Journal of Affective Disorders 267 (2020) 23–32

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Research paper

Exploring genetic variants in obsessive compulsive disorder severity: A GWAS approach

María Alemany-Navarro[a,b,*], Raquel Cruz[c], Eva Real[a,b], Cinto Segalàs[a,b], Sara Bertolín[b], Isabel Baenas[b], Laura Domènech[d,e], Raquel Rabionet[f,g], Ángel Carracedo[c,h], Jose M. Menchón[a,b,i,j], Pino Alonso[b,i,j]

[a] Institut d' Investigació Biomèdica de Bellvitge (IDIBELL), L'Hospitalet de Llobregat, Barcelona, Spain
[b] OCD Clinical and Research Unit, Psychiatry Department, Hospital Universitari de Bellvitge, Barcelona, Spain
[c] Grupo de Medicina Xenómica, CIBERER, Centre for Research in Molecular Medicine and Chronic Diseases, CIMUS-, Universidade de Santiago de Compostela, Santiago de Compostela, Spain
[d] Centre for Genomic Regulation (CRG), The Barcelona Institute of Science and Technology, Dr. Aiguader 88, Barcelona 08003, Spain
[e] Universitat Pompeu Fabra (UPF), Barcelona, Spain
[f] Institut de Recerca Sant Joan de Déu, Esplugues de Llobregat, Spain
[g] Institut de Biomedicina de la Universitat de Barcelona (IBUB), CIBERER, and Dept. Genetics, Microbiology & statistics, Faculty of Biology, University of Barcelona, Barcelona, Spain
[h] Fundación Pública Galega de Medicina Xenómica, SERGAS, Instituto de Investigación Sanitaria de Santiago de Compostela (IDIS), Santiago de Compostela, Spain
[i] Department of Clinical Sciences, Bellvitge Campus, University of Barcelona, Barcelona, Spain
[j] CIBERSAM (Centro de Investigación en Red de Salud Mental), Instituto de Salud Carlos III, Spain

ARTICLE INFO

Keywords:
Obsessive-compulsive disorder
Severity
Genomics
GWAS
Common variants
Rare variants

ABSTRACT

Background: : The severity of Obsessive-Compulsive Disorder (OCD) varies significantly among probands. No study has specifically investigated the genetic base of OCD severity. A previous study from our group found an OCD polygenic risk score to predict pre- and post-treatment severity. This study explores the genomic bases of OCD severity.

Methods: : We administered the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) to 401 patients at their first visit to our clinic to measure their OCD severity. Genotyping data was collected by using the Infinium PsychArray-24 BeadChip kit (Illumina). We analyzed genetic association with OCD severity in a linear regression analysis at single-nucleotide polymorphism (SNP)- and gene-levels, this last also considering rare variants. Enrichment analyses were performed from gene-based analyses' results.

Results: : No SNP reached significant association ($p < 10^{-8}$) with the YBOCS. Six markers showed suggestive association ($p < 10^{-5}$). The top SNP was an intergenic variant in chromosome 2: rs7578149 ($p < 1.89 \times 10^{-6}$), located in a region suggestively associated with MDD. Linkage disequilibrium was found for two clusters of SNPs located between *SLC16A14* and *SP110* in chromosome 2, all of them forming one peak of association. Enrichment analyses revealed OCD genes to be associated with porin activity (FDR = 0.01) and transmembrane structure (FDR = 0.04).

Limitations: : The size of the sample and the transversal nature of the severity measure are limitations of this study.

Conclusion: : This study contributes to better characterize OCD at an individual level, helping to know more about the prognosis of the disorder and develop more individualized treatments.

Introduction

Obsessive compulsive disorder (OCD) is a neuropsychiatric condition with an estimated prevalence of 2–3% (Richter and Ramos, 2018). It may cause significant functional disability in daily life depending partly on the severity of the disorder, which varies significantly from one individual to another (Ruscio et al., 2010). Clinically, greater OCD severity is associated with an earlier age of onset (Wang et al., 2012),

* Corresponding author at: OCD Clinical and Research Unit, Deparment of Psychiatry, Hospital de Bellvitge c/ Feixa Llarga s/n 08907 Hospitalet de Llobregat, Barcelona, Spain.
E-mail addresses: mariaalemany92@gmail.com, malemanyn@idibell.cat (M. Alemany-Navarro).

https://doi.org/10.1016/j.jad.2020.01.161
Received 26 June 2019; Received in revised form 22 November 2019; Accepted 28 January 2020
Available online 29 January 2020

lower response to pharmacological treatments (Tükel et al., 2006) and a lower remission rate (Eisen et al., 2013). Biologically, familial OCD (having relatives diagnosed with OCD) has been linked to greater disease severity compared to sporadic OCD (Arumugham et al., 2014). In addition, neuroimaging studies have indicated that gray matter volumes within the left medial orbitofrontal cortex and left putamen contain discriminative information for predicting OCD severity (Hoexter et al., 2013). Since some of these clinical and biological characteristics have been associated to specific genetic contribution (Atmaca et al., 2011; Dickel et al., 2006; Real et al., 2013, 2009; Samuels et al., 2011), it might suggest that genetic factors might contribute to OCD severity.

Symptom severity has been shown to have a genetic component in other psychiatric disorders. In schizophrenia (SCZ), three studies have linked genetic variation to disease severity. For example, the severity of chronic delusional syndrome has been associated with rs20544, which is not a risk variant for SCZ (Lepeta et al., 2017), while more severe SCZ, which is associated with greater symptom severity at a given moment (Schennach et al., 2012), has been linked to heterozygosity of the C677T polymorphism within *MTHFR* (Kevere et al., 2014). Furthermore, telomere length has been reported to positively correlate with symptom severity, discriminating between remitted and non-remitted patients with SCZ (Maurya et al., 2018). A variant (rs0994359) within *ANK3*, a gene related to bipolar disorder status, has been reported to be suggestively associated with the severity of social anxiety disorder (Forstner et al., 2017). In major depressive disorder (MDD), the severity of the episodes has been linked to two polygenic risk scores built from risk variants for MDD and bipolar disorder (Ferentinos et al., 2014). Thus, all these findings provide further support for a potential genetic basis of OCD severity.

In a previous study exploring the ability of a polygenic risk score (PRS) to predict pharmacological treatment response in OCD patients, we observed an association with baseline and post-treatment severity (Alemany-Navarro et al., 2019), suggesting that genetic factors might affect OCD severity independently of pharmacological treatment.

While candidate gene and genome-wide association studies (GWAS) have identified risk variants for OCD within catecholaminergic, glutamatergic and neurotrophic genes (Mattheisen et al., 2015; Stewart et al., 2013; Taylor, 2013), to our knowledge, there have been no studies specifically assessing whether OCD severity might be associated with genetic factors. The objective of this study was to explore the possible genomic bases of OCD severity. Knowing more about the genetic basis of OCD severity may help to know more about the prognosis of OCD patients and to develop more personalized treatments and prevention strategies.

Methods

Subjects

Four hundred and one Spanish Caucasian patients (n = 401; 210 females; mean age = 35.09 ± 10.66 years) with diagnosed OCD for at least one year were recruited from the OCD clinic at Bellvitge Hospital (Barcelona, Spain). Diagnoses were made by two psychiatrists with extensive clinical experience in OCD, following the DSM-IV criteria (American Psychiatric Association, 1994) and using the Structured Clinical Interview for DSM-IV Axis I Disorders - Clinician Version (SCID-I) (First et al., 1996). Patients presenting psychoactive substance abuse/dependence (current or in the past six months), psychotic disorders, intellectual disability, severe organic or neurological pathology (except tic disorders) or autism spectrum disorder (ASD) were excluded from the study. Other affective and anxiety disorders were not criteria for exclusion in the cases where OCD was the main diagnosis.

Patients were required to give their written informed consent after being fully informed about the study. This study was approved by the Ethical Committees of Bellvitge Hospital and was performed in accordance with the Declaration of Helsinki.

