseguit la significació estadística en la mostra de mida més gran.

8) No s'observa cap associació entre la combinació genotípica rs1264323AA-rs2267641AC/CC i la VP en la mostra de controls sans en les dues mostres independents (n=57 i n=160, respectivament).

9) En el subgrup de 54 pacients amb un TEEAP establert, la variant rs1264323 en la forma genotípica AA s'associa a una disminució del paràmetre de FA, que es pot interpretar com l'alteració de la integritat de la mielina, en regions que, al seu torn, s'associen a una disminució de la VP.

10) La interacció entre variants del tipus SNP del gen *DDR1* s'associa al risc de presentar un TEEAP, a una alteració de la integritat de la mielina i a un augment de la VP en primeres fases de la psicosi i, per contra, a una disminució en les formes establertes de TEEAP.

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# VII. REFERÈNCIES

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Aboitiz, F., Scheibel, A. B., Fisher, R. S., & Zaidel, E. (1992). Fiber composition of the human corpus callosum. *Brain Research*, *598*(1–2), 143–153. https://doi.org/10.1016/0006-8993(92)90178-C

Alba-Ferrara, L. M., & de Erausquin, G. A. (2013). What does anisotropy measure? Insights from increased and decreased anisotropy in selective fiber tracts in schizophrenia. In *Frontiers in Integrative Neuroscience* (Issue FEBRUARY 2013). https://doi.org/10.3389/fnint.2013.00009

American Psychiatric Association. (2013). *American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (5th ed.)* (5th ed.). American Psychiatric Publishing.

Andreasen, N. C., Carpenter, W. T., Kane, J. M., Lasser, R. A., Marder, S. R., & Weinberger, D. R. (2005). Remission in schizophrenia: Proposed criteria and rationale for consensus. In *American Journal of Psychiatry* (Vol. 162, Issue 3, pp. 441–449). Am J Psychiatry. https://doi.org/10.1176/appi.ajp.162.3.441

Andreou, C., & Borgwardt, S. (2020). Structural and functional imaging markers for susceptibility to psychosis. In *Molecular Psychiatry* (Vol. 25, Issue 11, pp. 2773–2785). Springer Nature. https://doi.org/10.1038/s41380-020-0679-7

Anttila, V., Bulik-Sullivan, B., Finucane, H. K., Walters, R. K., Bras, J., Duncan, L., Escott-Price, V., Falcone, G. J., Gormley, P., Malik, R., Patsopoulos, N. A., Ripke, S., Wei, Z., Yu, D., Lee, P. H., Turley, P., Grenier-Boley, B., Chouraki, V., Kamatani, Y., … Neale, B. M. (2018). Analysis of shared heritability in common disorders of the brain. *Science*, *360*(6395), 8757. https://doi.org/10.1126/science.aap8757

Ayesa-Arriola, R., Rodríguez-Sánchez, J. M., Suero, E. S., Reeves, L. E., Tabarés-Seisdedos, R., & Crespo-Facorro, B. (2016). Diagnosis and neurocognitive profiles in first-episode non-affective psychosis patients. *European Archives of Psychiatry and Clinical Neuroscience*, *266*(7), 619–628. https://doi.org/10.1007/s00406-015-0667-0

Bartzokis, G. (2002). Schizophrenia: Breakdown in the well-regulated lifelong process of brain development and maturation. *Neuropsychopharmacology*, *27*(4), 672–683. https://doi.org/10.1016/S0893-133X(02)00364-0

Basser, P. J., & Jones, D. K. (2002). Diffusion-tensor MRI: Theory, experimental design and data analysis - A technical review. In *NMR in Biomedicine* (Vol. 15, Issues 7–8, pp. 456–467). https://doi.org/10.1002/nbm.783

Benkovits, J., Magyarósi, S., Pulay, A., Makkos, Z., Égerházi, A., Balogh, N., Álmos, P., Likó, I., Konzorcium, M. S., Németh, G., Molnár, M. J., Nagy, L., & Réthelyi, J. (2016). Investigation of CNTF, COMT, DDR1, DISC1, DRD2, DRD3, and DTNBP1 candidate genes in schizophrenia: Results from the Hungarian SCHIZOBANK consortium. *Neuropsychopharmacologia Hungarica*, *18*(4), 181–187. https://pubmed.ncbi.nlm.nih.gov/28259861/

Bogaty, S. E. R., Lee, R. S. C., Hickie, I. B., & Hermens, D. F. (2018). *Meta-analysis of neurocognition in young psychosis patients with current cannabis use*. https://doi.org/10.1016/j.jpsychires.2018.01.010

Bolt, L. K., Amminger, G. P., Farhall, J., McGorry, P. D., Nelson, B., Markulev, C., Yuen, H. P., Schäfer, M. R., Mossaheb, N., Schlögelhofer, M., Smesny, S., Hickie, I. B., Berger, G. E., Chen, E. Y. H., de Haan, L., Nieman, D. H., Nordentoft, M., Riecher-Rössler, A., Verma, S., … Allott, K. A. (2019). Neurocognition as a predictor of transition to psychotic disorder and functional outcomes in ultra-high risk participants: Findings from the NEURAPRO randomized clinical trial. *Schizophrenia*

*Research*, *206*, 67–74. https://doi.org/10.1016/j.schres.2018.12.013

Bora, E., & Murray, R. M. (2014). Meta-analysis of cognitive deficits in ultra-high risk to psychosis and first-episode psychosis: Do the cognitive deficits progress over, or after, the onset of psychosis? *Schizophrenia Bulletin*. https://doi.org/10.1093/schbul/sbt085

Bora, E., Yücel, M., & Pantelis, C. (2010). Cognitive impairment in schizophrenia and affective psychoses: Implications for dsm-v criteria and beyond. *Schizophrenia Bulletin*, *36*(1), 36–42. https://doi.org/10.1093/schbul/sbp094

Bouwkamp, C. G., Kievit, A. J. A., Markx, S., Friedman, J. I., Van Zutven, L., Van Minkelen, R., Vrijenhoek, T., Xu, B., Sterrenburg-Van De Nieuwegiessen, I., Veltman, J. A., Bonifati, V., & Kushner, S. A. (2017). Copy number variation in syndromic forms of psychiatric illness: The emerging value of clinical genetic testing in psychiatry. *American Journal of Psychiatry*, *174*(11), 1036–1050. https://doi.org/10.1176/appi.ajp.2017.16080946

Brébion, G., David, A. S., Jones, H. M., & Pilowsky, L. S. (2009). Working memory span and motor and cognitive speed in schizophrenia. *Cognitive and Behavioral Neurology*, *22*(2), 101–108. https://doi.org/10.1097/WNN.0b013e3181a722a0

Carletti, F., Woolley, J. B., Bhattacharyya, S., Perez-Iglesias, R., Fusar Poli, P., Valmaggia, L., Broome, M. R., Bramon, E., Johns, L., Giampietro, V., Williams, S. C. R., Barker, G. J., & McGuire, P. K. (2012). Alterations in White Matter Evident Before the Onset of Psychosis. *Schizophrenia Bulletin*, *38*(6), 1170–1179. https://doi.org/10.1093/schbul/sbs053

