Cross-sectional and longitudinal assessment of the association between *DDR1* variants and processing speed in patients with early psychosis and healthy controls

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ABSTRACT

Recent evidence indicates that DDR1 participates in myelination and that variants of *DDR1* are associated with decreased cognitive processing speed (PS) in schizophrenia (SZ). Here, we explored whether DDR1 variants were associated with PS in subjects diagnosed with an early psychosis (EP), a condition often preceding SZ. Data from two Spanish independent samples (from Reus and Santander) including patients with EP (n = 75 and n = 312, respectively) and healthy controls (HCs; n = 57 and n = 160) were analyzed. The Trail Making Test part A was used to evaluate PS. Participants underwent genotyping to identify *DDR1* variants rs1264323 and rs2267641. Cross-sectional data were analyzed with general linear models and longitudinal data were analyzed using mixed models. We examined the combined rs1264323AA-rs2267641AC/CC genotypes (an SZ-risk combination) on PS. The SZ-risk combined genotypes were associated with increased PS in EP patients but not in HCs in the cross-sectional analysis. In the longitudinal analysis, the SZ-risk combined genotypes were significantly associated with increased PS in both HCs and EP patients throughout the 10-year follow-up but no genotype × time interaction was observed. These results provide further evidence that DDR1 is involved in cognition and should be replicated with other samples.

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 replicable 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 (Sekar et al., 2016). 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). Moreover, genome wide association studies (GWAS) have found associations between *DDR1* SNPs and multiple sclerosis (Mo et al., 2019), neuroticism (Kim et al., 2017) and SZ (Pardiñas et al., 2018), although the latter study did not include the *DDR1* locus in the final analyses; the data can be retrieved from the project website (htt p://www.szdb.org/clozuk1.php). The reason why some GWAS excluded the *DDR1* locus is because it falls inside of a linkage disequilibrium (LD) region wherein the highest SZ-associated locus is located. *DDR1* is expressed in oligodendrocytes and plays a role in myelination. *DDR1* SNP variants are involved in gene expression (Vilella et al., 2019). For instance, rs1264323, located in the *DDR1* putative promoter region, is included in the database of genetic variations affecting the regulation of gene expression (eQTL) due to its differential expression in human tibial nerve tissue and other tissues. In addition, rs2267641 is located in the A2RE sequence that participates in the alternative splicing of DDR1c and DDR1b isoforms and in the transport of messenger RNA before it is translated into protein (Roig et al., 2012b). We previously reported that *DDR1* rs1264323, associated with SZ in case-control designs, is associated with fractional anisotropy (FA) of some white matter areas correlating with PS in SZ patients (Gas et al., 2019). 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, that was associated with decreased PS (Gas et al., 2019). In the same sample, SZ patients who were carriers of the homozygous genotype CC of the functional SNP rs2267641 (Roig et al., 2012b) 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 patients with psychosis at the early phase, a time when early interventions are critical for preventing disease progression (Fusar-Poli et al., 2017). Different terms and criteria have been used to describe these early stages and one of the most accepted criteria is that illness duration is < 5 years (Newton et al., 2018). From here onward, we use the term early psychosis (EP) to refer to this period.

In the present study, we aimed to 1) determine whether *DDR1* SNP variants are associated with PS in subjects with diagnosed EP compared to healthy controls (HCs) in two different samples using a cross-sectional analysis, and 2) test whether the *DDR1* variants associated with PS changes during a 10-year follow-up in both HCs and patients with diagnosed EP using a longitudinal analysis.

2. Material and methods

2.1. Subjects

2.1.1. Reus sample

We included 75 EP outpatients attending the 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 ethnicity, DSM-IV diagnosis of drug dependence (except nicotine dependence) and a scalar score of less than 6 in the WAIS-III subset (Lezak, 1997). We included a HC group of 57 subjects who were nongenetic relatives or friends of the patients and were screened to rule out past or current history of psychiatric disorders. This sample (patients and HCs) was selected from a dataset used in previous studies (Montalvo et al., 2014).

2.1.2. Santander sample

We included 312 EP patients who attended the epidemiological and longitudinal intervention program of First Episode Psychosis (PAFIP) at the University Hospital Marqués de Valdecilla (Santander, Spain) (Crespo-Facorro et al., 2006). 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). EP patients and HCs were evaluated at the baseline and longitudinally after 1, 3 and 10 years (Ayesa-Arriola et al., 2021).

