

DDR1, MIELINA I PSICOSI

Elisabet Vilella

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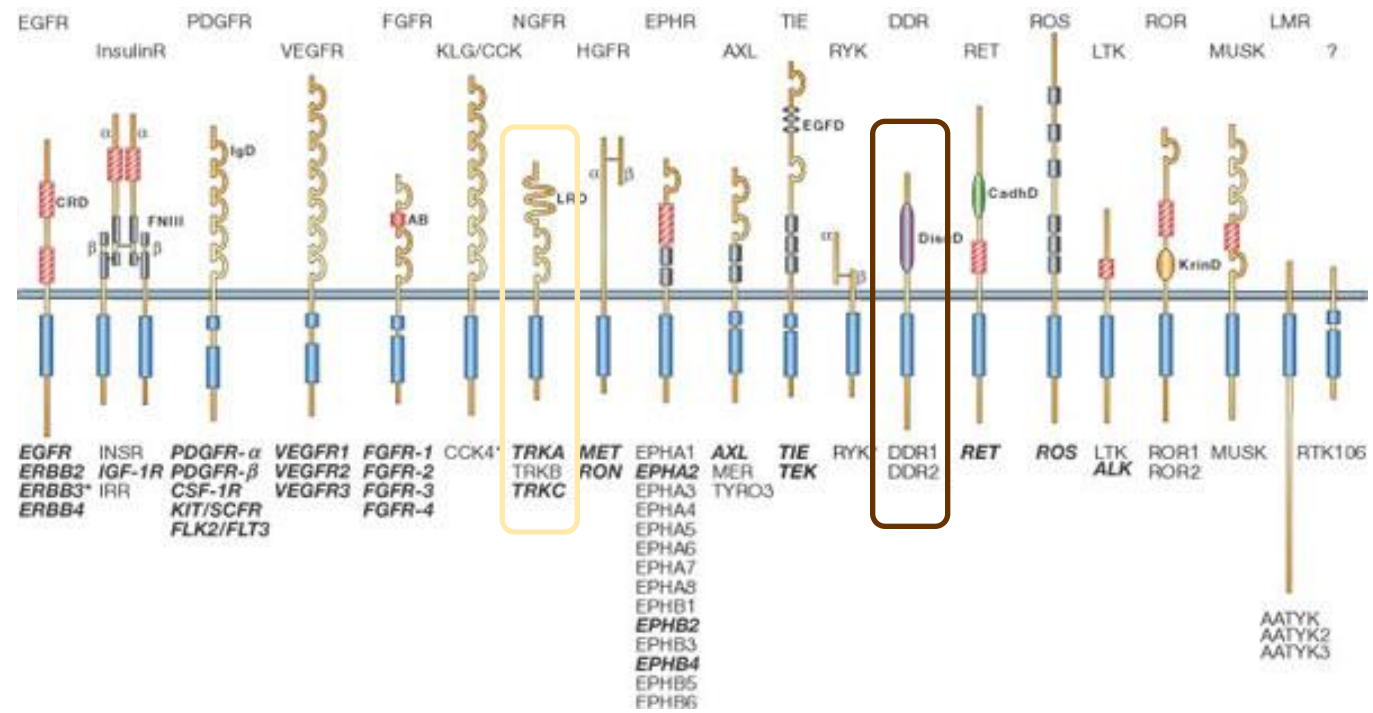


Esquizofrènia

- Psicosi endògena severa
 - Al·lucinacions
 - Deliris
 - Trastorns del pensament
 - Deteriorament cognitiu
- Edat d'inici 18 anys homes, 21 anys dones
- Prevalença 1%
- 70-80% causa genètica

Hipòtesi del neurodesenvolupament

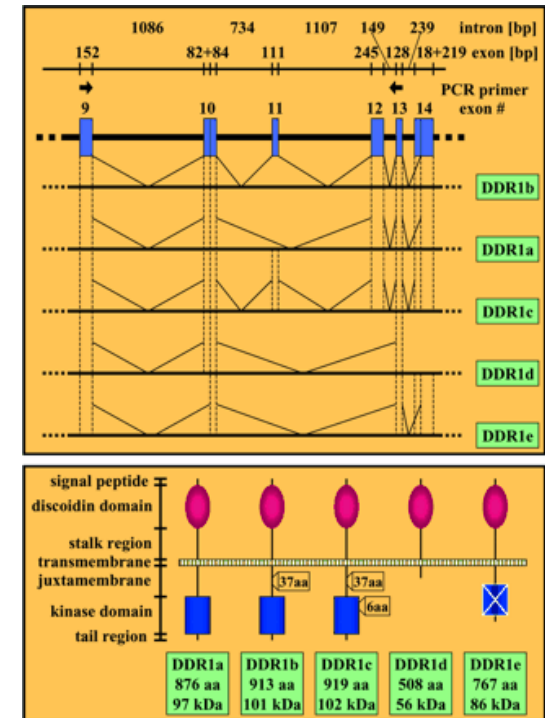
GIP, busca un nou gen candidat per l'esquizofrènia



Human receptor protein-tyrosine kinases
Blume-Jensen & Hunter. Nature 2001

Discoidin domain receptor 1 (DDR1)

- Receptor tirosina cinasa (TKR)
- Gen al cr. 6p21.3
- Expressió molt activa en la neurogènesi (rosegadors)
- Involucrat en proliferació (neoplàsies)
- Col·lagen, únic lligand identificat
- Cinc isoformes (DDR1 a, b, c, d, e)



Human DDR1 isoforms
Alves et al. FASEB J. 2001

Hipòtesi I (1999)

El receptor DDR1 s'expressa en neurones i és important per al neurodesenvolupament.

Mutacions en el gen DDR1 poden comportar alteracions en el neurodesenvolupament i conseqüentment estar associades a l'aparició de l'esquizofrènia.

Objectius

1. Rastreig del gen DDR1 humà en DNA de pacients esquizofrènics per identificar mutacions.
2. Caracteritzar l'expressió de DDR1 en les etapes del neurodesenvolupament en ratolí.

EXPRESSION OF DISCOIDIN DOMAIN RECEPTOR 1 DURING MOUSE BRAIN DEVELOPMENT FOLLOWS THE PROGRESS OF MYELINATION

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 J. M. UREÑA,^d E. SORIANO,^d J. A. DEL RIO^d
 AND E. VILELLA^{a,b*}

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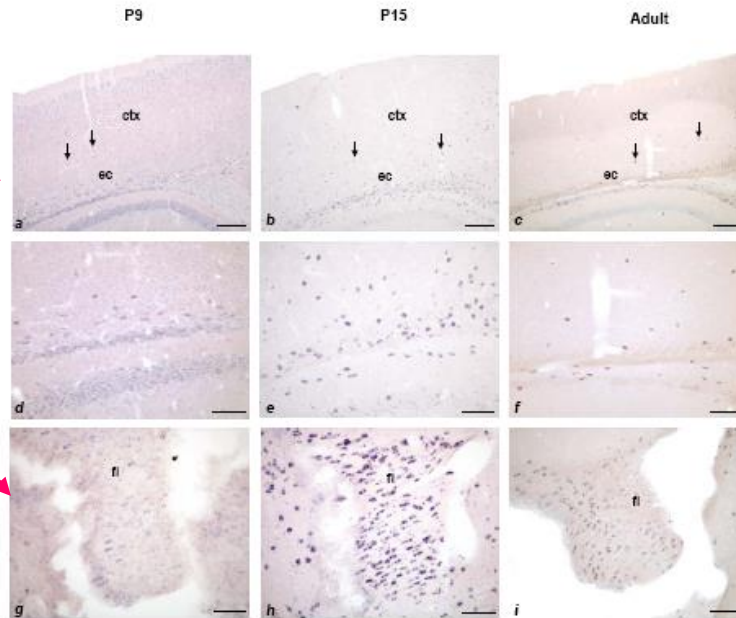
sheath. © 2006 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: carnosine, discoidin domain, myelin, oligodendrocytes.