Carlsson, A. (1988). The current status of the dopamine hypothesis of schizophrenia. *Neuropsychopharmacology*, *1*(3), 179–186. https://doi.org/10.1016/0893-133x(88)90012-7

Cohen, R. A., Marsiske, M. M., & Smith, G. E. (2019). Neuropsychology of aging. In *Handbook of Clinical Neurology* (Vol. 167, pp. 149–180). Elsevier B.V. https://doi.org/10.1016/B978-0-12-804766-8.00010-8

Correll, C. U., & Schooler, N. R. (2020). Negative symptoms in schizophrenia: A review and clinical guide for recognition, assessment, and treatment. In *Neuropsychiatric Disease and Treatment* (Vol. 16, pp. 519–534). Dove Medical Press Ltd. https://doi.org/10.2147/NDT.S225643

Coyle, J. T. (2006). Glutamate and schizophrenia: beyond the dopamine hypothesis. In *Cellular and molecular neurobiology* (Vol. 26, Issues 4–6, pp. 365–384). Cell Mol Neurobiol. https://doi.org/10.1007/s10571-006-9062-8

Coyle, J. T., Balu, D. T., Puhl, M. D., & Konopaske, G. T. (2016). History of the Concept of Disconnectivity in Schizophrenia. In *Harvard Review of Psychiatry* (Vol. 24, Issue 2, pp. 80–86). Taylor and Francis Ltd. https://doi.org/10.1097/HRP.0000000000000102

Crocker, C. E., & Tibbo, P. G. (2018). Confused connections? Targeting white matter to address treatment resistant schizophrenia. In *Frontiers in Pharmacology* (Vol. 9, Issue OCT). Frontiers Media S.A. https://doi.org/10.3389/fphar.2018.01172

Davies, R. W., Fiksinski, A. M., Breetvelt, E. J., Williams, N. M., Hooper, S. R., Monfeuga, T., Bassett, A. S., Owen, M. J., Gur, R. E., Morrow, B. E., McDonald-McGinn, D. M., Swillen, A., Chow, E. W. C., van den Bree, M., Emanuel, B. S., Vermeesch, J. R., van Amelsvoort, T., Arango, C., Armando, M., … Vorstman, J. A. S. (2020). Using common genetic variation to examine phenotypic expression and risk prediction in

22q11.2 deletion syndrome. *Nature Medicine*, *26*(12). https://doi.org/10.1038/s41591-020-1103-1

Dickinson, D., Ramsey, M. E., & Gold, J. M. (2007). Overlooking the obvious: A meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. *Archives of General Psychiatry*, *64*(5), 532–542. https://doi.org/10.1001/archpsyc.64.5.532

Dietz, A. G., Goldman, S. A., & Nedergaard, M. (2020). Glial cells in schizophrenia: a unified hypothesis. In *The Lancet Psychiatry* (Vol. 7, Issue 3, pp. 272–281). Elsevier Ltd. https://doi.org/10.1016/S2215-0366(19)30302-5

Domen, P., Peeters, S., Michielse, S., Gronenschild, E., Viechtbauer, W., Roebroeck, A., Os, J. van, Marcelis, M., & for Genetic Risk and Outcome of Psychosis (G.R.O.U.P.). (2017). Differential Time Course of Microstructural White Matter in Patients With Psychotic Disorder and Individuals at Risk: A 3-Year Follow-up Study. *Schizophrenia Bulletin*, *43*(1), 160–170. https://doi.org/10.1093/schbul/sbw061

Dwivedi, A. K., Mallawaarachchi, I., & Alvarado, L. A. (2017). Analysis of small sample size studies using nonparametric bootstrap test with pooled resampling method. *Statistics in Medicine*. https://doi.org/10.1002/sim.7263

Edelhoff, S., Sweetser, D. A., & Disteche, C. M. (1995). Mapping of the NEP receptor tyrosine kinase gene to human chromosome 6p21.3 and mouse chromosome 17C. *Genomics*, *25*(1), 309–311. https://doi.org/10.1016/0888-7543(95)80144-B

Farrell, M. S., Werge, T., Sklar, P., Owen, M. J., Ophoff, R. A., O'Donovan, M. C., Corvin, A., Cichon, S., & Sullivan, P. F. (2015). Evaluating historical candidate genes for schizophrenia. *Molecular Psychiatry*, *20*(5), 555–562. https://doi.org/10.1038/mp.2015.16

Fatouros-Bergman, H., Cervenka, S., Flyckt, L., Edman, G., & Farde, L. (2014). Meta-analysis of cognitive performance in drug-naïve patients with schizophrenia. *Schizophrenia Research*, *158*(1–3), 156–162. https://doi.org/10.1016/j.schres.2014.06.034

Feinberg, I. (1982). Schizophrenia: Caused by a fault in programmed synaptic elimination during adolescence? *Journal of Psychiatric Research*, *17*(4), 319–334. https://doi.org/10.1016/0022-3956(82)90038-3

Fett, A. K. J., Velthorst, E., Reichenberg, A., Ruggero, C. J., Callahan, J. L., Fochtmann, L. J., Carlson, G. A., Perlman, G., Bromet, E. J., & Kotov, R. (2020). Long-term Changes in Cognitive Functioning in Individuals with Psychotic Disorders: Findings from the Suffolk County Mental Health Project. *JAMA Psychiatry*, *77*(4), 387–396. https://doi.org/10.1001/jamapsychiatry.2019.3993

Fowler, A. J., Hebron, M., Missner, A. A., Wang, R., Gao, X., Kurd-Misto, B. T., Liu, X., & Moussa, C. E. H. (2019). Multikinase Abl/DDR/Src Inhibition Produces Optimal Effects for Tyrosine Kinase Inhibition in Neurodegeneration. *Drugs in R and D*, *19*(2), 149–166. https://doi.org/10.1007/s40268-019-0266-z

Franco-Pons, N., Tomàs, J., Roig, B., Auladell, C., Martorell, L., & Vilella, E. (2009). Discoidin domain receptor 1, a tyrosine kinase receptor, is upregulated in an experimental model of remyelination and during oligodendrocyte differentiation in vitro. *Journal of Molecular Neuroscience : MN*, *38*(1), 2–11. https://doi.org/10.1007/s12031-008-9151-x

Franco-Pons, N., Virgos, C., Vogel, W. F., Ureña, J. M., Soriano, E., del Rio, J. A., & Vilella, E. (2006a). Expression of discoidin domain receptor 1 during mouse brain

development follows the progress of myelination. *Neuroscience*, *140*(2), 463–475. http://www.sciencedirect.com/science/article/pii/S0306452206002223

Franco-Pons, N., Virgos, C., Vogel, W. F., Ureña, J. M., Soriano, E., del Rio, J. A., & Vilella, E. (2006b). Expression of discoidin domain receptor 1 during mouse brain development follows the progress of myelination. *Neuroscience*, *140*(2), 463–475. https://doi.org/10.1016/j.neuroscience.2006.02.033

Friston, K. J. (2002). Dysfunctional connectivity in schizophrenia. *World Psychiatry : Official Journal of the World Psychiatric Association (WPA)*, *1*(2), 66–71.