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. All participants signed an informed consent prior to their inclusion in the study.

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). Since rs2267641 was neither genotyped nor imputed in the Santander sample, we searched for it within the 1000 Genomes (IBS) dataset for SNPs in the total LD ($r^2 = 1$). We used rs3213644 as a proxy for rs2267641, but refer to this variant as 'rs2267641' hereafter to increase clarity. 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 SZ-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 both 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. Therefore, higher values of TMT-A indicate more time spent in the task and hence a lower PS.

Psychopathological symptoms were assessed with Positive and Negative Syndrome Scale (PANSS), Spanish version (Peralta and Cuesta, 1994) in the Reus sample and Brief Psychiatric Rating Scale (BPRS) (Overall and 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. (2010).

2.5. Statistical analyses

In both samples, categorical variables are reported as frequencies and percentages and continuous variables as the mean ± standard deviation (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 but not in the Santander sample, even after log-transformation. Nonetheless, log-transformed TMT-A scores were used to reduce skewness. Nonparametric correlation coefficients (Spearman's rho test) were calculated to assess associations between TMT-A scores and psychopathological symptoms and other continuous variables (age, years of education and antipsychotic dose as chlorpromazine equivalent). The association of TMT-A scores with categorical variables (sex and cannabis use at baseline) was evaluated with the Mann-Whitney *U* test. Results are shown in Supplementary Table S2. *DDR1* genotypes were grouped into two combinations (see "Genotyping" section) to analyze the relationship between *DDR1* variants and PS. First, to compare PS among *DDR1* genotype groups at the baseline assessment (at first episode of psychosis) in the Reus and Santander samples (cross-sectional analysis), we used a general linear model (analysis of covariance, ANCOVA), including variables associated with PS in the previous univariate analysis as covariates. We used the same covariates in both samples for consistency, though fewer correlating variables were found in the Reus sample. Analysis was complicated by the following issues: 1) the dependent variable (TMT-A) was not normally distributed among the genotype groups, 2) the groups (risk and nonrisk combined genotypes) had unequal sample sizes, and 3) the risk group had a small sample size. To address these issues, we used an approach with a bootstrapping method that resamples with replacement

a large number of times (Dwivedi et al., 2017). Therefore, in the ANCOVA, we estimated means, standard errors, and confidence intervals for TMT-A in each subgroup using 1000 bootstrap samples. The P values displayed for the ANCOVA are those from the bootstrap samples. These analyses were conducted using SPSS v22.0 (IBM Corp., New York, NY, USA). Second, to explore the time-dependent relationships of the combined *DDR1* genotypes and PS (lnTMT-A) with follow-up data from the Santander sample (longitudinal analysis), linear mixed models were fitted (using "Linear and Nonlinear Mixed Effects Models", "nlme", script from the R package [R package nlme version 3.1–160 (2022). https://CRAN.R-project.org/package=nlme]). TMT-A scores were log-transformed and included as a continuous variable and participants were included as a random intercept. Linear mixed models handle missing data by accounting for the correlations among repeated measures of the same participant. Thus, participants were included if they had data available from at least one of the four-time points in the current study (baseline, 1-year, 3-year, 10-year follow-up). The models adjusted for the following variables in HCs: time, sex, age, years of education, and cannabis use in HCs. In EP patients, the models adjusted for time, sex, age, years of education, cannabis use, SANS, SAPS, antipsychotic dose, and illness duration. These analyses were conducted using R v 4.2.1. (R Core Team, 2019). Statistical significance was set at p < 0.05 for all analyses.

3. Results

Descriptive statistics for the participants at baseline are shown in Table 1. In both samples, men were more represented than women, but with a similar proportion in both the patient and the control groups and without statistical significance. Age was similar in the patients and the HCs in both samples. There were significantly more cannabis users in the patient group than in HCs in the Santander sample. Although the HCs showed a higher education level than the patients in both samples, it was only statistically significant in the Reus sample. The risk combined