Clinical assessment

Sociodemographic, clinical and medical data were collected through a structured interview with each patient during their first appointment at our clinic.

The age at onset was defined as the moment when the obsessive symptoms reached a clinically significant level. Family psychiatric history was recorded as a dichotomous score, with specific information on OCD, Tourette syndrome and depression also collected. Only family members with a formal diagnosis were considered.

Baseline severity of the obsessive and compulsive symptoms was assessed through the clinician-administered version of the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman et al., 1989) during the patient's first visit to our clinic. A global score, as well as separate ones for the obsessions and compulsions, respectively, was recorded.

Genotyping data and quality control

Our initial sample consisted of 401 OCD patients, who were genotyped using the Infinium PsychArray-24 BeadChip kit (Illumina). This array was developed in collaboration with the Psychiatric Genomics Consortium (PGC) and includes 50,000 variants associated with common psychiatric disorders. Variant calling was performed using three different algorithms: GenCall, which is Illumina's default calling algorithm, and Birdseed were used for common variants, while zCall was applied for rare variants. A unique set of genotypes was made from a consensus merge between the results from GenCall and Birdseed for the common variants, also including the rare variants called by zCall.

Quality control filtering was carried out for the obtained genotype data using PLINK (Purcell et al., 2007). Only non-monomorphic autosomal biallelic variants were analyzed. Markers with a genotype call rate <98% or those showing clear deviation from the Hardy-Weinberg equilibrium (HWE) ($p < 0.0001$) were discarded.

Samples with a call rate below 98% were removed. Identity by descent was calculated using independent SNPs, filtering out those with a pi-hat greater than 0.2 (Marees et al., 2018). Population stratification was analyzed by principal component analysis, removing the samples that were more than 5 standard deviations (sd) away from the mean in the first two components.

Statistical analysis

SNP-level association analysis was performed using the GenABEL library for R (Aulchenko et al., 2007). Association with OCD severity was evaluated by linear regression analyses, using as dependent variables the global Y-BOCS score and the obsession and compulsion subscale scores. In the regression model SNPs were coded under a log-additive model (in which the genotypes were coded as 0, 1 or 2 in relation to the number of minor alleles); age and sex were included as covariates in the model. These analyses were performed for autosomal SNPs (markers showing a minor allele frequency (MAF) > 0.05 in non-sex chromosomes). Linkage disequilibrium (LD) plots were obtained with the LocusZoom software, based on the 1000 Genomes CEU population data (hg19/1000 Genomes Mar 2012 EUR) (Pruim et al., 2010). For SNP annotation, we used the Infinium PsychArray Gene Annotation File provided by Illumina (https://support.illumina.com/downloads/infinium-psycharray-product-support-files.html).

Gene-based association analyses were performed with the Sequence Kernel Association Test (SKAT) (Wu et al., 2011) using the SKATMeta library (Voorman et al., 2013) for R to explore the cumulative effect of SNPs and the rare variants of a given gene on OCD severity, using global YBOCS score as the dependent variable. Only the results from genes with at least two genotyped markers were considered. False discovery rate (FDR) correction was used to determine statistical significance.

Table 1
Sociodemographic and clinical characteristics of the sample of 376 OCD patients.

Age, years	35.15 ± 10.73 (18–71)
Male/Female	186/190 (49.47/ 50.53)
Age at onset of OCD	19.87 ± 8.98 (4–46)*
Y-BOCS score	
Global	25.80 ± 5.53 (9–40)
Obsessions	12.62 ± 3.58 (0–20)
Compulsions	12.30 ± 3.96 (0- 20)
Baseline HDRS score	12.21 ± 5.97 (0–29)
Current comorbidity	
No comorbidity	212 (56.38)
Mood disorder	71 (18.88)
Tics	52 (13.83)
Eating disorders	19 (05.05)
Presence of dimensions in worst-ever period	
Aggresive/checking	278 (73.94)
Symmetry/ordering	162 (43.09)
Contamination/cleaning	172 (45.74)
Hoarding	91 (24.20)
Sexual/religious	95 (25.27)
Family psychiatric history	
No psychiatric diagnosis	138 (36.70)
OCD	81 (21.54)
Mood disorder	114 (30.32)
Tics/ Tourette sydrome	35 (9.31)

OCD, obsessive compulsive disorder; Y-BOCS, Yale-Brown Obsessive Compulsive Scale; HDRS, Hamilton Depression Rating Scale.
Data are mean ± SD (range) or percentage (%).
* Age at onset was collected for 374 patients (n = 374).

Enrichment analyses were performed for the genes with at least two genotyped markers and a SKAT p-value lower than 0.01, using web-accessible DAVID (Database for Annotation, Visualization and Integrated Discovery) Bioinformatics Resources v6.8 (Huang et al., 2009a, b).

Results

Genotyping and quality control

After quality control, 376 samples remained. Table 1 presents the sociodemographic and clinical data, including the Y-BOCS scores, of the final sample (n = 376).

SNP-level association analyses

Our total data set consisted of 338,357 autosomal markers, of which 258,937 were SNPs (MAF ≥ 0.05). We found nominal (α = 0.05) association for 13,661 SNPs. Among these, 335 had a p-value < 0.001 and 55 a p-value < 1×10^{-4}. No SNP reached genome-wide significance ($p < 5 \times 10^{-8}$) or passed the multiple comparison correction ($p = 1.97 \times 10^{-7}$). The SNP with the lowest p-value was an intergenic variant within chromosome 2 (rs7578149, $p = 1.89 \times 10^{-6}$, β = 1.92; SE = 0.40). There were 5 other SNPs showing suggestive association at $p < 1 \times 10^{-5}$ (Lander, E., Kruglyak, 1995) (rs9615637, rs11924650, rs6436908, rs229836 and rs7599478). Fig. 1 shows a 'Manhattan plot' (Fig. 1a) and a 'Q-Q plot' (Fig. 1b) of the association results for the common variants under a log-additive model. Association values for the top 55 SNPs ($p < 1 \times 10^{-4}$) are presented in Table 2. MAF values for some of the top SNPs in cases (our sample) and two control populations (Spanish DNA biobank and 1000g-EUR) are reported in Table S1. In general terms, we did not observe a tendency towards a greater MAF in cases for those SNPs positively associated *(positive β coefficient)* with severity, or a lower MAF for the SNPs with a negative β coefficient - as it could be expected.

Two of the top 55 SNPs, rs7599478 ($p = 8.68 \times 10^{-6}$, β = 1.86; SE = 0.42) and rs6436908 ($p = 7.94 \times 10^{-6}$, β = −1.75; SE = 0.39), occur in the same genomic region and have an intermediate LD (r2 = 0.36; D' = 1) between them, as reported by the LDlink database (Machiela and Chanock, 2018, 2015). Both are in high LD with the genotyped intergenic variants located between *SP110* and *SLC16A14* (rs6743476 ($p = 2.72 \times 10^{-5}$, β = 1.76; SE = 0.42) and rs12694840 ($p = 9.29 \times 10^{-5}$, β = 1.58; SE = 0.40); Fig. 2a and b). All these markers should be considered as forming a single association peak, since none of them maintained their level of association when adjusting the model for the rest of the markers.

We then compared our top associated SNPs with those previously linked to OCD, using the data available on the PGC website from two case-control GWAS on OCD risk (Mattheisen et al., 2015; Stewart et al., 2013). From a total of 8409,516 SNPs in the PGC data, 251,129 were also present in our data. However, when selecting the variants with a p-value of association below 1×10^{-4} for both sets of data, there were no remaining markers shared between our data and the PGC results.