Frydecka, D., Beszłej, J. A., Gościmski, P., Kiejna, A., & Misiak, B. (2015). Profiling cognitive impairment in treatment-resistant schizophrenia patients. *Psychiatry Research*, *235*, 133–138. https://doi.org/10.1016/j.psychres.2015.11.028

Fusar-Poli, P., & Meyer-Lindenberg, A. (2016). Forty years of structural imaging in psychosis: promises and truth. In *Acta Psychiatrica Scandinavica* (Vol. 134, Issue 3, pp. 207–224). Blackwell Publishing Ltd. https://doi.org/10.1111/acps.12619

Fusar-Poli, Paolo, Deste, G., Smieskova, R., Barlati, S., Yung, A. R., Howes, O., Stieglitz, R. D., Vita, A., McGuire, P., & Borgwardt, S. (2012). Cognitive functioning in prodromal psychosis: A meta-analysis. *Archives of General Psychiatry*, *69*(6), 562–571. https://doi.org/10.1001/archgenpsychiatry.2011.1592

Fusar-Poli, Paolo, McGorry, P. D., & Kane, J. M. (2017). Improving outcomes of first-episode psychosis: an overview. *World Psychiatry*. https://doi.org/10.1002/wps.20446

Garcia-Ruiz, B., Moreno, L., Muntané, G., Sánchez-Gistau, V., Gutiérrez-Zotes, A., Martorell, L., Labad, J., & Vilella, E. (2020). Leukocyte and brain DDR1 hypermethylation is altered in psychosis and is correlated with stress and inflammatory markers. *Epigenomics*, *12*(3), 251–265. https://doi.org/10.2217/epi-2019-0191

Garin-Muga, A., & Borro, D. (2014). Review and challenges of brain analysis through DTI measurements. *Studies in Health Technology and Informatics*, *207*, 27–36. https://doi.org/10.3233/978-1-61499-474-9-27

Gartner, L. P., & Hiatt, J. L. (2011). *Histología básica*. Elsevier.

Gas, C., Canales-Rodríguez, E. J., Radua, J., Abasolo, N., Cortés, M. J., Salvadó, E., Muntané, G., Alemán-Gómez, Y., Julià, T., Marsal, S., Sanjuan, J., Guitart, M., Costas, J., Martorell, L., Pomarol-Clotet, E., & Vilella, E. (2019). Discoidin domain receptor 1 gene variants are associated with decreased white matter fractional anisotropy and decreased processing speed in schizophrenia. *Journal of Psychiatric Research*, *110*(December 2018), 74–82. https://doi.org/10.1016/j.jpsychires.2018.12.021

Gibson, E. M., Purger, D., Mount, C. W., Goldstein, A. K., Lin, G. L., Wood, L. S., Inema, I., Miller, S. E., Bieri, G., Zuchero, J. B., Barres, B. A., Woo, P. J., Vogel, H., & Monje, M. (2014). Neuronal activity promotes oligodendrogenesis and adaptive myelination in the mammalian brain. *Science*, *344*(6183). https://doi.org/10.1126/science.1252304

Giddaluru, S., Espeseth, T., Salami, A., Westlye, L. T., Lundquist, A., Christoforou, A., Cichon, S., Adolfsson, R., Steen, V. M., Reinvang, I., Nilsson, L. G., Le Hellard, S., & Nyberg, L. (2016). Genetics of structural connectivity and information processing in the brain. *Brain Structure and Function*, *221*(9), 4643–4661. https://doi.org/10.1007/s00429-016-1194-0

Giotakos, O. (2019). Is psychosis a dysmyelination-related information-processing disorder? In *Psychiatrike = Psychiatriki* (Vol. 30, Issue 3, pp. 245–255). NLM (Medline). https://doi.org/10.22365/jpsych.2019.303.245

Glenthøj, L. B., Hjorthøj, C., Kristensen, T. D., Davidson, C. A., & Nordentoft, M. (2017). The effect of cognitive remediation in individuals at ultra-high risk for psychosis: A systematic review. *Npj Schizophrenia*, *3*(1). https://doi.org/10.1038/s41537-017-0021-9

Gómez-Gastiasoro, A., Peña, J., Ibarretxe-Bilbao, N., Lucas-Jiménez, O., Díez-Cirarda, M., Rilo, O., Montoya-Murillo, G., Zubiaurre-Elorza, L., & Ojeda, N. (2019). A Neuropsychological Rehabilitation Program for Cognitive Impairment in Psychiatric and Neurological Conditions: A Review That Supports Its Efficacy. In *Behavioural Neurology* (Vol. 2019). Hindawi Limited. https://doi.org/10.1155/2019/4647134

González-Blanch, C., Rodríguez-Sánchez, J. M., Pérez-Iglesias, R., Pardo-García, G., Martínez-García, O., Vázquez-Barquero, J. L., & Crespo-Facorro, B. (2010). First-episode schizophrenia patients neuropsychologically within the normal limits: evidence of deterioration in speed of processing. *Schizophrenia Research*, *119*(1–3), 18–26. https://doi.org/10.1016/j.schres.2010.02.1072

Gottesman, I. I. (1991). *Shizophrenia Genesis: The Origins of Madness.* W H Freeman/Times Books/Henry Holt & Co.

Gouvêa-Junqueira, D., Falvella, A. C. B., Antunes, A. S. L. M., Seabra, G., Brandão-Teles, C., Martins-de-Souza, D., & Crunfli, F. (2020). Novel Treatment Strategies Targeting Myelin and Oligodendrocyte Dysfunction in Schizophrenia. In *Frontiers in Psychiatry* (Vol. 11, p. 1). Frontiers Media S.A. https://doi.org/10.3389/fpsyt.2020.00379

Guintivano, J., & Kaminsky, Z. A. (2016). Role of epigenetic factors in the development of mental illness throughout life. In *Neuroscience Research* (Vol. 102, pp. 56–66). Elsevier Ireland Ltd. https://doi.org/10.1016/j.neures.2014.08.003

Guloksuz, S., & Van Os, J. (2018). The slow death of the concept of schizophrenia and the painful birth of the psychosis spectrum. In *Psychological Medicine* (Vol. 48, Issue 2, pp. 229–244). Cambridge University Press. https://doi.org/10.1017/S0033291717001775