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

	Reus sample			Santander sample		
	Patients	Controls		Patients	Controls	
	N = 75	N = 57	*P*	N = 312	N = 160	*P*
Sex (% male)	65.3	59.6	0.503[a]	56.4	61.9	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]
Cannabis use (% yes/no)	42.3/57.7	33.9/66.1	0.339[a]	41.7/58.3	20.6/79.4	<0.001[a]
TMT-A direct scores[c] (mean ± SD)	32.6 ± 9.6	24.4 ± 6.4	<0.001[b]	45.6 ± 18.0	34.5 ± 10.4	<0.001[b]
Antipsychotic dose (CPZ equivalents in mg/day)	371.0 ± 288.7	–		200.8 ± 79.9	–	
DDR1 combined genotypes[d] (%)						
Risk (AA-AC/CC)	6.7	5.3	0.738[a]	8.0	6.9	0.748[a]
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	–	
Delusional disorder	0	–		0.3	–	
Bipolar disorder	8.0	–		0	–	
Depressive disorder with psychotic symptoms	4.0	–		0	–	
Manic episode with psychotic symptoms	1.3	–		0	–	
Psychopathological 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	–		61.7 ± 13.71	–	

[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 Sample 2, as described in Materials and Methods.
[e] Measured with PANSS (Positive and Negative Syndrome Scale) in Reus sample and with SAPS (Scale for the Assessment of Positive Symptoms), SANS (Scale for the Assessment of Negative Symptoms) and BPRS (Brief Psychiatric Rating Scale) in Santander sample.

genotype group (AA-AC/CC) was detected at higher frequencies in patients compared to HCs in both samples, but without reaching statistical significance. In the longitudinal data-set (Santander Sample, Table 2), patients showed improvement in their positive, negative and general symptoms at 1- and 3-years follow-up, but subsequently slightly relapsed after 10-years from their first psychotic phase. Notably, a gradual mean increase in the antipsychotic equivalent dose (CPZ equivalents) was recorded.

In both samples, patients had higher TMT-A scores (decreased PS) than HCs (Table 1). Fig. 1, panel A, shows the results of the general linear model used to test the association between the *DDR1* risk genotype and PS (using ANCOVA with bootstrapping and a cross-sectional design). In both samples, patients with EP and carrying the risk combined genotype (AA-AC/CC) had lower TMT-A scores (faster PS) than nonrisk genotype carriers, yet the difference was 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 EP patients and HCs carrying the risk genotype combination in either sample. Fig. 1, panel B shows the longitudinal design results with the relationship between TMT-A scores and the *DDR1* genotype along the 10-year period of study. The mixed model's analysis for repeated

Table 2
Descriptive statistics of the longitudinal Santander sample.

	basal	1 year	3 years	10 years
Controls, N	160	123	107	77
Age (mean ± SD)	29.3 ± 7.8	30.3 ± 7.8	32.3 ± 7.8	39.3 ± 7.8
Years of education (mean ± SD)	11.0 ± 2.7	–	–	–
Cannabis use (%)	20.6	–	–	–
TMT-A direct scores[a]	34.5 ± 10.4	30.2 ± 10.7	30.3 ± 10.3	29.25 ± 12.5
DDR1 risk combined genotype (AA-AC/CC) (%)[b]	6.9	5.7	6.5	7.8
Patients, N	312	188	231	134
Age (mean ± SD)	29.7 ± 9.7	30.7 ± 9.7	32.7 ± 9.7	39.7 ± 9.7
Years of education (mean ± SD)	10.7 ± 3.3	–	–	–
Cannabis use (%)	41.7	–	–	–
Illness duration in years (mean ± SD)	0.6 ± 1.0	1.6 ± 1.0	3.6 ± 1.0	10.6 ± 1.0
Psychopathological symptoms				
Positive[c]	6.13 ± 5.8	3.8 ± 4.7	3.3 ± 4.8	3.9 ± 4.6
Negative[d]	13.4 ± 4.4	0.95 ± 2.4	1.5 ± 3.3	1.2 ± 2.7
General[e]	61.7 ± 13.7	29.5 ± 8.4	30.1 ± 10.2	30.1 ± 7.9
Antipsychotic dose[f]	200.8 ± 79.9	262.4 ± 217.1	257.5 ± 231.3	436.2 ± 293.3
TMT-A direct scores[a]	45.6 ± 18.0	40.4 ± 1.6	40.7 ± 17.6	43.9 ± 19.6
DDR1 risk combined genotype (AA-AC/CC) (%)[b]	8.0	7.4	6.9	9.7
Psychotic disorder diagnosis (%)				
Psychotic disorder not otherwise specified	6.7	–	5.3	5.7
Schizophrenia	44.9	–	66.5	69.8
Schizophreniform disorder	31.7	–	13.1	5.8
Schizoaffective disorder	2.6	–	9.8	15.1
Brief psychotic disorder	13.8	–	4.9	2.9
Delusional disorder	0.3	–	0.4	0.7