We also tested for association with the obsession and compulsion subscales separately to clarify if one of these showed greater genetic weight. The Manhattan plots for both subscales are shown in Supplementary Figures 1 and 2 (Figures S1 and S2). For the obsession subscale, we observed associations for 13,117, 311 and 27 SNPs at the nominal, $p < 0.001$ and $p < 0.0001$ levels, respectively, with two SNPs showing suggestive association: rs6764121 ($p = 9.41 \times 10^{-6}$, β = −1.14; SE = 0.26) and rs35647811 ($p = 9.75 \times 10^{-6}$, β = −1.45; SE = 0.33) (Table S2). For the compulsion subscale, there were 13,378, 294 and 36 SNPs at the nominal, $p < 0.001$ and $p < 0.0001$ levels, respectively, with 4 presenting suggestive association: rs6569819 ($p = 4.19 \times 10^{-6}$, β = 1.33; SE = 0.29), rs16876441 ($p = 9.34 \times 10^{-6}$, β = −2.76; SE = 0.62), rs1285950 ($p = 3.94 \times 10^{-6}$, β = −1.43; SE = 0.31) and rs2220130 ($p = 9.21 \times 10^{-6}$, β = −1.25; SE = 0.28) (Table S3).

Gene-based association analyses

Gene-based analyses were performed for 21,551 genes. Of these, 16,653 had at least two genotyped markers and were analyzed further. Nominal association was shown by 882 genes, none of them passing the multiple comparison correction. Results for the top 12 genes ($p < 0.001$) are shown in Supplementary Table 4 (Table S4). The genes with the lowest p-value were *SLC8A1* (solute carrier family 8 member A1; $p = 1 \times 10^{-4}$), *MAP4K4* (mitogen-activated protein kinase 4; $p = 3 \times 10^{-4}$), *WTAP* (WT1 associated protein; $p = 2 \times 10^{-4}$) and *SLC22A10* (solute carrier family 22 member A10; $p = 1 \times 10^{-4}$).

Functional annotation

After selecting those genes with at least two genotyped markers and a SKAT p-value lower than 0.01, functional annotation was performed for a final set of 161 genes - referred to as the OCD genes from now on. The porin activity category was significantly enriched ($p = 8.0 \times 10^{-4}$), passing multiple correction (FDR = 0.01), and was represented by three genes: *AQP9* (aquaporin 9), *VDAC1* (voltage-dependent anion channel 1) and *TOMM40L* (translocase of outer mitochondrial membrane 40 like).

A substantial number of the OCD genes were included in the transmembrane category, which presented a fold enrichment of 1.4, reaching the multiple comparison threshold (p = 0.0032; FDR = 0.04). This category included 56 of the OCD genes (35.9%).

The other enriched categories included MAPK signaling, specifically the regulation of N-methyl-D-aspartate (NMDA) selective glutamate receptor activity (fold enrichment = 25.8; p = 0.0058; FDR = 0.086), which included three OCD genes (*RASGRF1* (Ras-specific guanine nucleotide-releasing factor 1), *MAPK8IP2* (mitogen-activated protein kinase 8 interacting protein 2) and *MEF2C* (myocyte enhancer factor 2C)). NOTCH signaling was also represented by three OCD genes (*DLL4*

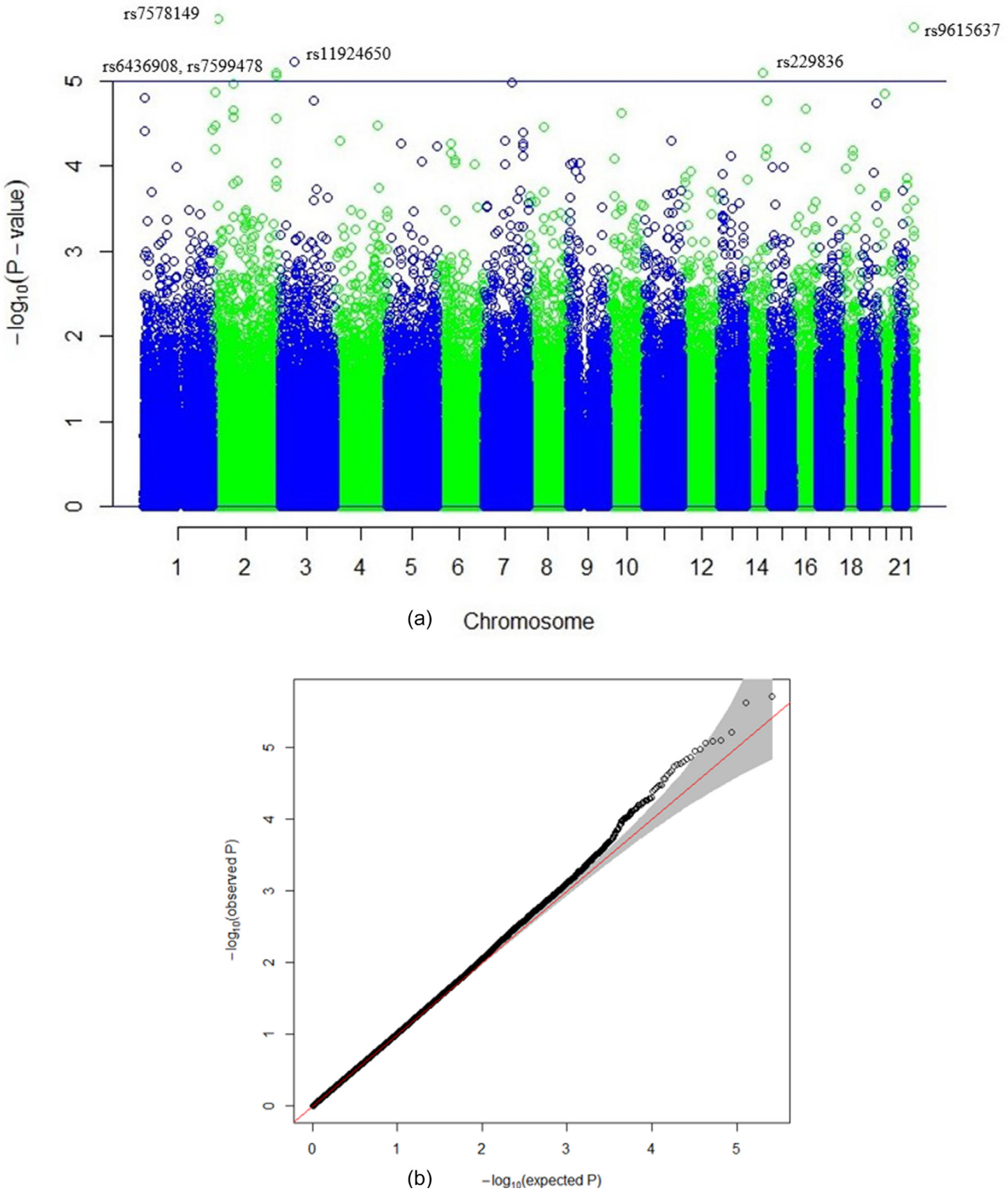

Fig. 1. Genome-wide association test of genetic variants and YBOCS scores (OCD global severity) **(a)** Manhattan plot for the association test. A blue line indicates the level of suggestive evidence of association (1×10^{-5}). (**b)** Q-Q plot for the association test.

(delta like canonical Notch ligand 4), *UBC* (ubiquitin C) and *PSEN2* (presenilin 2)). Activation of the Notch 1 and Notch 2 pathways showed nominal association ($p = 0.025$ and $p = 0.013$, respectively), displaying an enrichment score of 11.9 and 17.2, respectively, but not passing the multiple comparison correction (FDR = 0.16 and 0.29, respectively).

Three of the OCD genes (*MAPK8IP2, DPP4* (dipeptidyl peptidase 4) and *VDAC1*) were nominally associated with the behavioral fear response ($p = 0.02$), but they did not pass the multiple comparison correction (FDR = 0.28).

Discussion

To our knowledge, this is the first study attempting to analyze

Table 2
Results from the top SNPs associated with OCD severity from an additive model.