Harris, S. E., Cox, S. R., Bell, S., Marioni, R. E., Prins, B. P., Pattie, A., Corley, J., Muñoz Maniega, S., Valdés Hernández, M., Morris, Z., John, S., Bronson, P. G., Tucker-Drob, E. M., Starr, J. M., Bastin, M. E., Wardlaw, J. M., Butterworth, A. S., & Deary, I. J. (2020). Neurology-related protein biomarkers are associated with cognitive ability and brain volume in older age. *Nature Communications*, *11*(1), 1–12. https://doi.org/10.1038/s41467-019-14161-7

Harvey, P. D., & Rosenthal, J. B. (2018). Cognitive and functional deficits in people with schizophrenia: Evidence for accelerated or exaggerated aging? *Schizophrenia Research*, *196*, 14–21. https://doi.org/10.1016/j.schres.2017.05.009

Hilker, R., Helenius, D., Fagerlund, B., Skytthe, A., Christensen, K., Werge, T. M., Nordentoft, M., & Glenthøj, B. (2018). Heritability of Schizophrenia and Schizophrenia Spectrum Based on the Nationwide Danish Twin Register. *Biological Psychiatry*, *83*(6), 492–498. https://doi.org/10.1016/j.biopsych.2017.08.017

Insel, T. R. (2010). Rethinking schizophrenia. In *Nature* (Vol. 468, Issue 7321, pp. 187–193). https://doi.org/10.1038/nature09552

Kahn, R. S., Sommer, I. E., Murray, R. M., Meyer-Lindenberg, A., Weinberger, D. R., Cannon, T. D., O'Donovan, M., Correll, C. U., Kane, J. M., Van Os, J., & Insel, T. R.

# VII. REFERÈNCIES

(2015). Schizophrenia. *Nature Reviews Disease Primers*, *1*. https://doi.org/10.1038/nrdp.2015.67

Karbasforoushan, H., Duffy, B., Blackford, J. U., & Woodward, N. D. (2015). Processing speed impairment in schizophrenia is mediated by white matter integrity. *Psychological Medicine*, *45*(1), 109–120. https://doi.org/10.1017/S0033291714001111

Karlsgodt, K. H. (2016). Diffusion Imaging of White Matter in Schizophrenia: Progress and Future Directions. In *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* (Vol. 1, Issue 3, pp. 209–217). Elsevier Inc. https://doi.org/10.1016/j.bpsc.2015.12.001

Keefe, R. S. E., Perkins, D. O., Gu, H., Zipursky, R. B., Christensen, B. K., & Lieberman, J. A. (2006). A longitudinal study of neurocognitive function in individuals at-risk for psychosis. *Schizophrenia Research*, *88*(1–3), 26–35. https://doi.org/10.1016/j.schres.2006.06.041

Kelly, S., Jahanshad, N., Zalesky, A., Kochunov, P., Agartz, I., Alloza, C., Andreassen, O. A., Arango, C., Banaj, N., Bouix, S., Bousman, C. A., Brouwer, R. M., Bruggemann, J., Bustillo, J., Cahn, W., Calhoun, V., Cannon, D., Carr, V., Catts, S., … Donohoe, G. (2018). Widespread white matter microstructural differences in schizophrenia across 4322 individuals: Results from the ENIGMA Schizophrenia DTI Working Group. *Molecular Psychiatry*, *23*(5), 1261–1269. https://doi.org/10.1038/mp.2017.170

Kety, S. S. (1987). The significance of genetic factors in the etiology of schizophrenia: Results from the national study of adoptees in Denmark. *Journal of Psychiatric Research*, *21*(4), 423–429. https://doi.org/10.1016/0022-3956(87)90089-6

Kim, S. E., Kim, H. N., Yun, Y. J., Heo, S. G., Cho, J., Kwon, M. J., Chang, Y., Ryu, S., Shin, H., Shin, C., Cho, N. H., Sung, Y. A., & Kim, H. L. (2017). Meta-analysis of genome-wide SNP- A nd pathway-based associations for facets of neuroticism. *Journal of Human Genetics*, *62*(10), 903–909. https://doi.org/10.1038/jhg.2017.61

Kirov, G., Rees, E., Walters, J. T. R., Escott-Price, V., Georgieva, L., Richards, A. L., Chambert, K. D., Davies, G., Legge, S. E., Moran, J. L., McCarroll, S. A., O'Donovan, M. C., & Owen, M. J. (2014). The penetrance of copy number variations for schizophrenia and developmental delay. *Biological Psychiatry*, *75*(5), 378–385. https://doi.org/10.1016/j.biopsych.2013.07.022

Kochunov, P., Coyle, T. R., Rowland, L. M., Jahanshad, N., Thompson, P. M., Kelly, S., Du, X., Sampath, H., Bruce, H., Chiappelli, J., Ryan, M., Fisseha, F., Savransky, A., Adhikari, B., Chen, S., Paciga, S. A., Whelan, C. D., Xie, Z., Hyde, C. L., … Hong, L. E. (2017). Association of white matter with core cognitive deficits in patients with schizophrenia. *JAMA Psychiatry*, *74*(9), 958–966. https://doi.org/10.1001/jamapsychiatry.2017.2228

Kochunov, P., & Hong, L. E. (2014). Neurodevelopmental and neurodegenerative models of schizophrenia: White matter at the center stage. *Schizophrenia Bulletin*, *40*(4), 721–728. https://doi.org/10.1093/schbul/sbu070

Kochunov, P., Huang, J., Chen, S., Li, Y., Tan, S., Fan, F., Feng, W., Wang, Y., Rowland, L. M., Savransky, A., Du, X., Chiappelli, J., Chen, S., Jahanshad, N., Thompson, P. M., Ryan, M. C., Adhikari, B., Sampath, H., Cui, Y., … Elliot Hong, L. (2019). White matter in schizophrenia treatment resistance. *American Journal of Psychiatry*, *176*(10), 829–838. https://doi.org/10.1176/appi.ajp.2019.18101212

Konrad, A., & Winterer, G. (2008). Disturbed structural connectivity in schizophrenia - Primary factor in pathology or epiphenomenon? In *Schizophrenia Bulletin* (Vol. 34,

Issue 1, pp. 72–92). Oxford University Press. https://doi.org/10.1093/schbul/sbm034

Koshiyama, D., Fukunaga, M., Okada, N., Morita, K., Nemoto, K., Usui, K., Yamamori, H., Yasuda, Y., Fujimoto, M., Kudo, N., Azechi, H., Watanabe, Y., Hashimoto, N., Narita, H., Kusumi, I., Ohi, K., Shimada, T., Kataoka, Y., Yamamoto, M., … Hashimoto, R. (2020). White matter microstructural alterations across four major psychiatric disorders: mega-analysis study in 2937 individuals. *Molecular Psychiatry*, *25*(4), 883–895. https://doi.org/10.1038/s41380-019-0553-7

Krabbendam, L., Janssen, I., Bak, M., Bijl, R. V., de Graaf, R., & van Os, J. (2002). Neuroticism and low self-esteem as risk factors for psychosis. *Social Psychiatry and Psychiatric Epidemiology*, *37*(1), 1–6. https://doi.org/10.1007/s127-002-8207-y