[a] Trail Making Test A, direct scores are expressed as time (sec).
[b] rs3213644 SNP used as a proxy of rs2267641 in Sample 2, as described in Materials and Methods.
[c] SAPS: Scale for the Assessment of Positive Symptoms.
[d] SANS: Scale for the Assessment of Negative Symptoms.
[e] BPRS: Brief Psychiatric Rating Scale.
[f] CPZ equivalents in mg/day.

measures showed that in both patients and HCs the *DDR1* risk combined genotype was associated to lower TMT-A scores (increased PS) at all time points. No time by genotype interaction was identified (detailed data from the mixed model analysis are provided in Supplementary Table S3).

4. Discussion

Our main finding is that *DDR1* rs1264323 and rs2267641 combined genotypes (AA-AC/CC) are associated with faster PS (lower TMT-A scores) in two independent samples. Specifically, in the cross-sectional design the effect of *DDR1* AA-AC/CC combined genotypes was only observed in EP patients, and the difference was only statistically significant in the larger Santander sample; in the longitudinal design using the Santander sample DDR1 AA-AC/CC combined genotypes were associated with decreased TMT-A scores (increased PS) in both HC and EP patients. We previously found that carriers of AA-AC/CC combined genotypes were at risk of developing SZ and that carriers of the rs2267641 CC genotype had decreased (slower) PS than other genotype groups (Gas et al., 2019). These apparently contradictory results between our two studies, i.e., the association of the *DDR1* SNPs with faster PS in EP samples and slower PS in SZ samples may have different explanations. Patients in the present study met baseline inclusion criteria for EP which implicates that illness duration is < 5 years (Newton et al., 2018), whereas patients included in our previous study had an established diagnosis of SZ with a mean illness duration of >10 years. It is known that PS decreases with age (Cohen et al., 2019) but also with illness progression (Fett et al., 2020; Menkes et al., 2019). Moreover, one other finding published in the previous study (Gas et al., 2019) based on two neuropsychological evaluations with a mean of 6 years apart in SZ patients showed an interaction between DDR1 rs1264323 variant and worsening PS over time in SZ patients. This SNP-time interaction would support the differences observed between EP and SZ patients. In view of these findings, we can hypothesize that *DDR1* SNP variants may have a positive association with PS in the early illness phases but a negative association as the disease progresses. However, this hypothesis is not confirmed with the results from our longitudinal data where we did not find an interaction between time and the risk genotype. Several differential disease features between EP and SZ may also explain these results: (1) the highest prevalence of negative symptoms in SZ (Correll and Schooler, 2020) which is negatively associated with PS (Harvey et al., 2006; Rodríguez-Sánchez et al., 2008); (2) EP includes patients who do not develop SZ and that probably have high cognitive functioning scores (Vaskinn et al., 2020); (3) cannabis use in EP is more frequent and may influence PS (Bogaty et al., 2018); and (4) there are drug treatment differences between EP and SZ (Tsutsumi et al., 2011). For instance in the Santander sample, patients released from the early intervention psychosis program had higher antipsychotic doses (Ayesa-Arriola et al., 2021). Moreover, a high proportion (80%) of SZ patients take anxiolytics and antidepressants a part of antipsychotic medication (Gaviria et al., 2015).

The fact that the *DDR1*-PS association was observed also in the HC sample in the present study suggests that the DDR1 role may be at the molecular level. In this sense, rs2267641 has been associated with *DDR1* mRNA splicing, intracellular trafficking and expression (Roig et al., 2012b). In addition, *DDR1* rs1264323 is classified as an eQTL in the 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). Moreover, DDR1c isoform levels were found to be increased in brain tissue from patients with SZ compared to that of HCs (Roig et al., 2012a). 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