Tyrosine kinase receptors (RTKs) are important mediators of intracellular signal transduction pathways that govern growth, differentiation and developmental signals (Blume-Jensen and Hunter, 2001). Discoidin domain receptors, DDR1 and DDR2, are a novel subfamily of RTKs. In their extracellular region both contain a discoidin domain, a homology that was first described in the lectin *Discoideum discoideum* that contains the

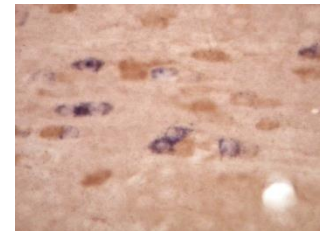


Feixos de mielina



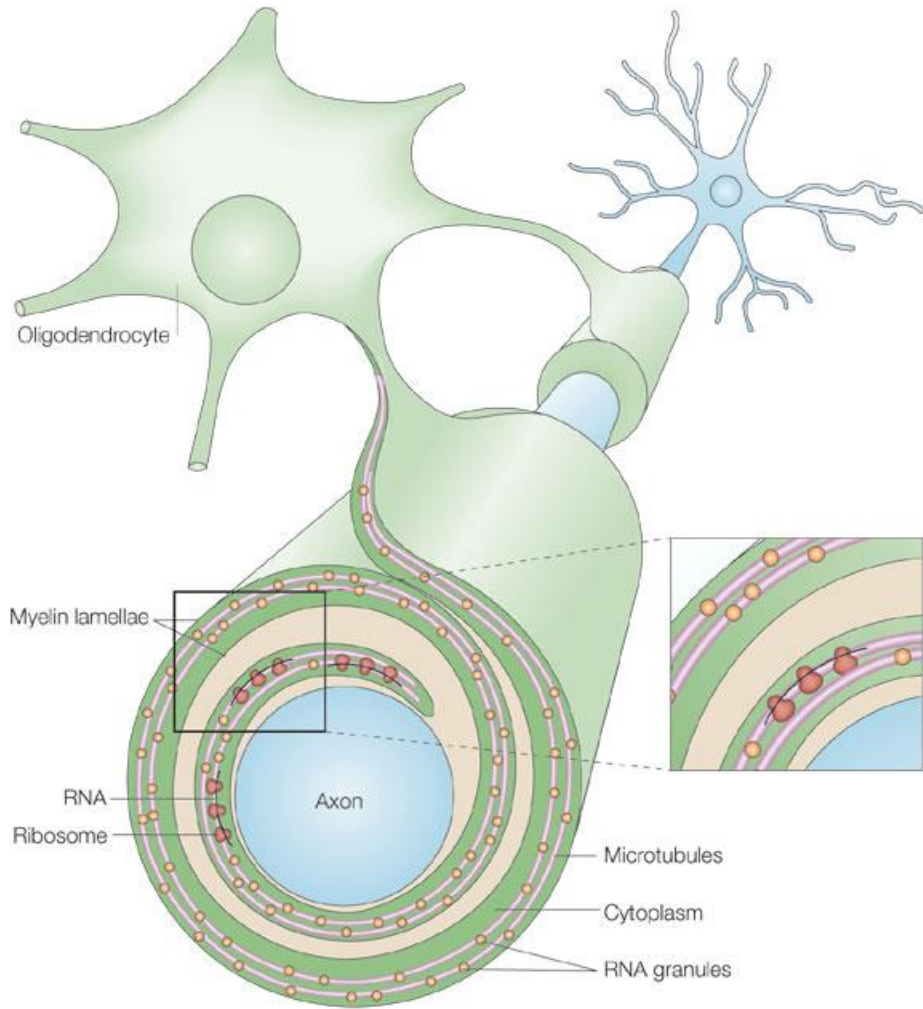
Càpsula externa

Fimbria



DDR1 mRNA
oligodendròcit

DDR1 s'expressa principalment en oligodendròcits, no en neurons



MAG
 MBP
 MOBP
 OLIG2

ORIGINAL ARTICLE

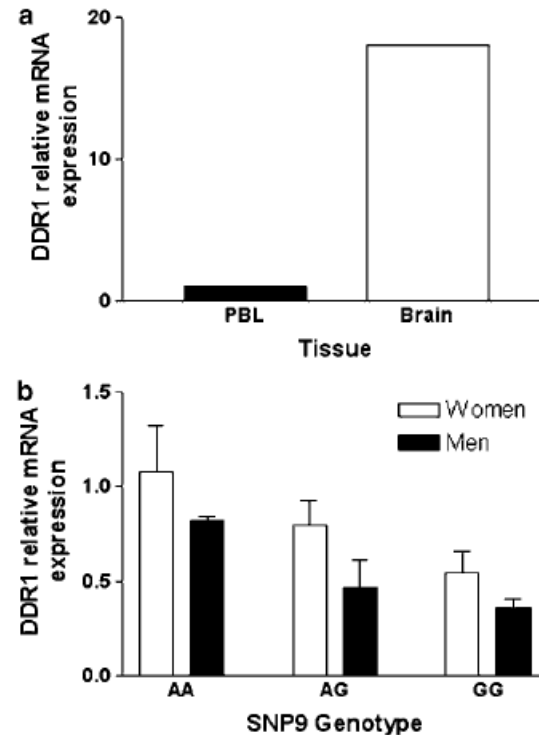
The discoidin domain receptor 1 as a novel susceptibility gene for schizophrenia

B Roig^{1,2,4}, C Virgos^{1,2,4,5}, N Franco^{1,2}, L Martorell^{1,2}, J Valero^{1,2}, J Costas³, A Carracedo³, A Labad^{1,2} and E Vilella^{1,2}

¹*Ctra. de l'Institut Pere Mata s/n, University Psychiatric Hospital, Pere Mata Institute, Reus, Tarragona, Spain;* ²*Psychiatric Unit of the Faculty of Medicine and Health Sciences, Rovira i Virgili University, Reus, Tarragona, Spain and* ³*Genomic Medicine Group-USC, Fundación Pública Galega de Medicina Xenómica, University of Santiago Hospital Complex, Santiago de Compostela, Spain*

Evidence suggests that myelin alterations could predispose to schizophrenia. Reduced expression of several myelin genes has been observed in schizophrenia patients. Recently, we identified the discoidin domain receptor 1 (*DDR1*; located at human chromosome 6p21.3) as a myelin gene in the mouse model and in a human oligodendroglial cell line. In the present study we screened for single nucleotide polymorphisms (SNPs) in the DNA from 100 schizophrenia patients. We identified a novel mutation within exon 10 that produces the amino-acid substitution N502S in the a–d isoforms, and M475V in the e isoform. However the frequency of the mutation (2%) was similar in schizophrenia patients and in control subjects. In a case–control assessment with 389 schizophrenic patients and 615 controls, we identified one SNP (SNP9, rs1049623) associated with schizophrenia (odds ratio = 1.44, 95% confidence interval: 1.15–1.79, adjusted $P=0.0016$). This association was confirmed in haplotype analysis; the SNPs 9–10–11 (rs1049623, rs2267641 and rs2239518) haplotype remaining significant even after adjustment for multiple testing (adjusted $P=0.0136$). Of note was a strong gender dependence in the association, that is, statistical significance restricted to men (adjusted P -value = 0.0002). Regression analysis of *DDR1* mRNA expression in peripheral blood lymphocytes from schizophrenia patients showed that the presence of the G allele significantly decreased the relative number of mRNA copies in a dose-dependent manner ($P=0.003$). These data suggest that the risk haplotype tags a *cis*-acting variant involved in the transcription regulation system of the gene. In conclusion, we propose the *DDR1* as a new susceptibility gene for schizophrenia.

Molecular Psychiatry advance online publication, 17 April 2007; doi:10.1038/sj.mp.4001995



Limfòcits perifèrics i cervell humà

Limfòcits perifèrics

Figure 2 Relative *DDR1* mRNA expression measured by real-time RT-PCR. (a) Brain *DDR1* mRNA expression compared to PBL. Whole brain expresses 18 times more *DDR1* mRNA than pooled RNA from control lymphocytes ($P=0.0001$). (b) Relative expression of *DDR1* in PBL RNA from schizophrenia patients segregated according to gender and SNP9 genotype. Each individual value was calculated with respect to the mean of the AA homozygote value. Linear regression analysis with gender, age and SNP9 genotype as independent variables showed a significant association of *DDR1* expression and SNP9 genotype ($P=0.003$). Although men showed a trend towards lower levels of *DDR1* expression, the gender variable did not significantly enter into the equation ($P=0.085$). Age was not associated with *DDR1* expression ($P=0.152$). Schizophrenia patients homozygous for the SNP9 G allele ($N=10$) had decreased expression of *DDR1* compared to those who were GA heterozygous ($N=10$) who, in turn, had less than those who were AA homozygous ($N=10$, $P=0.003$).