Kuhn, S., Gritti, L., Crooks, D., & Dombrowski, Y. (2019). Oligodendrocytes in Development, Myelin Generation and Beyond. In *Cells* (Vol. 8, Issue 11). NLM (Medline). https://doi.org/10.3390/cells8111424

La Barbera, L., Vedele, F., Nobili, A., Krashia, P., Spoleti, E., Latagliata, E. C., Cutuli, D., Cauzzi, E., Marino, R., Viscomi, M. T., Petrosini, L., Puglisi-Allegra, S., Melone, M., Keller, F., Mercuri, N. B., Conti, F., & D'Amelio, M. (2021). Nilotinib restores memory function by preventing dopaminergic neuron degeneration in a mouse model of Alzheimer's Disease. *Progress in Neurobiology*, 102031. https://doi.org/10.1016/j.pneurobio.2021.102031

Laere, E., Tee, S. F., & Tang, P. Y. (2018). Assessment of cognition in schizophrenia using trail making test: A meta-analysis. *Psychiatry Investigation*, *15*(10), 945–955. https://doi.org/10.30773/pi.2018.07.22

Lahera, G., Ruiz, A., Brañas, A., Vicens, M., & Orozco, A. (2017). Reaction time, processing speed and sustained attention in schizophrenia: impact on social functioning. *Revista de Psiquiatria y Salud Mental*, *10*(4), 197–205. https://doi.org/10.1016/j.rpsm.2017.04.001

Lam, M., Chen, C. Y., Li, Z., Martin, A. R., Bryois, J., Ma, X., Gaspar, H., Ikeda, M., Benyamin, B., Brown, B. C., Liu, R., Zhou, W., Guan, L., Kamatani, Y., Kim, S. W., Kubo, M., Kusumawardhani, A. A. A. A., Liu, C. M., Ma, H., … Huang, H. (2019). Comparative genetic architectures of schizophrenia in East Asian and European populations. *Nature Genetics*, *51*(12), 1670–1678. https://doi.org/10.1038/s41588-019-0512-x

Lee, P. H., Anttila, V., Won, H., Feng, Y. C. A., Rosenthal, J., Zhu, Z., Tucker-Drob, E. M., Nivard, M. G., Grotzinger, A. D., Posthuma, D., Wang, M. M. J., Yu, D., Stahl, E. A., Walters, R. K., Anney, R. J. L., Duncan, L. E., Ge, T., Adolfsson, R., Banaschewski, T., … Smoller, J. W. (2019). Genomic Relationships, Novel Loci, and Pleiotropic Mechanisms across Eight Psychiatric Disorders. *Cell*, *179*(7), 1469-1482.e11. https://doi.org/10.1016/j.cell.2019.11.020

Leitinger, B. (2014). Discoidin domain receptor functions in physiological and pathological conditions. In *International Review of Cell and Molecular Biology* (Vol. 310, pp. 39–87). Elsevier Inc. https://doi.org/10.1016/B978-0-12-800180-6.00002-5

Lemus, H. N., Warrington, A. E., & Rodriguez, M. (2018). Multiple Sclerosis: Mechanisms of Disease and Strategies for Myelin and Axonal Repair. In *Neurologic Clinics* (Vol. 36, Issue 1, pp. 1–11). W.B. Saunders. https://doi.org/10.1016/j.ncl.2017.08.002

Mandelbaum, D. E., & de la Monte, S. M. (2017). Adverse Structural and Functional Effects of Marijuana on the Brain: Evidence Reviewed. In *Pediatric Neurology* (Vol. 66, pp. 12–20). Elsevier Inc. https://doi.org/10.1016/j.pediatrneurol.2016.09.004

# VII. REFERÈNCIES

Marshall, C. R., Howrigan, D. P., Merico, D., Thiruvahindrapuram, B., Wu, W., Greer, D. S., Antaki, D., Shetty, A., Holmans, P. A., Pinto, D., Gujral, M., Brandler, W. M., Malhotra, D., Wang, Z., Fuentes Fajarado, K. V., Maile, M. S., Ripke, S., Agartz, I., Albus, M., … Sebat, J. (2017). Contribution of copy number variants to schizophrenia from a genome-wide study of 41,321 subjects. *Nature Genetics*, *49*(1), 27–35. https://doi.org/10.1038/ng.3725

McGorry, P., & Nelson, B. (2016). Why we need a transdiagnostic staging approach to emerging psychopathology, early diagnosis, and treatment. In *JAMA Psychiatry* (Vol. 73, Issue 3, pp. 191–192). American Medical Association. https://doi.org/10.1001/jamapsychiatry.2015.2868

McGuffin, P. & Gottesman, I. I. (1999). Risk factors for schizophrenia. *The New England Journal of Medicine*, *341*(5), 370–372. https://www-proquest-com.sabidi.urv.cat/docview/223939080/fulltextPDF/9E4E780144684220PQ/1?accountid=14733

Menkes, M. W., Armstrong, K., Blackford, J. U., Heckers, S., & Woodward, N. D. (2019). Neuropsychological functioning in early and chronic stages of schizophrenia and psychotic bipolar disorder. *Schizophrenia Research*, *206*, 413–419. https://doi.org/10.1016/j.schres.2018.10.009

Michaelson, J. J. (2017). Genetic Approaches to Understanding Psychiatric Disease. In *Neurotherapeutics* (Vol. 14, Issue 3, pp. 564–581). Springer New York LLC. https://doi.org/10.1007/s13311-017-0551-x

Mighdoll, M. I., Tao, R., Kleinman, J. E., & Hyde, T. M. (2015). Myelin, myelin-related disorders, and psychosis. In *Schizophrenia Research* (Vol. 161, Issue 1, pp. 85–93). Elsevier. https://doi.org/10.1016/j.schres.2014.09.040

Mo, X. B., Lei, S. F., Qian, Q. Y., Guo, Y. F., Zhang, Y. H., & Zhang, H. (2019). Integrative analysis revealed potential causal genetic and epigenetic factors for multiple sclerosis. *Journal of Neurology*, *266*(11), 2699–2709. https://doi.org/10.1007/s00415-019-09476-w

Mollon, J., & Reichenberg, A. (2018). Cognitive development prior to onset of psychosis. In *Psychological Medicine* (Vol. 48, Issue 3, pp. 392–403). Cambridge University Press. https://doi.org/10.1017/S0033291717001970

Moreno-Küstner, B., Martín, C., & Pastor, L. (2018). Prevalence of psychotic disorders and its association with methodological issues. A systematic review and meta-analyses. In *PLoS ONE* (Vol. 13, Issue 4). Public Library of Science. https://doi.org/10.1371/journal.pone.0195687

Muzio, M. R., & Cascella, M. (2020). Histology, Axon. In *StatPearls*. http://www.ncbi.nlm.nih.gov/pubmed/32119275