A
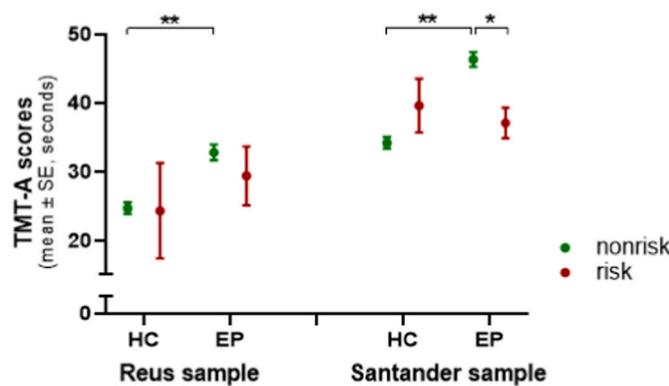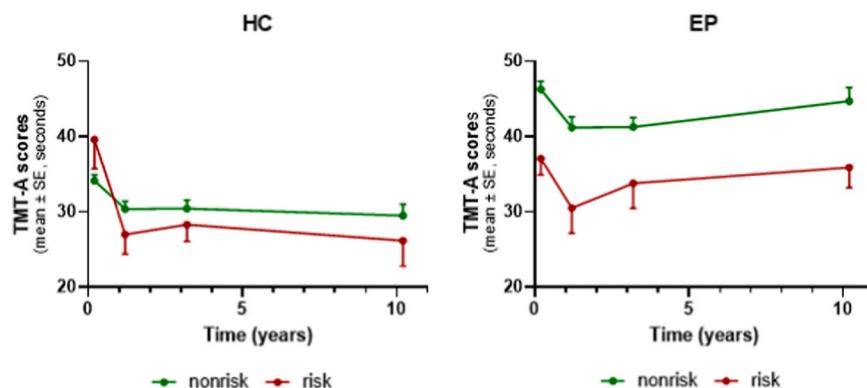
Cross-sectional design

Fig. 1. Effect of the *DDR1* risk combined genotype on PS (TMT-a scores) in patients with EP and HC

A. Results of the general linear model analysis (ANCOVA with bootstrapping) to compare mean TMT-A scores between carriers and noncarriers of the risk combined genotype of *DDR1* in EP patients and HCs in the two samples. Covariates included in the analysis (based on the bivariate analysis shown in Supplementary Table 2) were age at assessment, sex, cannabis use, years of education and antipsychotic dose in EP patients' groups in both samples. Covariates included in the analysis (based on the bivariate analysis shown in Supplementary Table 2) were age at assessment, sex, cannabis use and years of education in HC groups in both samples. P values were calculated using bootstrapping. *P < 0.05, **P < 0.001. B. Results of the mixed models for repeated measures analysis of association between *DDR1* risk combined genotype and TMT-A scores. The model was adjusted for time, sex, age, education and cannabis use in the group of HC and time, sex, age, education, cannabis use, SANS, SAPS, CPZ equivalents and illness duration in the EP patient group.

B

Longitudinal design

Mixed models for repeated measures analysis: effect of *DDR1* risk combined genotype on TMT-A scores along the study period

Group	Coefficient ± EE	p-value
HC[a]	-0.927 ± 0.303	0.003
EP[b]	-0.116 ± 0.047	0.013

[a]Adjusted for time, sex, age, years of education and cannabis use
[b]Adjusted for time, sex, age, years of education, cannabis use, CPZ equivalents, illness duration, SAPS (Scale for the Assessment of Positive Symptoms), SANS (Scale for the Assessment of Negative Symptoms) and BPRS (Brief Psychiatric Rating Scale).

of plasma DDR1 correlated negatively with cognitive ability in three Scottish 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 DDR1 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 complex LD structure at the 6p21.33 (Tsunoda et al., 2004) region

where *DDR1* is located must be considered when interpreting results, especially when results from different samples are compared. Second, both samples are representative of EP 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). Third, the sample size is an important limitation regarding the low frequency of minor alleles for both SNPs. Fourth, we

only had basal data on cannabis consumption.

In summary, we report statistically significant associations between combined genotypes of two *DDR1* variants (rs1264323 and rs2267641) and PS in subjects diagnosed with psychosis as well as in HC.

Future studies with larger samples are needed to obtain more robust results to identify whether *DDR1* SNP variants can predict 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.

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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, J G-G and GM performed the statistical analyses. CG and EV took the lead in writing the manuscript. All authors discussed the results and commented on the manuscript.

Declaration of conflict of interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2022.12.020.

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