SNP	*N*	OR	P	Chr.	Position	Alleles	Region	Nearest gene (Distance in BP)
rs903908	374	−1.704501	1.57×10^{-05}	1	2,202,967	[T/C]	intronic	*SKI*
rs260513	376	1.633388	3.86×10^{-05}	1	2,180,524	[A/G]	intronic	*SKI*
rs7578149	376	1.917254	1.89×10^{-06}	2	20,312,438	[A/C]	intergenic	*RPS16P2* (42,896)
rs6436908	376	−1.754016	7.94×10^{-06}	2	230,995,447	[T/C]	intronic	*LOC107985997*
rs7599478	376	1.8553	8.68×10^{-06}	2	230,947,503	[A/C]	intergenic	*SLC16A14* (13,788)
rs3771875	375	−1.783821	1.10×10^{-05}	2	75,877,812	[A/G]	intronic	*MRPL19*
rs7591166	376	−1.841773	1.36×10^{-05}	2	9,616,035	[A/G]	intronic	*IAH1*
rs7588344	376	−1.707379	2.23×10^{-05}	2	75,846,558	T/C	intergenic	*MRPL19* (49,734)
rs2422230	376	−1.607521	2.70×10^{-05}	2	75,873,217	[T/C]	regulatory region variant	*MRPL19* (692)
rs6743476	376	1.764152	2.72×10^{-05}	2	230,992,756	[A/G]	intergenic	*SP110* (40,878)
rs2001658	375	−1.758046	3.28×10^{-05}	2	9,613,289	[T/C]	intergenic	*CPSF3* (50)
rs11674954	376	1.940089	3.66×10^{-05}	2	1,283,031	[T/G]	intronic	*SNTG2*
rs1048610	376	−1.721889	6.22×10^{-05}	2	9,634,856	[A/G]	exonic	*ADAM17*
rs12694840	376	1.576828	9.29×10^{-05}	2	230,997,403	[A/G]	intergenic	*SP110* (36,231)
rs11924650	376	1.979962	6.00×10^{-06}	3	54,258,938	[T/C]	intronic	*CACNA2D3*
rs870429	376	−1.780959	1.72×10^{-05}	3	122,878,019	[A/G]	intronic	*PDIA5*
rs2227421	376	−1.670388	3.30×10^{-05}	4	155,492,224	[A/C]	exonic	*FGB*
rs1495509	376	1.89329	5.11×10^{-05}	4	21,393,616	[T/C]	intronic	*KCNIP4*
rs2648727	376	2.010023	5.34×10^{-05}	5	52,074,401	[T/G]	intergenic	*PELO* (9373)
rs603852	376	1.590302	5.90×10^{-05}	5	177,905,384	[T/G]	intronic	*COL23A1*
rs6884946	376	1.832425	8.80×10^{-05}	5	122,899,301	[T/C]	intronic	*CSNK1G3*
rs10484428	375	1.640033	5.38×10^{-05}	6	48,871,002	[A/C]	intergenic	*LOC100418956* (48,704)
exm2270472	376	−1.958047	6.96×10^{-05}	6	48,608,329	[T/C]	intergenic	*LOC100418956* (311,377)
rs9296598	376	−1.973384	7.02×10^{-05}	6	48,564,858	[A/G]	intergenic	*RBMXP1* (322,153)
rs3010531	376	−1.954349	7.16×10^{-05}	6	48,581,776	[T/C]	intergenic	*LOC100418956* (337,930)
rs13191280	376	1.91115	8.63×10^{-05}	6	66,491,725	[T/C]	intergenic	*SLC25A51P1* (6047)
rs4299807	376	2.239835	8.99×10^{-05}	6	66,528,177	[A/G]	intergenic	*ADH5P4* (17,193)
rs6569819	376	−1.58711	9.51×10^{-05}	6	132,963,041	[T/G]	intergenic	*TAAR1* (3082)
rs7777145	376	2.832898	1.04×10^{-05}	7	97,688,936	[T/C]	intergenic	*LMTK2* (47,261)
kgp1254867	376	−1.823998	4.06×10^{-05}	7	141,551,958	[T/C]	intergenic	*ATP1A1OS* (12,897)
rs4731231	376	1.953784	5.02×10^{-05}	7	75,264,463	[A/G]	intronic	*HIP1*
rs1285950	376	−1.763092	5.33×10^{-05}	7	141,636,563	[A/C]	intronic	*CLEC5A*
rs10464444	376	−1.799561	5.78×10^{-05}	7	141,532,187	[A/G]	intergenic	*PRSS37* (3891)
rs11765575	375	−1.792576	5.79×10^{-05}	7	141,537,968	[A/G]	intronic	*PRSS37*
rs7794708	376	−1.749431	7.49×10^{-05}	7	141,653,637	[T/C]	intergenic	*CLEC5A* (6854)
rs12534422	376	1.719212	9.61×10^{-05}	7	75,263,792	[T/C]	intronic	*HIP1*
rs2719401	376	1.703063	3.42×10^{-05}	8	55,198,858	[A/C]	intergenic	*RNU105C*
rs519761	376	1.75594	9.03×10^{-05}	9	15,357,041	[T/C]	intergenic	*RPL7P33* (4331)
rs776022	376	−1.652346	9.23×10^{-05}	9	37,934,780	[T/C]	intronic	*SHB*
rs10815211	376	−1.960053	9.58×10^{-05}	9	5,412,546	[T/C]	intronic	*PLGRKT*
rs10857636	376	−3.222238	2.41×10^{-05}	10	49,985,110	[T/C]	intronic	*WDFY4*
exm2267086	376	2.012957	8.09×10^{-05}	10	26,505,496	[A/G]	exonic	*GAD2*
rs4144614	376	−1.594181	5.10×10^{-05}	11	95,742,703	[A/C]	intronic	*MAML2*
rs1575432	376	1.542177	7.70×10^{-05}	13	61,212,933	[T/C]	intergenic	*EIF4A1P6* (702)
rs229836	376	1.950295	8.17×10^{-06}	14	83,867,535	[A/G]	intergenic	*LOC100421611* (1597,087)
rs2626595	375	1.813838	1.68×10^{-05}	14	97,956,267	[T/C]	intergenic	*LOC101929241* (25,771)
rs11628827	376	2.001054	6.33×10^{-05}	14	97,929,204	[A/C]	intronic	*LOC101929241*
rs1861085	376	1.924046	7.68×10^{-05}	14	92,371,234	[T/C]	intronic	*FBLN5*
rs11647643	376	−1.840045	2.09×10^{-05}	16	49,259,509	[T/C]	intergenic	*CBLN1* (52,319)
rs12599955	375	1.653458	6.17×10^{-05}	16	49,257,835	[T/C]	intergenic	*CBLN1* (53,993)
rs321849	376	−1.657241	6.55×10^{-05}	18	48,957,511	[A/G]	intronic	*LOC100287225*
rs321858	376	−1.637564	7.70×10^{-05}	18	48,974,344	[T/C]	intronic	*LOC100287225*
rs10410689	376	−2.800791	1.80×10^{-05}	19	51,769,145	[T/C]	intronic	*SIGLECL1*
rs6132764	376	−1.857997	1.43×10^{-05}	20	24,752,226	[A/C]	regulatory region variant	*SYNDIG1* (104,937)
rs9615637	376	−2.343338	2.36×10^{-06}	22	48,184,882	[A/G]	intronic	*LOC284930*

SNP, single nucleotide polymorphism; Chr., chromosome number; OR, odds ratio; bp, base pairs.

genetic associations of OCD severity, measured with the Y-BOCS (Goodman et al., 1989), at the whole-genome level. Although further research with a larger sample is needed, the present study contributes to the understanding of how genetic variants may influence OCD severity. Although no SNP reached genome-wide significance, six markers showed suggestive association ($p < 1 \times 10^{-5}$), the top SNP being rs7578149 ($p < 1.89 \times 10^{-6}$, β = 1.92; SE = 0.40) located between *RPS16P2* and *LAPTM4A* (42,896 and 60,649 bp, respectively). The association analyses for the obsession and compulsion subscales revealed rs6764121 ($p = 9.41 \times 10^{-6}$, β = −1.14; SE = 0.26; *ATP13A4*) and rs1285950 ($p = 3.94 \times 10^{-6}$, β = −1.43; SE = 0.31; *CLEC5A*) as the top SNPs, respectively. Gene-based analyses, which simultaneously considered the effects of both rare and common variants, highlighted 12 genes that were suggestively associated ($p < 0.001$) with the Y-BOCS scores. In this case, the top two significant genes belonged to the solute carrier gene family (*SLC8A1* and *SLC22A10;* $p = 0.0001$). Enrichment analyses revealed that the OCD genes were associated with porin activity ($p = 8.0 \times 10^{-4}$; FDR = 0.01) and transmembrane structure ($p = 0.0032$; FDR = 0.04), and a trend of association with NMDA activity regulation ($p = 0.0058$; FDR = 0.086), the NOTCH signaling pathways ($p = 0.025/0.013$; FDR = 0.16/0.29) and the behavioral fear response ($p = 0.02$; FDR = 0.28).