Nucifora, F. C., Woznica, E., Lee, B. J., Cascella, N., & Sawa, A. (2019). Treatment resistant schizophrenia: Clinical, biological, and therapeutic perspectives. In *Neurobiology of Disease* (Vol. 131, p. 104257). Academic Press Inc. https://doi.org/10.1016/j.nbd.2018.08.016

Nuechterlein, K. H., Barch, D. M., Gold, J. M., Goldberg, T. E., Green, M. F., & Heaton, R. K. (2004). Identification of separable cognitive factors in schizophrenia. *Schizophrenia Research*, *72*(1), 29–39. https://doi.org/10.1016/j.schres.2004.09.007

Ojeda, N., Peña, J., Sánchez, P., Elizagárate, E., & Ezcurra, J. (2008). Processing speed mediates the relationship between verbal memory, verbal fluency, and functional

outcome in chronic schizophrenia. *Schizophrenia Research*, *101*(1–3), 225–233. https://doi.org/10.1016/j.schres.2007.12.483

Owen, M J, Williams, N. M., & O'Donovan, M. C. (2004). The molecular genetics of schizophrenia: new findings promise new insights. *Molecular Psychiatry*, *9*(1), 14–27. http://www.ncbi.nlm.nih.gov/pubmed/14581932

Owen, Michael J., Sawa, A., & Mortensen, P. B. (2016). Schizophrenia. In *The Lancet* (Vol. 388, Issue 10039, pp. 86–97). Lancet Publishing Group. https://doi.org/10.1016/S0140-6736(15)01121-6

Pagan, F. L., Hebron, M. L., Wilmarth, B., Torres-Yaghi, Y., Lawler, A., Mundel, E. E., Yusuf, N., Starr, N. J., Arellano, J., Howard, H. H., Peyton, M., Matar, S., Liu, X., Fowler, A. J., Schwartz, S. L., Ahn, J., & Moussa, C. (2019). Pharmacokinetics and pharmacodynamics of a single dose Nilotinib in individuals with Parkinson's disease. *Pharmacology Research and Perspectives*, *7*(2). https://doi.org/10.1002/prp2.470

Pasternak, O., Kelly, S., Sydnor, V. J., & Shenton, M. E. (2018). Advances in microstructural diffusion neuroimaging for psychiatric disorders. In *NeuroImage* (Vol. 182, pp. 259–282). Academic Press Inc. https://doi.org/10.1016/j.neuroimage.2018.04.051

Penke, L., Maniega, S. M., Murray, C., Gow, A. J., Valdés Hernández, M. C., Clayden, J. D., Starr, J. M., Wardlaw, J. M., Bastin, M. E., & Deary, I. J. (2010). A general factor of brain white matter integrity predicts information processing speed in healthy older people. *Journal of Neuroscience*, *30*(22), 7569–7574. https://doi.org/10.1523/JNEUROSCI.1553-10.2010

Peralta, V., Moreno-Izco, L., Calvo-Barrena, L., & Cuesta, M. J. (2013). The low- and higher-order factor structure of symptoms in patients with a first episode of psychosis. *Schizophrenia Research*, *147*(1), 116–124. https://doi.org/10.1016/j.schres.2013.03.018

Peters, B. D., Blaas, J., & de Haan, L. (2010). Diffusion tensor imaging in the early phase of schizophrenia: what have we learned? *Journal of Psychiatric Research*, *44*(15), 993–1004. https://doi.org/10.1016/j.jpsychires.2010.05.003

Peters, B. D., & Karlsgodt, K. H. (2015). White matter development in the early stages of psychosis. In *Schizophrenia Research* (Vol. 161, Issue 1, pp. 61–69). Schizophr Res. https://doi.org/10.1016/j.schres.2014.05.021

Picton, J. D., Brackett Marino, A., & Lovin Nealy, K. (2018). Benzodiazepine use and cognitive decline in the elderly. In *American Journal of Health-System Pharmacy* (Vol. 75, Issue 1, pp. e6–e12). American Society of Health-Systems Pharmacy. https://doi.org/10.2146/ajhp160381

Poletti, S., Mazza, E., Bollettini, I., Falini, A., Smeraldi, E., Cavallaro, R., & Benedetti, F. (2016). The COMT Val158Met polymorphism moderates the association between cognitive functions and white matter microstructure in schizophrenia. *Psychiatric Genetics*, *26*(5), 193–202. https://doi.org/10.1097/YPG.0000000000000130

Pomarol-Clotet, E., Canales-Rodríguez, E., Salvador, R., Sarró, S., Gomar, J., Vila, F., Ortiz-Gil, J., Iturria-Medina, Y., Capdevila, A., & Mckenna, P. (2010). Medial prefrontal cortex pathology in schizophrenia as revealed by convergent findings from multimodal imaging. *Molecular Psychiatry*, *15*, 823–830. https://doi.org/10.1038/mp.2009.146

Prado, C. E., Watt, S., & Crowe, S. F. (2018). A meta-analysis of the effects of antidepressants on cognitive functioning in depressed and non-depressed samples.

In *Neuropsychology Review* (Vol. 28, Issue 1, pp. 32–72). Springer New York LLC. https://doi.org/10.1007/s11065-018-9369-5

Prata, D. P., Kanaan, R. A., Barker, G. J., Shergill, S., Woolley, J., Georgieva, L., Picchioni, M. M., Kravariti, E., Walshe, M., Allin, M., Toulopoulou, T., Bramon, E., Mcdonald, C., Giampietro, V., Murray, R. M., Brammer, M., O'donovan, M., & Mcguire, P. (2013). ) r Risk Variant of Oligodendrocyte Lineage Transcription Factor 2 Is Associated With Reduced White Matter Integrity. *Human Brain Mapping*, *34*, 2025–2031. https://doi.org/10.1002/hbm.22045

Raabe, F. J., Slapakova, L., Rossner, M. J., Cantuti-Castelvetri, L., Simons, M., Falkai, P. G., & Schmitt, A. (2019). Oligodendrocytes as A New Therapeutic Target in Schizophrenia: From Histopathological Findings to Neuron-Oligodendrocyte Interaction. In *Cells* (Vol. 8, Issue 12). NLM (Medline). https://doi.org/10.3390/cells8121496

Radua, J., Ramella-Cravaro, V., Ioannidis, J. P. A., Reichenberg, A., Phiphopthatsanee, N., Amir, T., Yenn Thoo, H., Oliver, D., Davies, C., Morgan, C., McGuire, P., Murray, R. M., & Fusar-Poli, P. (2018). What causes psychosis? An umbrella review of risk and protective factors. In *World Psychiatry* (Vol. 17, Issue 1, pp. 49–66). Blackwell Publishing Ltd. https://doi.org/10.1002/wps.20490

Rammal, H., Saby, C., Magnien, K., Van-Gulick, L., Garnotel, R., Buache, E., El Btaouri, H., Jeannesson, P., & Morjani, H. (2016). Discoidin domain receptors: Potential actors and targets in cancer. In *Frontiers in Pharmacology* (Vol. 7, Issue MAR, p. 55). https://doi.org/10.3389/fphar.2016.00055

Reitan, R. M., & Wolfson, D. (1985). *The Halstead-Reitan Neuropsychological Test Battery: Therapy and clinical interpretation*. Neuropsychological Press.