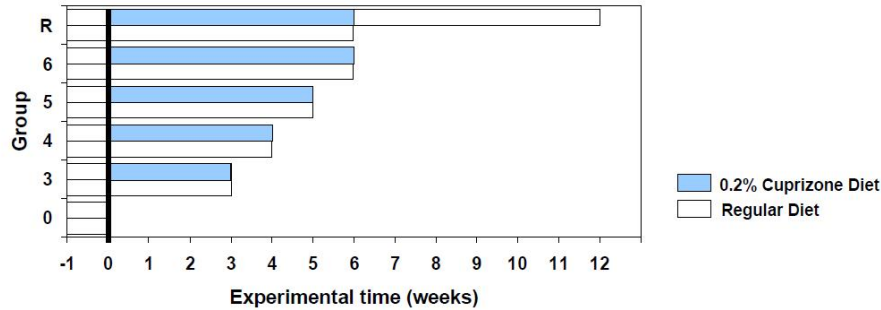
Discoidin Domain Receptor 1, a Tyrosine Kinase Receptor, is Upregulated in an Experimental Model of Remyelination and During Oligodendrocyte Differentiation In Vitro

Neus Franco-Pons · Jordi Tomàs · Bàrbara Roig ·
Carme Auladell · Lourdes Martorell · Elisabet Vilella

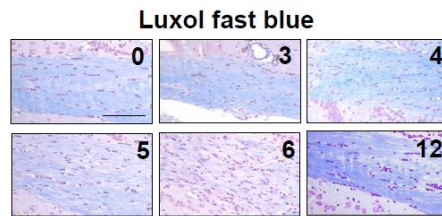
Received: 22 Jan
© Humana Press

Abstract The expression of Discoidin Domain Receptor 1 (DDR1) is upregulated in experimental myelin damage areas (corpus callosum and corpus striatum) in schizophrenic patients. The involvement of oligodendrocyte differentiation in the regulation of myelin matter areas (corpus callosum) during time reverse remyelination showed that DDR1 mRNA was

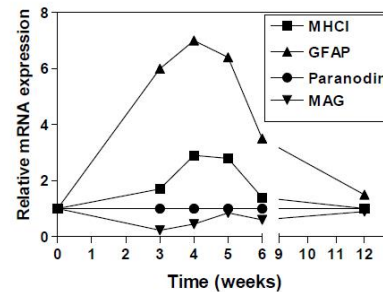
A



B

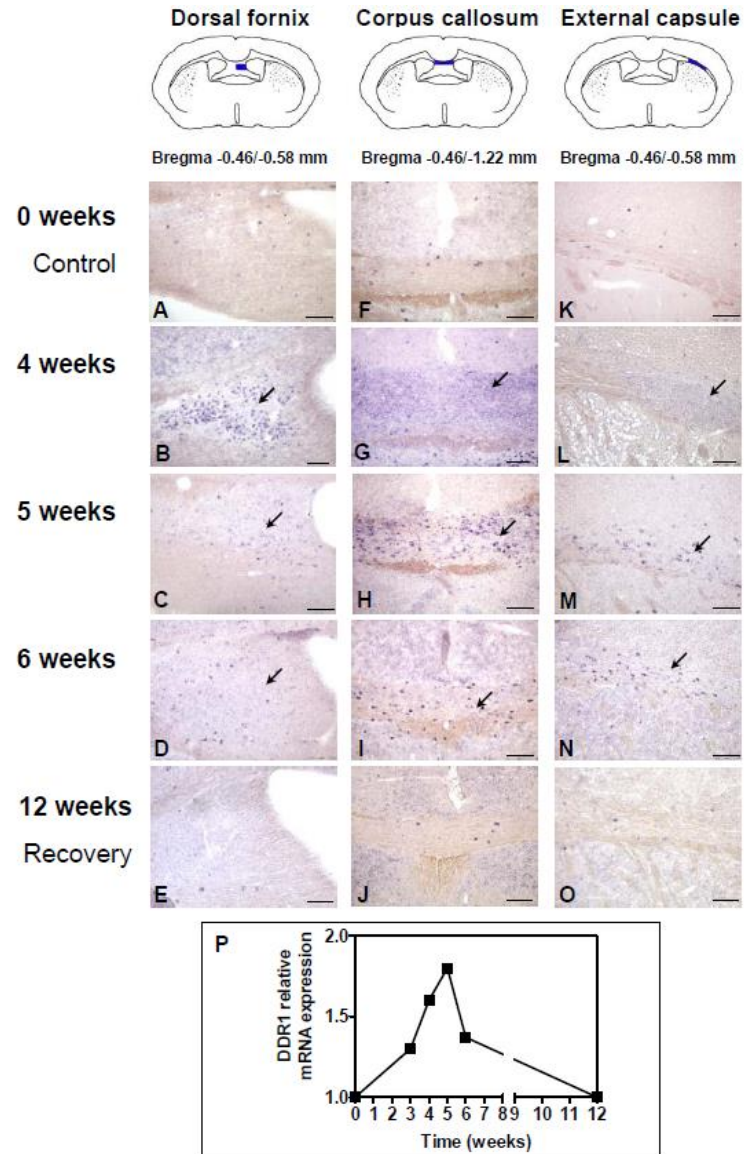


C

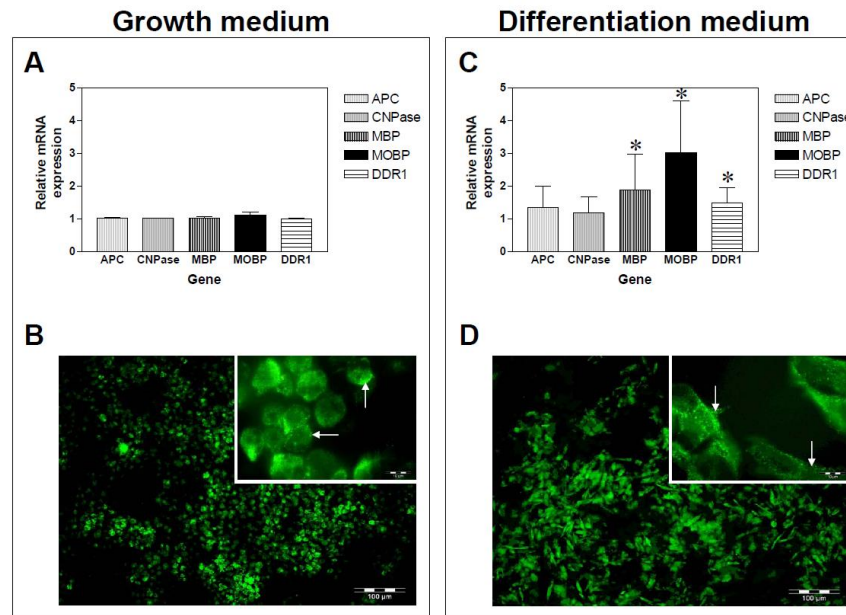


Spearman correlation analysis showed that the expression of markers of oligodendrocyte differentiation (CNPase), myelin basic protein, and several markers of astrocyte activation (GFAP) and microglia (MHC I) were needed for remyelination.

cells.



Sobreexpressió de DDR1 durant la remielinització



Model cel·lular (HOG) de mielinització

CONCLUSIONS

- 1. El gen *ddr1* en ratolí s'expressa majoritàriament en oligodendròcits.**
- 2. El gen *ddr1* no s'expressa en neurones.**
- 3. El gen *ddr1* en ratolí participa en els processos de mielinització i remielinització.**
- 4. Identifiquem polimorfismes (SNPs) al gen *DDR1* que s'associen a esquizofrènia.**
- 5. El gen *DDR1* en cervell humà té un alt grau d'expressió**

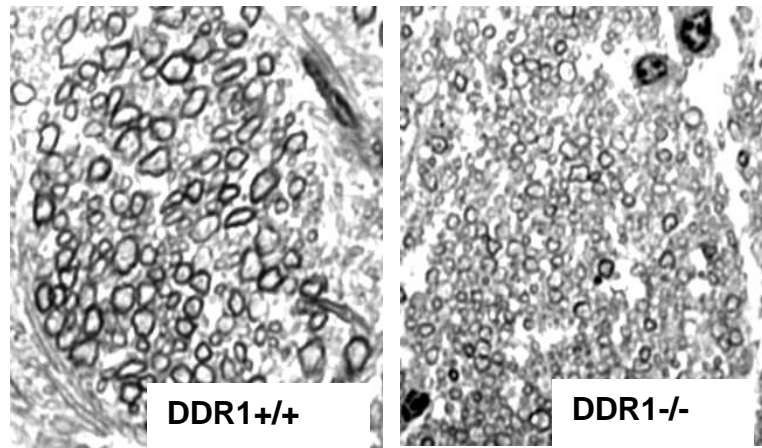
Hipòtesi II (2008)

L'expressió de DDR1 en oligodendròcits és important per a la formació i el manteniment de la capa de la mielina des del neurodesenvolupament fins a l'edat adulta.