The top associated SNP (rs7578149) is located in a region reported to have a marker suggestively associated with MDD in females (rs7565124; $p = 3.05 \times 10^{-6}$) (Aragam et al., 2011). While there is no LD between these two SNPs, as reported on the LDlink database (Machiela and Chanock, 2018, 2015), they may both be associated with differences in the expression of the same gene. We observed two more

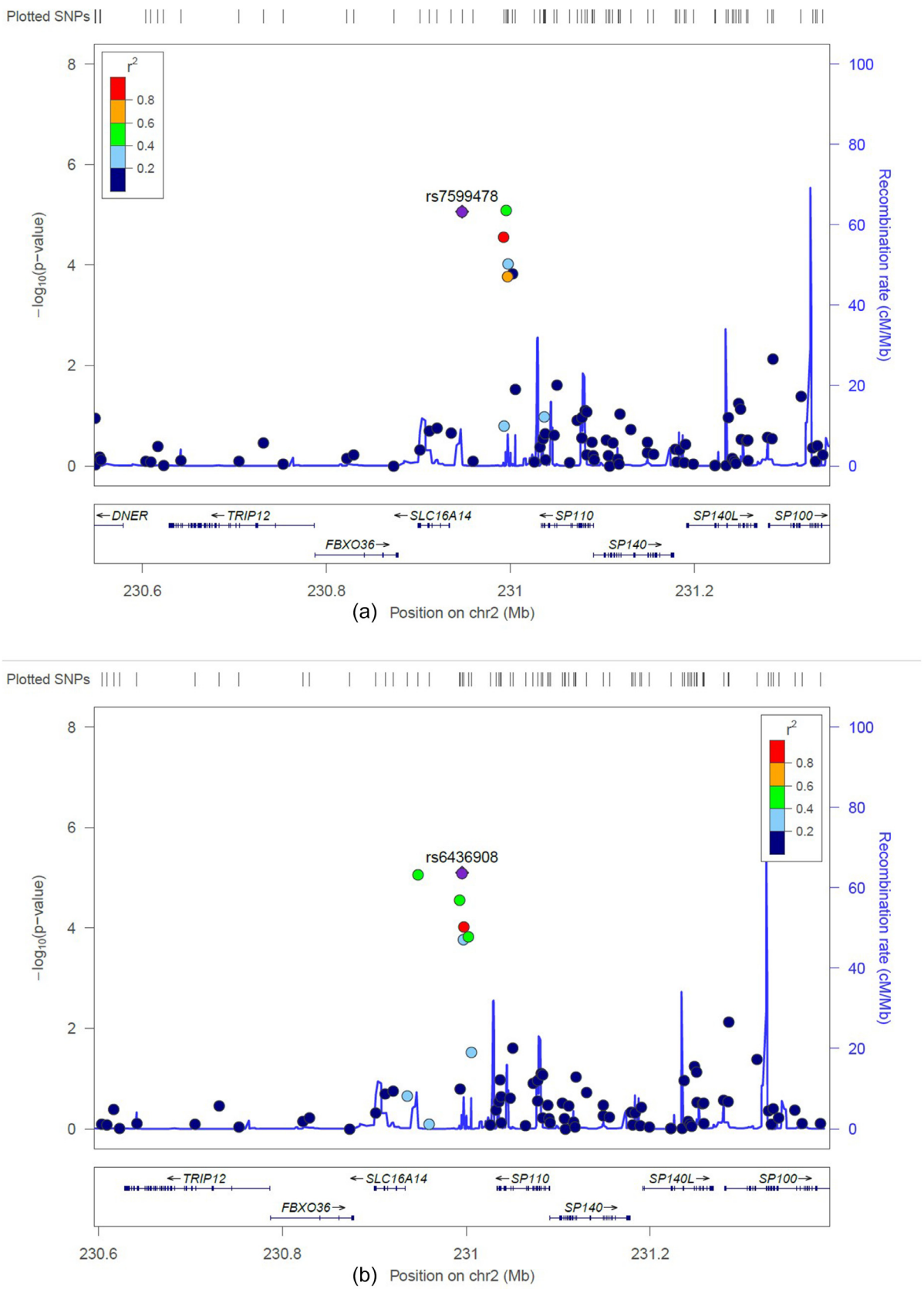

Fig. 2. Regional association plots with LD reported for suggestively associated ($p < 10^{-5}$) single-nucleotide polymorphisms (SNPs) in chromosome 2. (**a**) Plot of rs7599478 for the association test with the YBOCS (**b**) Plot of rs6436908.

suggestively associated SNPs also in chromosome 2: rs6436908 ($p = 7.94 \times 10^{-6}$, $\beta = -1.75$; SE = 0.39) and rs7599478 ($p = 8.68 \times 10^{-6}$, $\beta = 1.86$; SE = 0.42). Of these, rs6436908 falls within a GENCODE gene (*LOC107985997*) of unknown function and has been described as an eQTL for both *SLC16A14* in the liver and *SP110* in blood (Bonder et al., 2011; Lusis et al., 2008), with rs7599478 located between these two genes. *SLC16A14* is a member of the monocarboxylic acid transporter gene family, which is involved in energy metabolism, drug transport and T cell activation, and may also be associated with memory and learning processes and neurodegenerative diseases (Halestrap, 2013; Pérez-Escuredo et al., 2016). *SP110*, on the other hand, is involved in immunological responses and transcription regulation (Cliffe et al., 2012; Lei et al., 2012; Leu et al., 2018), with a variant of this gene being reported to be associated with suicide (rs181058279, $p = 5.45 \times 10^{-6}$) (Coon et al., 2018). Given the suggestively associated SNPs near these two genes, as well as *LOC107985997* (rs6436908) and the LD findings for this region (Fig. 2), it would be interesting to perform further research on this whole genomic domain to elucidate the genetic bases of OCD severity.

The three other SNPs with suggestive association were: rs229836 ($p = 8.17 \times 10^{-6}$, $\beta = 1.95$; SE = 0.44), an intergenic variant located between the two pseudogenes LOC100421611 and RNU7-51P that do not have relevant information available; rs11924650 ($p = 6.00 \times 10^{-6}$, $\beta = 1.98$; SE = 0.44), a SNP in an intronic region of *CACNA2D3,* a gene that has been suggestively associated with schizophrenia and schizoaffective disorders (rs9311525, $p = 1.03 \times 10^{-5}$), antipsychotic response, Alzheimer's disease (AD) (rs7431992, $p = 2.00 \times 10^{-6}$) and child development disorders (rs1467179, $p = 6.17 \times 10^{-5}$) (Li et al., 2017; Moons et al., 2016; Tosto et al., 2015); and rs9615637 ($p = 2.36 \times 10^{-6}$, $\beta = -2.34$; SE = 0.50) located in *LOC284930*, a gene linked to paliperidone response in schizophrenic patients (rs147466853; $p = 2.00 \times 10^{-6}$) (Li et al., 2017).