Ríos-Lago, M., & Periañez, J. A. (2010). Attention and Speed of information processing. In R. F. T. In G. Koob & M. Le Moal (Eds.), *Encyclopedia of Behavioral Neuroscience*.

Ripke, S., Neale, B. M., Corvin, A., Walters, J. T. R., Farh, K. H., Holmans, P. A., Lee, P., Bulik-Sullivan, B., Collier, D. A., Huang, H., Pers, T. H., Agartz, I., Agerbo, E., Albus, M., Alexander, M., Amin, F., Bacanu, S. A., Begemann, M., Belliveau, R. A., … O'Donovan, M. C. (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature*, *511*(7510), 421–427. https://doi.org/10.1038/nature13595

Roig, B., Abasolo, N., Moyano, S., Martorell, L., & Vilella, E. (2012). Increased expression of the spliced DDR1c isoform in brain tissues from schizophrenia patients. *Journal of Psychiatric Research*, *46*(6), 825–827. http://www.ncbi.nlm.nih.gov/pubmed/22421314

Roig, B., Franco-Pons, N., Martorell, L., Tomas, J., Vogel, W. F., & Vilella, E. (2010). Expression of the tyrosine kinase discoidin domain receptor 1 (DDR1) in human central nervous system myelin. *Brain Research*, *1336*, 22–29. https://doi.org/10.1016/j.brainres.2010.03.099

Roig, B., Moyano, S., Martorell, L., Costas, J., & Vilella, E. (2012). The discoidin domain receptor 1 gene has a functional A2RE sequence. *Journal of Neurochemistry*, *120*(3), 408–418. http://www.ncbi.nlm.nih.gov/pubmed/22077590

Roig, B., Virgos, C., Franco, N., Martorell, L., Valero, J., Costas, J., Carracedo, A., Labad, A., & Vilella, E. (2007). The discoidin domain receptor 1 as a novel susceptibility gene for schizophrenia. *Molecular Psychiatry*, *12*(9), 833–841. http://www.ncbi.nlm.nih.gov/pubmed/17440435

Roussos, P., & Haroutunian, V. (2014). Schizophrenia: susceptibility genes and

oligodendroglial and myelin related abnormalities. *Frontiers in Cellular Neuroscience*, *8*, 5. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3896818&tool=pmcentrez&rendertype=abstract

Saczynski, J. S., Rosen, A. B., McCammon, R. J., Zivin, K., Andrade, S. E., Langa, K. M., Vijan, S., Pirraglia, P. A., & Briesacher, B. A. (2015). Antidepressant use and cognitive decline: The health and retirement study. *American Journal of Medicine*, *128*(7), 739–746. https://doi.org/10.1016/j.amjmed.2015.01.007

Samartzis, L., Dima, D., Fusar-Poli, P., & Kyriakopoulos, M. (2014). White Matter Alterations in Early Stages of Schizophrenia: A Systematic Review of Diffusion Tensor Imaging Studies. *Journal of Neuroimaging*, *24*(2), 101–110. https://doi.org/10.1111/j.1552-6569.2012.00779.x

Schaefer, J., Giangrande, E., Weinberger, D. R., & Dickinson, D. (2013). The global cognitive impairment in schizophrenia: Consistent over decades and around the world. In *Schizophrenia Research* (Vol. 150, Issue 1, pp. 42–50). Schizophr Res. https://doi.org/10.1016/j.schres.2013.07.009

Scheel, M., Prokscha, T., Bayerl, M., Gallinat, J., & Montag, C. (2013). Myelination deficits in schizophrenia: evidence from diffusion tensor imaging. *Brain Structure & Function*, *218*(1), 151–156. https://doi.org/10.1007/s00429-012-0389-2

Sheffield, J. M., Karcher, N. R., & Barch, D. M. (2018). Cognitive Deficits in Psychotic Disorders: A Lifespan Perspective. In *Neuropsychology Review* (Vol. 28, Issue 4, pp. 509–533). Springer New York LLC. https://doi.org/10.1007/s11065-018-9388-2

Skene, N. G., Bryois, J., Bakken, T. E., Breen, G., Crowley, J. J., Gaspar, H. A., Giusti-Rodriguez, P., Hodge, R. D., Miller, J. A., Muñoz-Manchado, A. B., O'Donovan, M. C., Owen, M. J., Pardiñas, A. F., Ryge, J., Walters, J. T. R., Linnarsson, S., Lein, E. S., Sullivan, P. F., & Hjerling-Leffler, J. (2018). Genetic identification of brain cell types underlying schizophrenia. *Nature Genetics*, *50*(6), 825–833. https://doi.org/10.1038/s41588-018-0129-5

Smigielski, L., Jagannath, V., Rössler, W., Walitza, S., & Grünblatt, E. (2020). Epigenetic mechanisms in schizophrenia and other psychotic disorders: a systematic review of empirical human findings. *Molecular Psychiatry*, *25*(8), 1718–1748. https://doi.org/10.1038/s41380-019-0601-3

Smoller, J. W., Kendler, K., Craddock, N., Lee, P. H., Neale, B. M., Nurnberger, J. N., Ripke, S., Santangelo, S., Sullivan, P. S., Neale, B. N., Purcell, S., Anney, R., Buitelaar, J., Fanous, A., Faraone, S. F., Hoogendijk, W., Lesch, K. P., Levinson, D. L., Perlis, R. P., … O'Donovan, M. (2013). Identification of risk loci with shared effects on five major psychiatric disorders: A genome-wide analysis. *The Lancet*, *381*(9875), 1371–1379. https://doi.org/10.1016/S0140-6736(12)62129-1

Suen, Y. N., Wong, S. M. Y., Hui, C. L. M., Chan, S. K. W., Lee, E. H. M., Chang, W. C., & Chen, E. Y. H. (2019). *International Review of Psychiatry Late-onset psychosis and very-late-onset-schizophrenia-like-psychosis: an updated systematic review Late-onset psychosis and very-late-onset-schizophrenia-like-psychosis: an updated systematic review*. https://doi.org/10.1080/09540261.2019.1670624

Sullivan, K. E. (2019). Chromosome 22q11.2 deletion syndrome and DiGeorge syndrome. In *Immunological Reviews* (Vol. 287, Issue 1, pp. 186–201). Blackwell Publishing Ltd. https://doi.org/10.1111/imr.12701

Takahashi, N., Sakurai, T., Davis, K. L., & Buxbaum, J. D. (2011). Linking oligodendrocyte and myelin dysfunction to neurocircuitry abnormalities in

schizophrenia. *Progress in Neurobiology*, *93*(1), 13–24. https://doi.org/10.1016/j.pneurobio.2010.09.004

Tirapu Ustárroz, J., Luna Lario, P., Hernáez Goñi, P., & García Suescun, I. (2011). Relación entre la sustancia blanca y las funciones cognitivas. *Revista de Neurología*, *52*(12), 725. https://doi.org/10.33588/rn.5212.2010554

Tirapu Ustárroz, J., Maestú Unturbe, F., & Ríos Lago, M. (2008). Neurocognición y esquizofrenia. In *Manual de Neuropsicología* (Vol. 2008, p. 389). Viguera Editores SL.