El paper de DDR1 en oligodendròcits mielinitzants pot ser alterat per mutacions en la regió codificant del gen i per tant les persones portadores d'aquestes mutacions tindran augmentada la susceptibilitat per desenvolupar l'esquizofrènia.

Objectius

1. Caracteritzar la mielina en el ratolí knock-out ddr1.
2. Demostrar l'expressió de DDR1 en cervell humà.
3. Explorar l'expressió de DDR1 en cervell de pacients esquizofrènics.



Alteració del gruix de la mielina en el ratolí knock-out *ddr1*



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RESEARCH

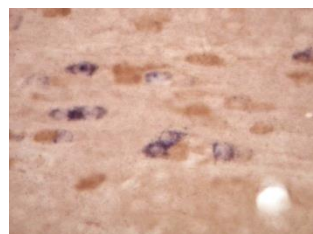
Research Report

Expression of the tyrosine kinase discoidin domain receptor 1 (DDR1) in human central nervous system myelin

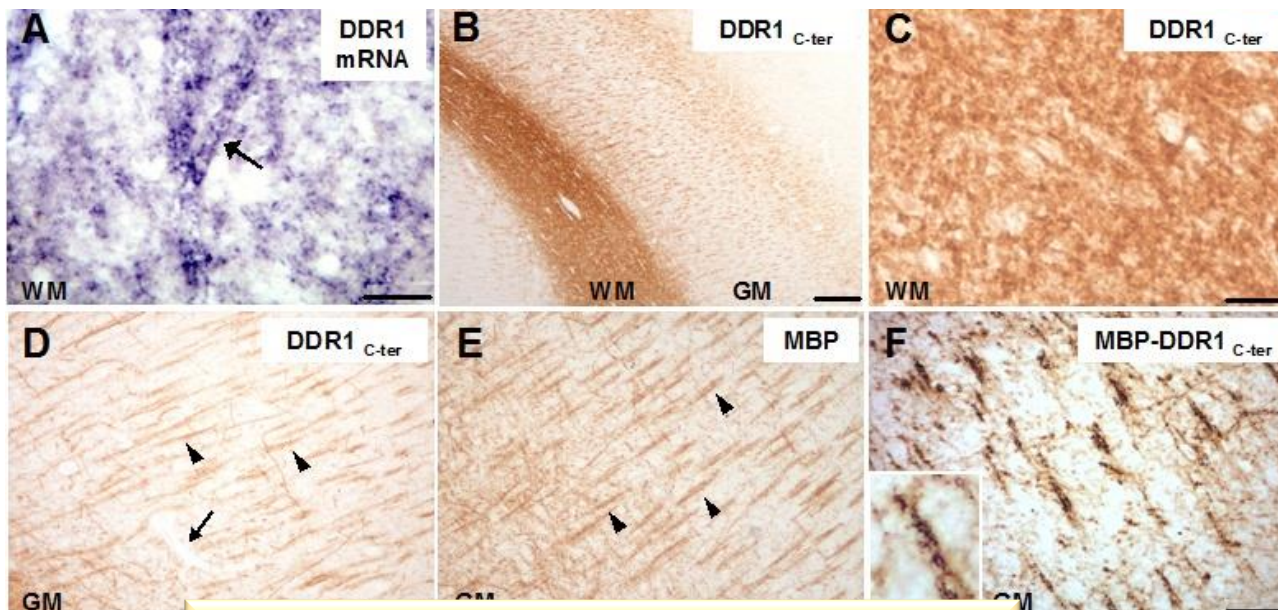
Bàrbara Roig^a, Neus Franco-Pons^a, Lourdes Martorell^a, Jordi Tomàs^a,
Wolfgang F. Vogel^{b,†}, Elisabet Vilella^{a,*}

^aHospital Psiquiàtric Universitari Institut Pere Mata, IISPV, Universitat Rovira i Virgili, C/Sant Llorenç 21, 43201 Reus, Spain

^bDepartment of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada M5S 1A8



ratolí



DDR1 en cervell humà s'expressa en mielina

Material procedent de cervell humà proveït per Stanley Foundation i BTN Hospital Clínic

ORIGINAL
ARTICLEThe Discoidin domain receptor 1 gene has
a functional A2RE sequenceBarbara Roig,^{*,1} Sílvia Moyano,^{*,1} Lourdes Martorell,^{*} Javier Costas[†]
and Elisabet Vilella^{*}^{*}Hospital Universitari Psiquiàtric Institut Pere Mata, IISPV, Universitat Rovira i Virgili, Reus, Spain[†]Fundación Pública Galega de Medicina Xenómica-SERGAS, Hospital Clínico Universitario de
Santiago, Santiago de Compostela, Spain**Abstract**

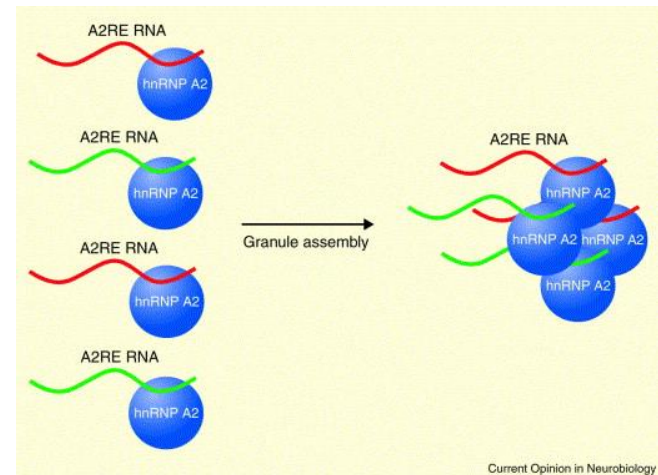
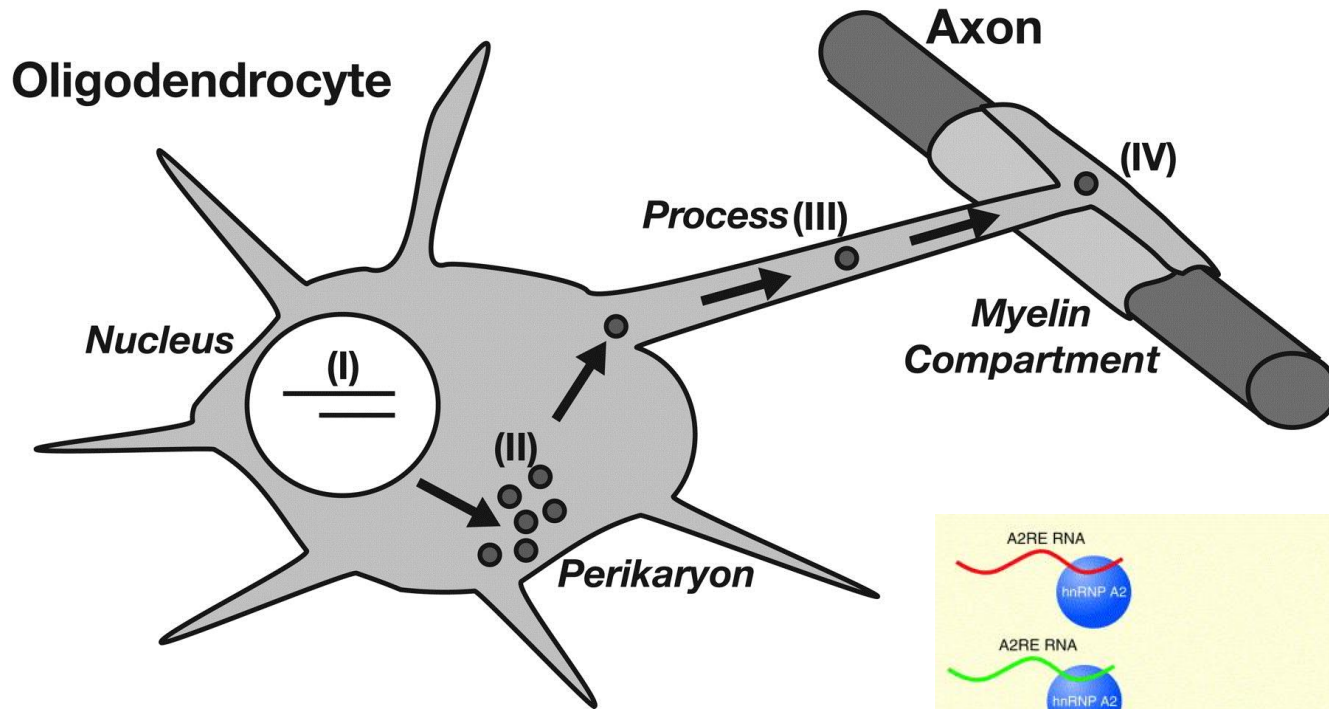
Discoidin domain receptor 1 (DDR1) is expressed in myelin oligodendrocytes and co-localizes with myelin basic protein (MBP). Alternative splicing of DDR1 generates five isoforms designated DDR1a–e. The MBP mRNA contains an hnRNP A2 response element (A2RE) sequence that is recognized by heterogeneous nuclear ribonucleoprotein (hnRNP) A2/B1, which is responsible for transport of the MBP mRNA to oligodendrocyte processes. We hypothesized that DDR1 could have a functional A2RE sequence. By *in silico* analysis, we identified an A2RE-like sequence in the human DDR1 mRNA. We observed nuclear and dendrite cytoplasmic immunofluorescence, indicating that DDR1 and hnRNP A2/B1 co-localize in human oligodendrocytes and in differentiated HOG16 cells. The A2RE-like sequence of DDR1 contains the single nucleotide polymorphism rs2267641, and we found that