The top SNPs for the obsession and compulsion subscales were two intronic variants within *ATP13A4* and *CLEC5A*, respectively. The first, which encodes an ATPase protein, has been linked to impaired language acquisition, dyslexia and an increased risk for ASD (Biamino et al., 2015; Kwasnicka-crawford et al., 2005; Vallipuram et al., 2010; Worthey et al., 2013). The second, although not directly associated with any neuropsychiatric condition, is involved in functions that have been previously reported to be associated with OCD (Renna et al., 2018; Rodríguez et al., 2017; Uhl and Martinez, 2019; Vilboux et al., 2016; Zamanian-azodi et al., 2018), such as cell adhesion, cell-cell signaling, inflammation and immune responses (Batliner et al., 2011; Gupta et al., 2010; Teng et al., 2016).

Enrichment analyses revealed that porin activity was significantly represented by three of our OCD genes: *AQP9, VDAC1* and *TOMM40L*. Porins are integral membrane proteins that function as pores through which different molecules can enter or leave a cell. Efficient porin activity is needed for optimal gradient concentrations and water homeostasis, which are essential for correct brain functioning (Min and van der Knaap, 2018). In fact, VDAC1 has been suggested to be relevant in the pathogenesis and pathophysiology of AD (Ferrer, 2009; Manczak et al., 2013; Manczak and Reddy, 2013), while *TOMM40L* is associated with different neurological conditions such as amyotrophic lateral sclerosis, AD, frontotemporal lobar degeneration, Parkinson's disease and dementia, as well as with non-pathological cognitive aging (Heinemeyer et al., 2018). Meanwhile, *AQP9* has been observed to be involved in neuronal damage in an *in vitro* Parkinson's disease model (Avola et al., 2018).

It is interesting to note that 35.9% of our OCD genes (56 out of 161) are related to transmembrane structure and functioning ($p = 0.0032$; FDR = 0.04), with the three genes associated with porin activity also included in this functional category. The role of transmembrane proteins in different neurodevelopmental and neuropsychiatric disorders has been widely reported (Cao and Tabuchi, 2017; Eggert et al., 2018; Kasem et al., 2018). Some of the OCD genes included in this category have been previously suggested to be involved in different psychiatric disorders and neurological conditions (Gai et al., 2016; Krohn et al., 2011; Murray and Zhou, 2017; Schumacher et al., 2012).

Our results also indicated that the regulation of NMDA activity might be associated with OCD as there was also an overrepresentation of OCD genes in this category ($p = 0.0058$; FDR = 0.086), which included *RASGRF1, MPK8IP2* and *MEF2C*. The involvement of glutamatergic activity, specifically NMDA receptor activity, in OCD has been well established (Albelda et al., 2010; Alonso et al., 2012; Mataix-Cols et al., 2017).

Three of the OCD genes were associated with NOTCH signaling pathways (*DLL4, UBC* and *PSEN2*) (Activation of Notch 1: $p = 0.025$, FDR = 0.16; Activation of Notch 2: $p = 0.013$, FDR = 0.29). NOTCH signaling has been linked to dopaminergic responsiveness in the striatum (Toritsuka et al., 2017). Disturbed NOTCH signaling has been observed in schizophrenia and bipolar disorder (Hoseth et al., 2018). In the adult central nervous system, NOTCH signaling in brain regions such as the basolateral amygdala and hippocampus seems to be involved in instrumental conditioning and fear-related learning through the modulation of synaptic plasticity (Dias Brian George et al., 2014; Yoon et al., 2012). These results, together with the three OCD genes associated with the behavioral fear response (*MAPK8IP2, DPP4* and *VDAC1*), support the implication of the fear response dysfunction observed in OCD (Dougherty et al., 2018).

This study has some strengths to be noted. Our study cohort was thoroughly characterized phenotypically and our results, although only exploratory, are encouraging, highlighting several relevant pathways and providing suggestive evidence of linkage for some interesting genes. In addition, given the growing importance of rare variants in neuropsychiatry, their effect in addition to those of the common variants were considered in the gene-based analyses (Ament et al., 2015; Amin et al., 2018; Singh et al., 2017).

Limitations

Although we obtained interesting results passing multiple comparison correction in the enrichment analyses, we think the lack of findings reaching whole-genome significance at SNP-level analyses might be due in part to our sample size ($n = 376$). Since this study conforms a very exploratory analysis on the genomic bases of OCD severity, we think a larger sample might be required in order to obtain some positive results at this level of analysis. In addition, our OCD severity measure does not report a whole course severity, but rather a transversal measure of the severity. Longitudinal variables accounting for the course of the disorder, such as worst-ever period severity, might be important to elucidate the genetic influences on OCD severity. Similar approaches with larger sample sizes will help unravel the genetic influences on OCD severity.

Conclusions

The relevance of this study is through its contribution in better characterizing OCD at an individual level, which might help in knowing more about the prognosis of the disorder and developing more individualized treatments. Further research with larger samples and different methodologies is needed. Moreover, next-generation sequencing could provide more information on the rare variants and *de novo* mutations that might be involved in OCD severity.

Acknowledgments and disclosures

This study was supported in part by the Carlos III Health Institute (PI16/00950, PI18/00856); FEDER funds ('A way to build Europe') and by the Agency for Management of University and Research Grants of the Catalan Government (2014SGR1672).

MA was supported by the Secretariat for Universities and Research

of the Ministry of Business and Knowledge of the Government of Catalonia. Grant co-funded by the European Social Fund (ESF) “ESF, Investing in your future” (2017 FI_B 00327). ER was supported by a Juan Rodés contract (JR14/00038).

None of these funding sources participated in the preparation of the research article.

We thank all the study participants from the Department of Psychiatry of Hospital Universitari de Bellvitge who collaborated to obtain the sample of this study.

CRediT authorship contribution statement

María Alemany-Navarro: Conceptualization, Investigation, Software, Visualization, Writing - original draft, Writing - review & editing, Data curation, Formal analysis, Methodology, Supervision. **Raquel Cruz:** Software, Supervision, Visualization, Writing - review & editing, Data curation, Formal analysis, Methodology. **Eva Real:** Investigation, Project administration, Supervision, Writing - review & editing. **Cinto Segalàs:** Investigation, Supervision. **Sara Bertolín:** Conceptualization, Investigation, Supervision. **Isabel Baenas:** Conceptualization, Investigation, Supervision. **Laura Domènech:** Supervision. **Raquel Rabionet:** Writing - review & editing, Supervision. **Ángel Carracedo:** Supervision. **Jose M. Menchón:** Project administration, Validation, Funding acquisition, Supervision. **Pino Alonso:** Investigation, Project administration, Resources, Supervision, Validation, Visualization, Writing - review & editing, Funding acquisition, Methodology.

Declaration of Competing Interest

The authors declare not having any conflict of interests.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.01.161.

References

Albelda, N., Bar-On, N., Joel, D., 2010. The role of NMDA receptors in the signal attenuation rat model of obsessive-compulsive disorder. Psychopharmacology (Berl). https://doi.org/10.1007/s00213-010-1808-9.

Alemany-Navarro, M., Costas, J., Real, E., Segalàs, C., Bertolín, S., Domènech, L., Rabionet, R., Carracedo, Á., Menchón, J.M., Alonso, P., 2019. Do polygenic risk and stressful life events predict pharmacological treatment response in obsessive compulsive disorder? A gene–environment interaction approach. Transl. Psychiatry. https://doi.org/10.1038/s41398-019-0410-0.

Alonso, P., Gratacós, M., Segalàs, C., Escaramís, G., Real, E., Bayés, M., Labad, J., López-Solà, C., Estivill, X., Menchón, J.M., 2012. Association between the NMDA glutamate receptor GRIN2B gene and obsessive-compulsive disorder. J. Psychiatry Neurosci. https://doi.org/10.1503/jpn.110109.