Tiwari, A. K., Zai, C. C., Muller, D. J., & Kennedy, J. L. (2010). Genetics in schizophrenia: where are we and what next? *Dialogues in Clinical Neuroscience*, *12*(3), 289–303.

Tomassy, G. S., Dershowitz, L. B., & Arlotta, P. (2016). Diversity Matters: A Revised Guide to Myelination. In *Trends in Cell Biology* (Vol. 26, Issue 2, pp. 135–147). Elsevier Ltd. https://doi.org/10.1016/j.tcb.2015.09.002

Uranova, N., Orlovskaya, D., Vikhreva, O., Zimina, I., Kolomeets, N., Vostrikov, V., & Rachmanova, V. (2001). Electron microscopy of oligodendroglia in severe mental illness. *Brain Research Bulletin*, *55*(5), 597–610. https://doi.org/10.1016/S0361-9230(01)00528-7

Valent, A., Meddeb, M., Danglot, G., Duverger, A., Nguyen, V. C., & Bernheim, A. (1996). Assignment of the NTRK4 (trkE) gene to chromosome 6p21. *Human Genetics*, *98*(1), 12–15. https://doi.org/10.1007/s004390050152

Van Assche, L., Morrens, M., Luyten, P., Van de Ven, L., & Vandenbulcke, M. (2017). The neuropsychology and neurobiology of late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: A critical review. In *Neuroscience and Biobehavioral Reviews* (Vol. 83, pp. 604–621). Elsevier Ltd. https://doi.org/10.1016/j.neubiorev.2017.08.024

Van Os, J., Rutten, B. P., & Poulton, R. (2008). Gene-environment interactions in schizophrenia: review of epidemiological findings and future directions. *Schizophrenia Bulletin*, *34*(6), 1066–1082. https://doi.org/10.1093/schbul/sbn117

Vaskinn, A., Haatveit, B., Melle, I., Andreassen, O. A., Ueland, T., & Sundet, K. (2020). Cognitive Heterogeneity across Schizophrenia and Bipolar Disorder: A Cluster Analysis of Intellectual Trajectories. *Journal of the International Neuropsychological Society*, *26*(9), 860–872. https://doi.org/10.1017/S1355617720000442

Vilella, E., Gas, C., Garcia-Ruiz, B., & Rivera, F. J. (2019). Expression of DDR1 in the CNS and in myelinating oligodendrocytes. *Biochimica et Biophysica Acta - Molecular Cell Research*, *1866*(11), 0–1. https://doi.org/10.1016/j.bbamcr.2019.04.010

Voineskos, A. N. (2015). Genetic underpinnings of white matter "connectivity": Heritability, risk, and heterogeneity in schizophrenia. *Schizophrenia Research*, *161*(1), 50–60. http://www.sciencedirect.com/science/article/pii/S0920996414002485

Voineskos, A. N., Felsky, D., Kovacevic, N., Tiwari, A. K., Zai, C., Chakravarty, M. M., Lobaugh, N. J., Shenton, M. E., Rajji, T. K., Miranda, D., Pollock, B. G., Mulsant, B. H., McIntosh, A. R., & Kennedy, J. L. (2013). Oligodendrocyte genes, white matter tract integrity, and cognition in schizophrenia. *Cerebral Cortex (New York, N.Y. : 1991)*, *23*(9), 2044–2057. https://doi.org/10.1093/cercor/bhs188

Vos, T., Barber, R. M., Bell, B., Bertozzi-Villa, A., Biryukov, S., Bolliger, I., Charlson, F., Davis, A., Degenhardt, L., Dicker, D., Duan, L., Erskine, H., Feigin, V. L., Ferrari, A.

J., Fitzmaurice, C., Fleming, T., Graetz, N., Guinovart, C., Haagsma, J., … Murray, C. J. L. (2015). Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: A systematic analysis for the Global Burden of Disease Study 2013. *The Lancet*, *386*(9995), 743–800. https://doi.org/10.1016/S0140-6736(15)60692-4

Weinberger, D. R. (1987). Implications of Normal Brain Development for the Pathogenesis of Schizophrenia. *Archives of General Psychiatry*, *44*(7), 660–669. https://doi.org/10.1001/archpsyc.1987.01800190080012

Wendt, F. R., Pathak, G. A., Tylee, D. S., Goswami, A., & Polimanti, R. (2020). Heterogeneity and Polygenicity in Psychiatric Disorders: A Genome-Wide Perspective. *Chronic Stress*, *4*, 247054702092484. https://doi.org/10.1177/2470547020924844

Wozniak, J. R., & Lim, K. O. (2006). Advances in white matter imaging: A review of in vivo magnetic resonance methodologies and their applicability to the study of development and aging. In *Neuroscience and Biobehavioral Reviews* (Vol. 30, Issue 6, pp. 762–774). NIH Public Access. https://doi.org/10.1016/j.neubiorev.2006.06.003

Wykes, T., Huddy, V., Cellard, C., McGurk, S. R., & Czobor, P. (2011). A meta-analysis of cognitive remediation for schizophrenia: Methodology and effect sizes. In *American Journal of Psychiatry* (Vol. 168, Issue 5, pp. 472–485). Am J Psychiatry. https://doi.org/10.1176/appi.ajp.2010.10060855

Yang, A. C., & Tsai, S. J. (2017). New targets for schizophrenia treatment beyond the dopamine hypothesis. In *International Journal of Molecular Sciences* (Vol. 18, Issue 8). MDPI AG. https://doi.org/10.3390/ijms18081689

Yang, M., Gao, S., & Zhang, X. (2020). Cognitive deficits and white matter abnormalities in never-treated first-episode schizophrenia. *Translational Psychiatry*, *10*(1). https://doi.org/10.1038/s41398-020-01049-0

Young, K. M., Psachoulia, K., Tripathi, R. B., Dunn, S. J., Cossell, L., Attwell, D., Tohyama, K., & Richardson, W. D. (2013). Oligodendrocyte dynamics in the healthy adult CNS: Evidence for myelin remodeling. *Neuron*, *77*(5), 873–885. https://doi.org/10.1016/j.neuron.2013.01.006

Zwicker, A., Denovan-Wright, E. M., & Uher, R. (2018). Gene-environment interplay in the etiology of psychosis. *Psychological Medicine*, *48*(12), 1925–1936. https://doi.org/10.1017/S003329171700383X

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