in the human brain, the minor allele is associated with lower and higher levels DDR1b and DDR1c mRNA expression, respectively. Moreover, a positive correlation between DDR1c and the myelin genes myelin-associated glycoprotein and oligodendrocyte lineage transcription factor 2 was found. Differentiated HOG16 cells transfected with an hnRNP A2/B1 siRNA simultaneously show a decrease and an increase in the DDR1c and DDR1b mRNA expression levels, respectively, which was accompanied by a decrease in DDR1 protein levels at the cytoplasmic edges. These results suggest that the DDR1 A2RE sequence is functionally involved in the hnRNP A2/B1-mediated splicing and transport of the DDR1c mRNA.

Keywords: DDR1, hnRNP A2/B1, immunofluorescence, mRNA trafficking, oligodendrocytes, SNP.

J. Neurochem. (2011) 10.1111/j.1471-4159.2011.07580.x

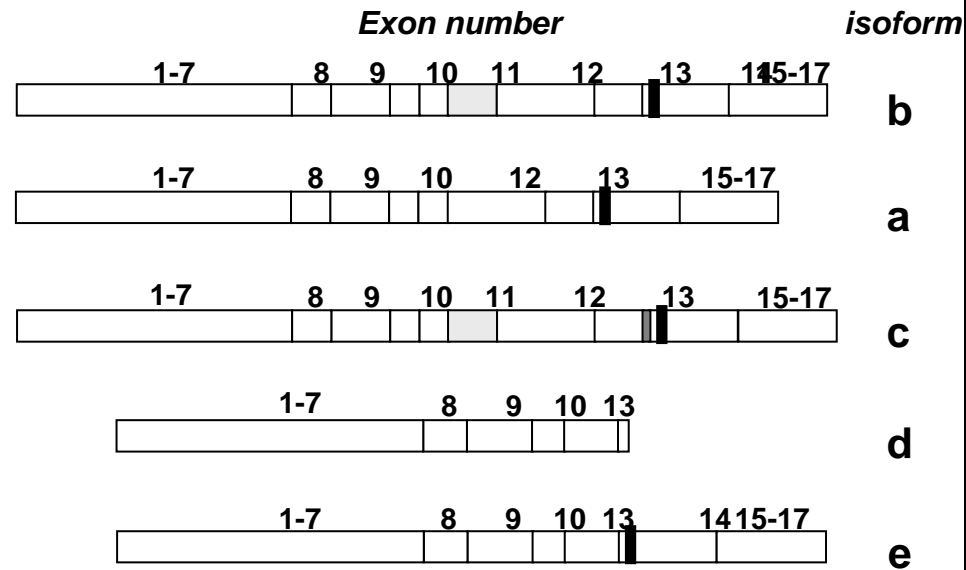
Stages of the post-transcriptional regulation of MBP mRNA in oligodendrocyte glial cells.



RYDER S P , WILLIAMSON J R RNA 2004;10:1449-1458

A

MBP	GC-CAA-GGAGCCAGAGAGCATG	21
MOBP	AC-CCC-CGAGACACAGAGCATG	21
CAII	GACAAACGGA-CCAGAGAAC-TG	21
TAU	GC-CAA-GCAGGGAAA-AGC-TG	19
APP	GC-CAA-GCACCGAGAGAGAATG	21
DDR1	GCTCAA-GGACCCAAACATCATT	22