Ament, S.A., Szelinger, S., Glusman, G., Ashworth, J., Hou, Liping, Akula, N., Shekhtman, T., Badner, J.A., Brunkow, M.E., Mauldin, D.E., Stittrich, A.-B., Rouleau, K., Detera-Wadleigh, S.D., Nurnberger, J.I., Edenberg, H.J., Gershon, E.S., Schork, N., Study, G., Price, N.D., Gelinas, R., Hood, Leroy, Craig, D., Mcmahon, F.J., Kelsoe, J.R., Roach, J.C., Hood, L, Hou, L, 2015. Rare variants in neuronal excitability genes influence risk for bipolar disorder. Proc. Natl. Acad. Sci. U.S.A. 112, 3576–3581. https://doi.org/10.1073/pnas.1424958112.

American Psychiatric Association, 1994. DSM-IV-TR : Diagnostic and Statistical Manual of Mental Disorders, fourth ed. American Psychiatric Press, Washington, DC.

Amin, N., De Vrij, F.M.S., Baghdadi, M., Brouwer, R.W.W., Van Rooij, J.G.J., Jovanova, O., Uitterlinden, A.G., Hofman, A., Janssen, H.L.A., Darwish Murad, S., Kraaij, R., Stedehouder, J., Van Den Hout, M.C.G.N., Kros, J.M., Van Ijcken, W.F.J., Tiemeier, H., Kushner, S.A., Van Duijn, C.M., 2018. A rare missense variant in RCL1 segregates with depression in extended families. Mol. Psychiatry. https://doi.org/10.1038/mp.2017.49.

Aragam, N., Wang, K., Pan, Y., 2011. Genome-wide association analysis of gender differences in major depressive disorder in the Netherlands NESDA and NTR population-based samples. J. Affect. Disord. 133, 516–521. https://doi.org/10.1016/j.jad.2011.04.054.

Arumugham, S.S., Cherian, A.V., Baruah, U., Viswanath, B., Narayanaswamy, J.C., Math, S.B., Reddy, Y.C.J., 2014. Comparison of clinical characteristics of familial and sporadic obsessive-compulsive disorder. Compr. Psychiatry 55, 1520–1525. https://doi.org/10.1016/j.comppsych.2014.07.006.

Atmaca, M., Onalan, E., Yildirim, H., Yuce, H., Koc, M., Korkmaz, S., Mermi, O., 2011. Serotonin transporter gene polymorphism implicates reduced orbito-frontal cortex in obsessive-compulsive disorder. J. Anxiety Disord. 25, 680–685. https://doi.org/10.1016/j.janxdis.2011.03.002.

Aulchenko, Y.S., Ripke, S., Isaacs, A., van Duijn, C.M., 2007. GenABEL: an R library for genome-wide association analysis. Bioinformatics. https://doi.org/10.1093/bioinformatics/btm108.

Avola, R., Graziano, A.C.E., Pannuzzo, G., Albouchi, F., Cardile, V., 2018. New insights on Parkinson's disease from differentiation of SH-SY5Y into dopaminergic neurons: an involvement of aquaporin4 and 9. Mol. Cell. Neurosci. 88, 212–221. https://doi.org/10.1016/j.mcn.2018.02.006.

Batliner, J., Mancarelli, M.M., Jenal, M., Reddy, V.A., Fey, M.F., Torbett, B.E., Tschan, M.P., 2011. CLEC5A (MDL-1) is a novel PU.1 transcriptional target during myeloid differentiation. Mol. Immunol. https://doi.org/10.1016/j.molimm.2010.10.016.

Biamino, E., Di Gregorio, E., Belligni, E.F., Keller, R., Riberi, E., Gandione, M., Calcia, A., Mancini, C., Giorgio, E., Simona, C., Pappi, P., Talarico, F., Fea, A.M., De Rubeis, S., Silengo, M.C., Ferrero, G.B., Brusco, A., 2015. A novel 3q29 deletion associated with autism, intellectual disability, psychiatric disorders, and obesity. Am. J. Med. Genet. Part B Neuropsychiatr. Genet 171, 290–299. https://doi.org/10.1002/ajmg.b.32406.

Bonder, M.J., Elbers, C.C., Westra, H.-J., Hofstra, R.M.W., Zhernakova, A., Arends, D., Groen, H.J.M., Hofker, M.H., Wolfs, M.G.M., Fu, J., Weersma, R.K., te Meerman, G.J., Veldink, J.H., Rensen, S., Smolonska, A., Trynka, G., Jansen, R.C., Platteel, M., Ophoff, R.A., Buurman, W.A., Festen, E.M., Deelen, P., Franke, L., Wijmenga, C., Saris, C.G.J., Fehrmann, R.S.N., van Heel, D.A., van den Berg, L.H., 2011. Trans-eQTLs reveal that independent genetic variants associated with a complex phenotype converge on intermediate genes, with a major role for the HLA. PLoS Genet. 7, e1002197. https://doi.org/10.1371/journal.pgen.1002197.

Cao, X., Tabuchi, K., 2017. Functions of synapse adhesion molecules neurexin/neuroligins and neurodevelopmental disorders. Neurosci. Res. https://doi.org/10.1016/j.neures.2016.09.005.

Cliffe, S.T., Bloch, D.B., Suryani, S., Kamsteeg, E.-J., Avery, D.T., Palendira, U., Church, J.A., Wainstein, B.K., Trizzino, A., Lefranc, G., Akatcherian, C., Megarbané, A., Gilissen, C., Moshous, D., Reichenbach, J., Misbah, S., Salzer, U., Abinun, M., Ong, P.Y., Stepensky, P., Ruga, E., Ziegler, J.B., Wong, M., Tangye, S.G., Lindeman, R., Buckley, M.F., Roscioli, T., 2012. Clinical, molecular, and cellular immunologic findings in patients with SP110-associated veno-occlusive disease with immunodeficiency syndrome. J. Allergy Clin. Immunol. 130, 735–742. https://doi.org/10.1016/j.jaci.2012.02.054.

Coon, H., Darlington, T.M., DiBlasi, E., Callor, W.B., Ferris, E., Fraser, A., Yu, Z., William, N., Das, S.C., Crowell, S.E., Chen, D., Anderson, J.S., Klein, M., Jerominski, L., Cannon, D., Shabalin, A., Docherty, A., Williams, M., Smith, K.R., Keeshin, B., Bakian, A.V, Christensen, E., Li, Q.S., Camp, N.J., Gray, D., 2018. Genome-wide significant regions in 43 Utah high-risk families implicate multiple genes involved in risk for completed suicide. Mol. Psychiatry. https://doi.org/10.1038/s41380-018-0282-3.

Dias Brian, George, Goodman, J.V., Ahluwalia, R., Easton, A.E., Andero, R., Ressler, K.J., 2014. Amygdala-dependent fear memory consolidation via miR-34a and notch signaling. Neuron. https://doi.org/10.1016/j.neuron.2014.07.019.

Dickel, D.E., Veenstra-VanderWeele, J., Cox, N.J., Wu, X., Fischer, D.J., Van Etten-Lee, M., Himle, J.A., Leventhal, B.L., Cook, E.H., Hanna, G.L., 2006. Association testing of the positional and functional candidate gene SLC1A1/EAAC1 in early-onset obsessive-compulsive disorder. Arch. Gen. Psychiatry 63, 778–785. https://doi.org/10.1001/archpsyc.63.7.778.

Dougherty, D.D., Brennan, B.P., Stewart, S.E., Wilhelm, S., Widge, A.S., Rauch, S.L., 2018. Neuroscientifically informed formulation and treatment planning for patients with obsessive-compulsive disorder: a review. JAMA Psychiatry. https://doi.org/10.1001/jamapsychiatry.2018.0930.