B

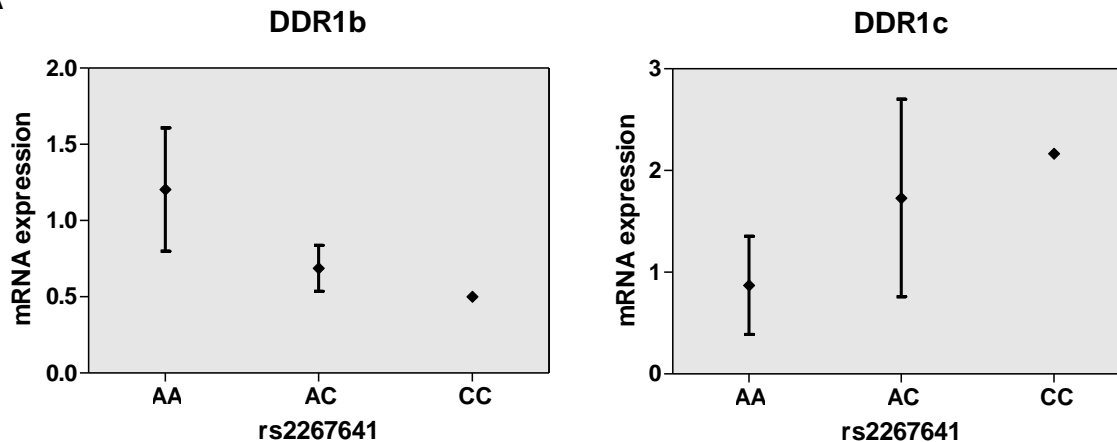
El gen DDR1 té un element A2RE

DDR1 A2RE

GCTCAAGGACCC [A/C] AACATCATT

rs2267641

A



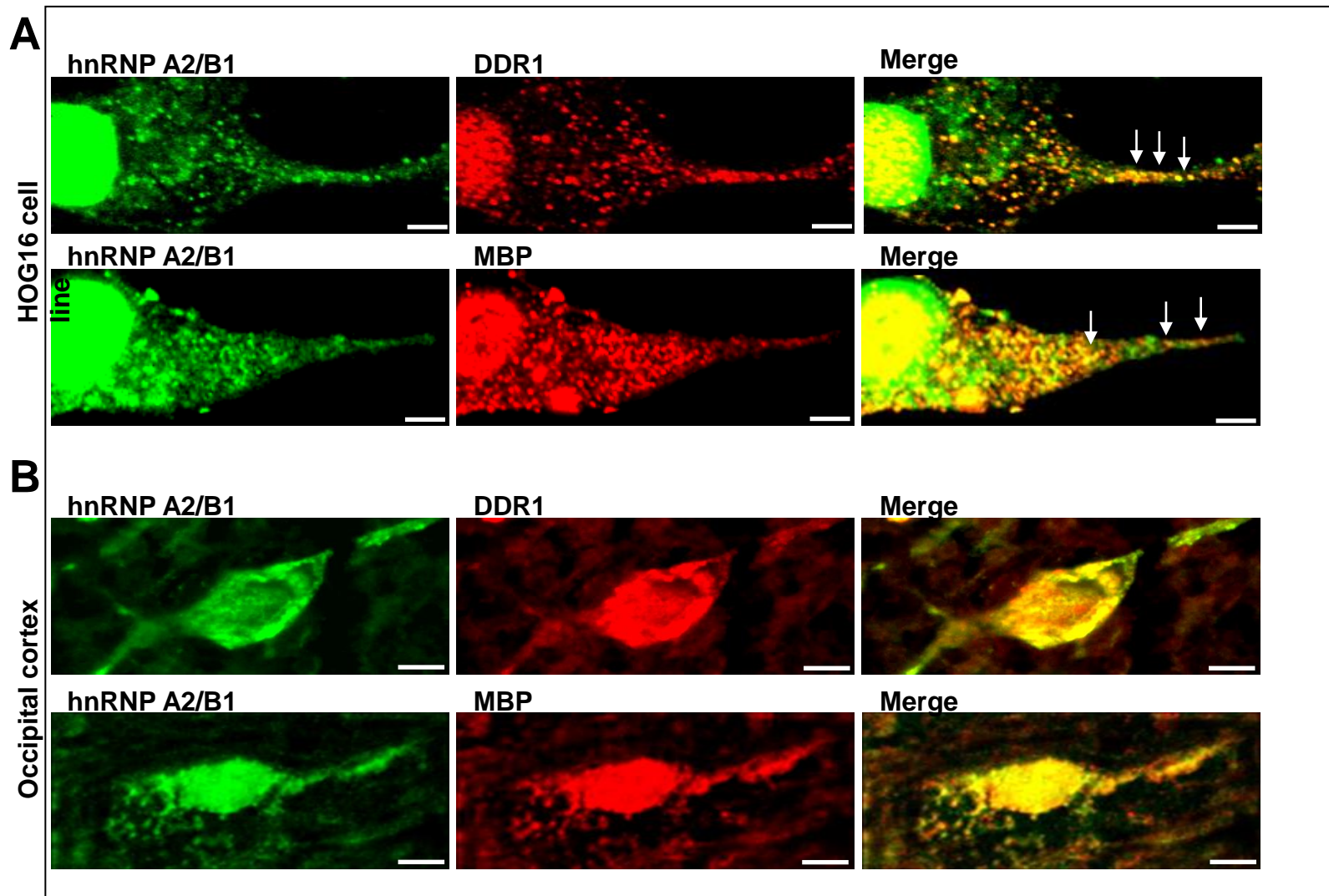
B

Table 1. Spearman's correlation coefficients between DDR1b and DDR1c isoforms and oligodendrocyte myelin markers MAG and OLIG2 in human DLPFC

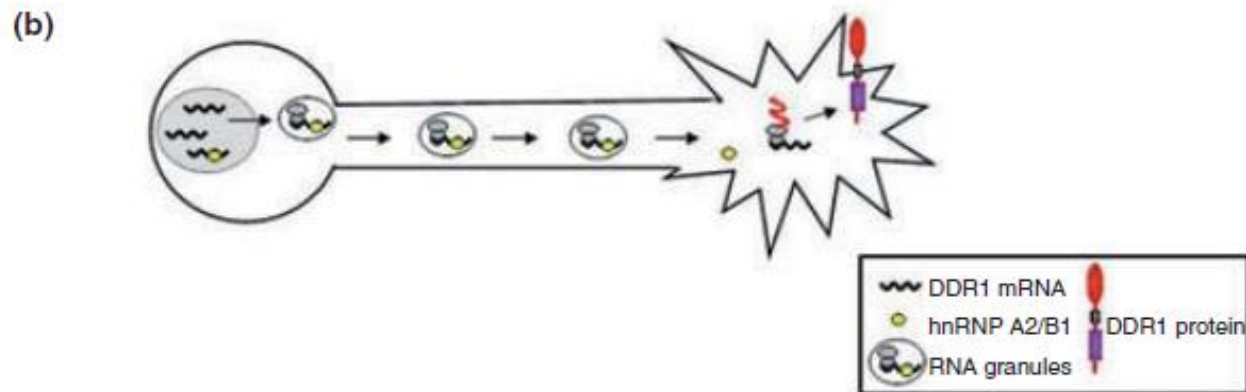
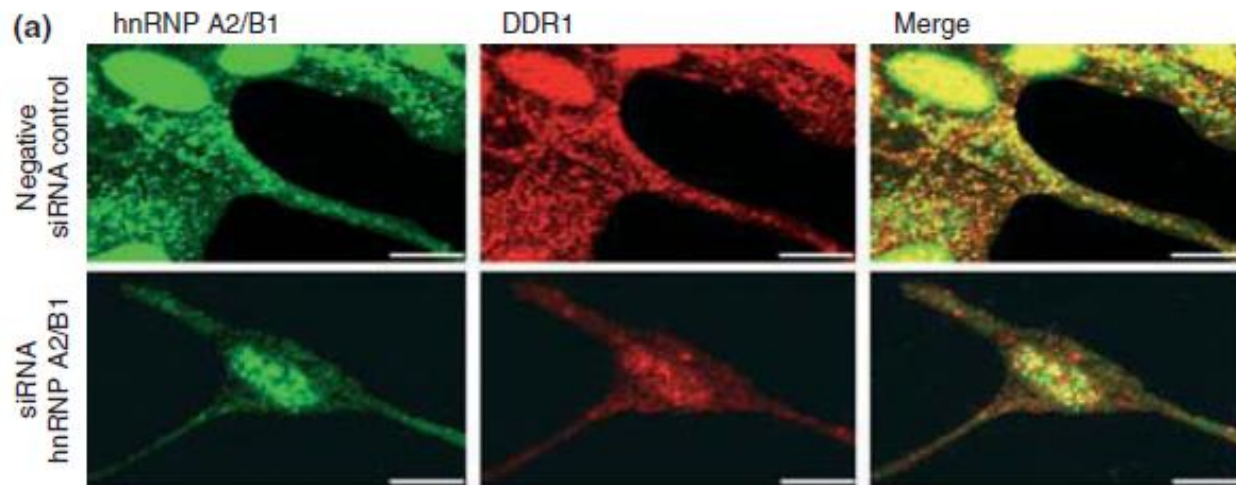
Genes	MAG	OLIG2	DDR1	DDR1b	DDR1c
MAG					
OLIG2	0,793*				
DDR1	0,589*	0,761*			
DDR1b	0,049	0,035	0,002		
DDR1c	0,488*	0,599*	0,597*	-0,280	

GAPDH was used as endogenous control. In bold $p < 0.01$ and $*p < 0.001$.

A2RE conté l'SNP rs2267641 que intervé en l'expressió de les isoformes DDR1 b i c



DDR1 co-localitza amb MBP i hnRNP A2/B1 *in vitro* i *in vivo*



Quan silenciem hnRNP A2/B1 disminueix l'expressió de DDR1 en oligodendròcits *in vitro*

CONCLUSIONS

1. El gen DDR1 en cervell humà s'expressa en oligodendròcits (mielina).
2. El gen DDR1 en cervell humà no s'expressa en neurones.
3. El ratolí knock-out *ddr1* presenta la mielina alterada.
4. Identifiquem un element A2RE al gen DDR1 humà que conté l'SNP rs2267641 que determina diferent expressió de les isoformes DDR1b i DDR1c.

Hipòtesi III (2009)

Els individus portadors de l'al·lel rar dels SNPs rs1049623 i rs2267641 de DDR1 tenen alterada l'expressió de les isoformes del receptor que els provoca una alteració en la mielina que els fa més susceptibles a patir esquizofrènia.

Objectius

1. Comparar l'expressió de les isoformes DDR1 en cervell de pacients esquizofrènics i controls sans.
2. Comparar l'estructura dels feixos de mielina en pacients esquizofrènics portadors de l'al·lel rar rs1049623 i rs2267641 i els no portadors.
3. Comparar el funcionament cognitiu i la gravetat de la simptomatologia entre els pacients esquizofrènics portadors de l'al·lel rar rs1049623 i rs2267641 i els no portadors.



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2011

Letter to the Editor

Increased expression of the spliced DDR1c isoform in brain tissues from schizophrenia patients

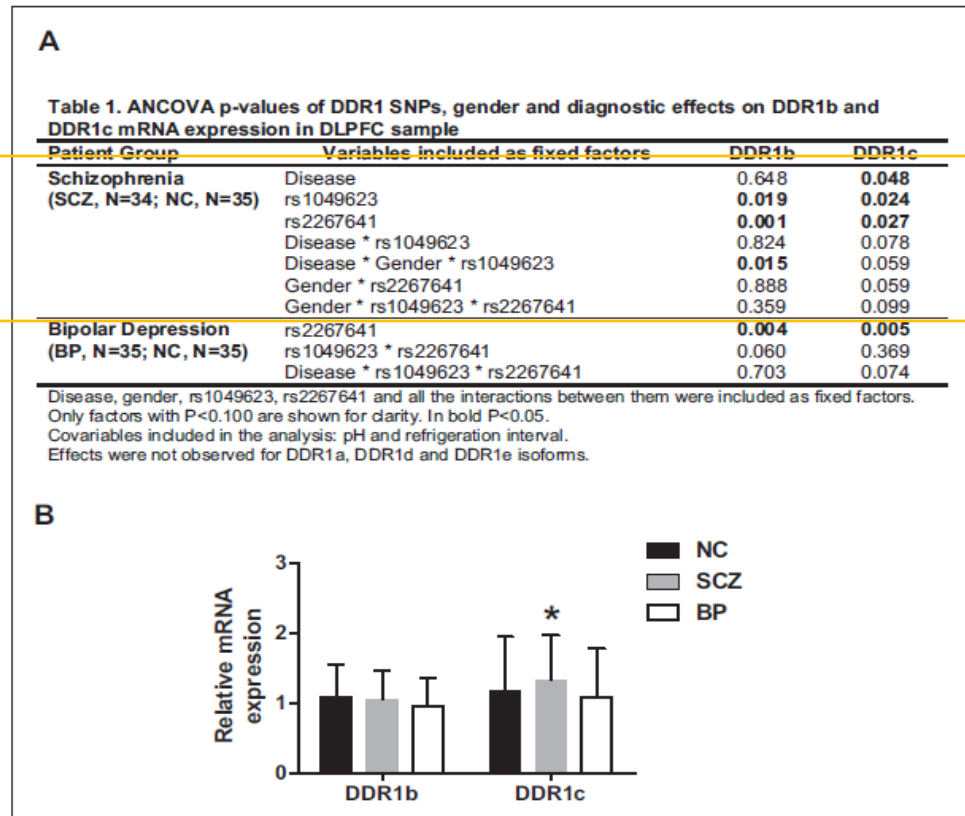


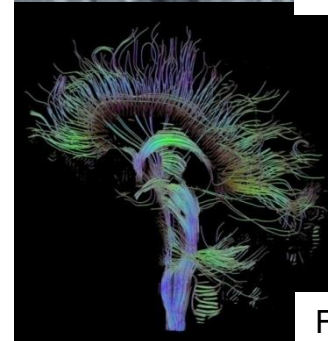
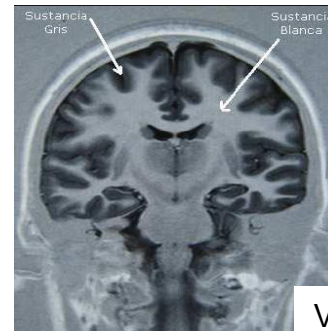
Fig. 1. The effect of DDR1 genotype on DDR1b and DDR1c isoform mRNA expression levels in the DLPFC. Panel A shows the ANCOVA P -values for DDR1 SNPs, gender and diagnostic effects on DDR1b and DDR1c mRNA expression. Panel B shows the mRNA expression of DDR1b and DDR1c isoforms in normal control (NC), schizophrenia (SCZ) and bipolar disorder subjects (BP), normalized to RN18S.

Els pacients esquizofrèncs expressen més DDR1 c

Pacients esquizofrènics rs1049623



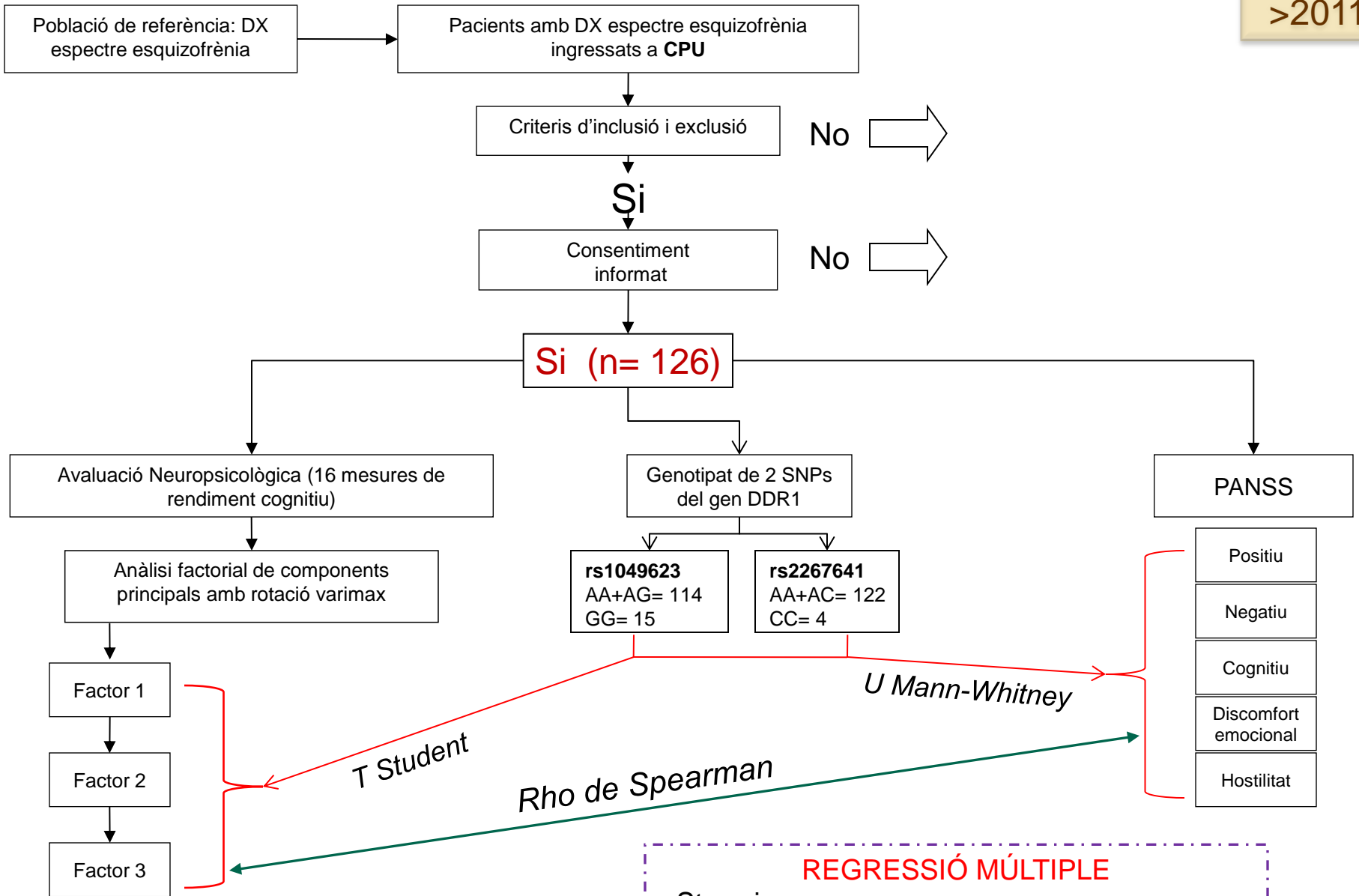
1. **Avaluació neuropsicològica i psicopatològica**
2. **Resonància magnètica (RM)**



IDI, Hospital Joan XXIII

Dra. Ester Salvadó Geli, Helena Buixadera
Sr. Francesc Ramón Anglada

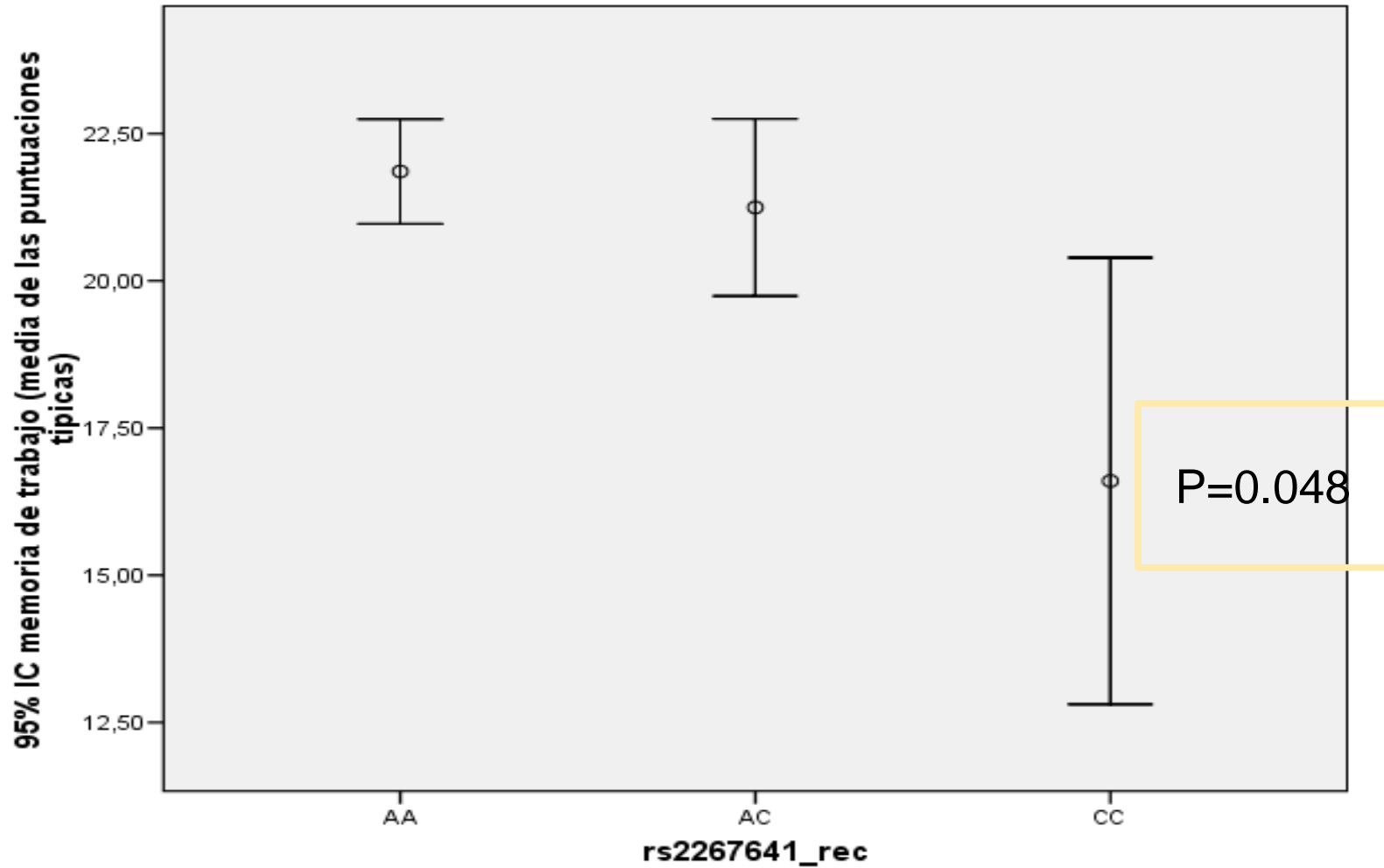
Hospital General Gregorio Marañón
Manuel Desco



REGRESSIÓ MÚLTIPLE

- Stepwise
- Y= memòria de treball
- X= símpt. negatius, cognitius, anys d'escolaritat, temps d'evolució i rs2267641

Relació entre el factor memòria de treball i DDR1 rs2267641



Regressió lineal que mostra la relació dels anys d'escolaritat, el component negatiu de la PANSS i el rs2267641 amb la memòria de treball

		B	ET B	β	p
Pas 1	Constant	16.53	1.35		
	Anys d'escolaritat	0.447	0.117	0.354	0.000
Pas 2	Constant	18.63	1.57		
	Anys d'escolaritat	0.467	0.114	0.369	0.000
	Component negatiu	-0.12	0.049	-0.219	0.017
Pas 3	Constant	18.96	1.56		
	Anys d'escolaritat	0.439	0.113	0.347	0.000
	Component negatiu	-0.112	0.048	-0.207	0.022
	rs2267641	-4.00	1.92	-0.187	0.039

Nota. R2 corregida= 0.116 per al pas 1, canvi a R quadrat corregida= 0.048 per al pas 2 ($p < 0.05$), canvi R quadrat corregida= 0.034 per al pas 3 ($p < 0.05$); rs2267641 0=AA+AC 1=CC

CONCLUSIONS

1. S'observa més expressió de DDR1 isoforma c, en cervell de pacients esquizofrènics.
2. Els pacients amb genotip CC del DDR1 rs2267641, tenen un pitjor rendiment cognitiu en memòria de treball (corregint per anys d'escolaritat i per simptomatologia).

CONCLUSIONS FINALS

1. El gen DDR1 en cervell s'expressa en oligodendròcits (mielina).
2. El gen DDR1 en cervell no s'expressa en neurones.
3. El gen DDR1 participa en la mielinització i remielinització de SNC.
4. DDR1c és la isoforma principal d'oligodendròcits.
5. DDR1c està augmentada en cervell de pacients esquizofrènics.
6. Identifiquem un element A2RE al gen DDR1 que conté l'SNP rs2267643 que determina diferent expressió de les isoformes DDR1b i DDR1c.
7. Identifiquem un dèficit en la memòria de treball en pacients esquizofrènics portadors de l'al·lel de risc de rs2267643.
8. Existeix una associació entre el gen DDR1 i l'esquizofrènia.

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- [The association of white matter volume in psychotic disorders with genotypic variation in NRG1, MOG and CNP: a voxel-based analysis in affected individuals and their unaffected relatives.](#)
 Cannon DM, Walshe M, Dempster E, Collier DA, Marshall N, Bramon E, Murray RM, McDonald C. *Transl Psychiatry*. 2012 Oct 9;2:e167. doi: 10.1038/tp.2012.82.
 PMID: 23032943 [PubMed - in process]
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- [Polyunsaturated Fatty Acid Concentration Predicts Myelin Integrity in Early-Phase Psychosis.](#)
 Peters BD, Machielsen MW, Hoen WP, Caan MW, Malhotra AK, Szeszko PR, Duran M, Olabarriaga SD, de Haan L. *Schizophr Bull*. 2012 Aug 27. [Epub ahead of print]
 PMID: 22927668 [PubMed - as supplied by publisher]
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 Mothersill O, Kelly S, Rose EJ, Donohoe G. *Front Psychiatry*. 2012;3:18. Epub 2012 Mar 9.
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 Lu LH, Zhou XJ, Keedy SK, Reilly JL, Sweeney JA. *Bipolar Disord*. 2011 Nov-Dec;13(7-8):604-13. doi: 10.1111/j.1399-5618.2011.00958.x.
 PMID: 22085473 [PubMed - indexed for MEDLINE]
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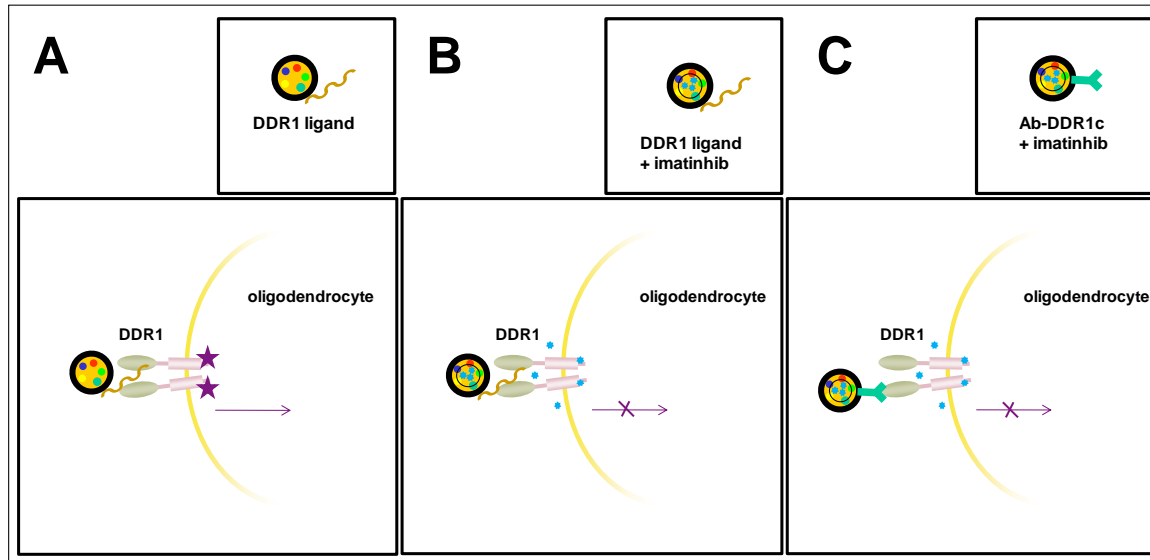
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