Eggert, S., Thomas, C., Kins, S., Hermey, G., 2018. Trafficking in alzheimer’s disease: modulation of APP transport and processing by the transmembrane proteins LRP1, SorLA, SorCS1c, Sortilin, and Calsyntenin. Mol. Neurobiol. https://doi.org/10.1007/s12035-017-0806-x.

Eisen, J.L., Sibrava, N.J., Boisseau, C.L., Mancebo, M.C., Stout, R.L., Pinto, A., Rasmussen, S.A., 2013. Five-year course of obsessive-compulsive disorder: predictors of remission and relapse. J. Clin. Psychiatry 74, 233–239. https://doi.org/10.4088/JCP.12m07657.

Ferentinos, P., Rivera, M., Ising, M., Spain, S.L., Cohen-Woods, S., Butler, A.W., Craddock, N., Owen, M.J., Korszun, A., Jones, L., Jones, I., Gill, M., Rice, J.P., Maier, W., Mors, O., Rietschel, M., Lucae, S., Binder, E.B., Preisig, M., Tozzi, F., Muglia, P., Breen, G., Craig, I.W., Farmer, A.E., Müller-Myhsok, B., McGuffin, P., Lewis, C.M., 2014. Investigating the genetic variation underlying episodicity in major depressive disorder: suggestive evidence for a bipolar contribution. J. Affect. Disord. 155, 81–89. https://doi.org/10.1016/j.jad.2013.10.027.

Ferrer, I., 2009. Altered mitochondria, energy metabolism, voltage-dependent anion channel, and lipid rafts converge to exhaust neurons in Alzheimer's disease. J. Bioenerg. Biomembr. https://doi.org/10.1007/s10863-009-9243-5.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1996. Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version (SCID-CV). American Psychiatric Press, Washington.

Forstner, A.J., Rambau, S., Friedrich, N., Ludwig, K.U., Böhmer, A.C., Mangold, E., Maaser, A., Hess, T., Kleiman, A., Bittner, A., Nöthen, M.M., Becker, J., Geiser, F., Schumacher, J., Conrad, R., 2017. Further evidence for genetic variation at the serotonin transporter gene SLC6A4 contributing toward anxiety. Psychiatr. Genet. 27, 96–102. https://doi.org/10.1097/YPG.0000000000000171.

Gai, Y., Liu, Z., Cervantes-Sandoval, I., Davis, R.L., 2016. Drosophila SLC22A transporter is a memory suppressor gene that influences cholinergic neurotransmission to the mushroom bodies. Neuron. https://doi.org/10.1016/j.neuron.2016.03.017.

Goodman, W.K., Price, L.H., Rasmussen, S.A., Mazure, C., Fleischmann, R.L., Hill, C.L.,

Heninger, G.R., Charney, D.S., 1989. The yale-brown obsessive compulsive scale. I. Development, use, and reliability. Arch. Gen. Psychiatry 46, 1006–1011.
Gupta, N., Lomash, V., Rao, P.V.L., 2010. Expression profile of Japanese encephalitis virus induced neuroinflammation and its implication in disease severity. J. Clin. Virol. 49, 4–10. https://doi.org/10.1016/j.jcv.2010.06.009.
Halestrap, A.P., 2013. Monocarboxylic acid transport. Compr Physiol. 3, 1611–1643. https://doi.org/10.1002/cphy.c130008.
Heinemeyer, T., Stemmet, M., Bardien, S., Neethling, A., 2018. Underappreciated roles of the translocase of the outer and inner mitochondrial membrane protein complexes in human disease. DNA Cell Biol. https://doi.org/10.1089/dna.2018.4292.
Hoexter, M.Q., Miguel, E.C., Diniz, J.B., Shavitt, R.G., Busatto, G.F., Sato, J.R., 2013. Predicting obsessive–compulsive disorder severity combining neuroimaging and machine learning methods. J. Affect. Disord. 150, 1213–1216. https://doi.org/10.1016/j.jad.2013.05.041.
Hoseth, E.Z., Krull, F., Dieset, I., Mørch, R.H., Hope, S., Gardsjord, E.S., Steen, N.E., Melle, I., Brattbakk, H.-R., Steen, V.M., Aukrust, P., Djurovic, S., Andreassen, O.A., Ueland, T., 2018. Attenuated Notch signaling in schizophrenia and bipolar disorder. Sci. Rep. https://doi.org/10.1038/s41598-018-23703-w.
Huang, DW, Sherman, BT, Lempicki, RA, 2009a. Systematic and integrative analysis of large gene lists using DAVID Bioinformatics Resources. Nat. Protoc. 4, 44–57.
Huang, D.W., Sherman, B.T., Lempicki, R.A., 2009b. Bioinformatics enrichment tools: paths toward the comprehensive functional analysis of large gene lists. Nucl. Acids Res. 37, 1–13.
Kasem, E., Kurihara, T., Tabuchi, K., 2018. Neurexins and neuropsychiatric disorders. Neurosci. Res. https://doi.org/10.1016/j.neures.2017.10.012.
Kevere, L., Purvina, S., Bauze, D., Zeibarts, M., Andrezina, R., Piekuse, L., Brekis, E., Purvins, I., 2014. Homocysteine and MTHFR C677T polymorphism in children and adolescents with psychotic and mood disorders. Nord. J. Psychiatry 68, 129–136. https://doi.org/10.3109/08039488.2013.782066.
Krohn, M., Lange, C., Hofrichter, J., Scheffler, K., Stenzel, J., Steffen, J., Schumacher, T., Brüning, T., Plath, A.-S., Alfen, F., Schmidt, A., Winter, F., Rateitschak, K., Wree, A., Gsponer, J., Walker, L.C., Pahnke, J., 2011. Cerebral amyloid-β proteostasis is regulated by the membrane transport protein ABCC1 in mice. J. Clin. Invest. 121, 3924–3931. https://doi.org/10.1172/JCI57867DS1.
Kwasnicka-crawford, D.A., Carson, A.R., Roberts, W., Summers, A.M., Rehnström, K., Järvelä, I., Sherer, S.W., 2005. Characterization of a novel cation transporter ATPase gene (ATP13A4) interrupted by 3q25–q29 inversion in an individual with language delay. Genomics 86, 182–194. https://doi.org/10.1016/j.ygeno.2005.04.002.
Lander, E., Kruglyak, L., 1995. Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results. Nat. Genet. 11, 241.
Lei, X., Zhu, H., Zha, L., Wang, Y., 2012. SP110 gene polymorphisms and tuberculosis susceptibility: a systematic review and meta-analysis based on 10 624 subjects. Infect. Genet. Evol. https://doi.org/10.1016/j.meegid.2012.05.011.
Lepeta, K., Purzycka, K.J., Pachulska-Wieczorek, K., Mitjans, M., Begemann, M., Vafadari, B., Bijata, K., Adamiak, R.W., Ehrenreich, H., Dziembowska, M., Kaczmarek, L., 2017. A normal genetic variation modulates synaptic MMP-9 protein levels and the severity of schizophrenia symptoms. EMBO Mol. Med. 9, 1100–1116. https://doi.org/10.15252/emmm.201707723.
Leu, J.S., Chang, S.Y., Mu, C.Y., Chen, M.L., Yan, B.S., 2018. Functional domains of SP110 that modulate its transcriptional regulatory function and cellular translocation. J. Biomed. Sci. https://doi.org/10.1186/s12929-018-0434-4.
Li, J., Yoshikawa, A., Brennan, M.D., Ramsey, T.L., Meltzer, H.Y., 2017. Genetic predictors of antipsychotic response to lurasidone identified in a genome wide association study and by schizophrenia risk genes. Schizophr. Res. https://doi.org/10.1016/j.schres.2017.04.009.
Li, Q., Wineinger, N.E., Fu, D., Libiger, O., Alphs, L., Savitz, A., Gopal, S., Cohen, N., Schork, N.J., 2017. Genome-wide association study of paliperidone efficacy. Pharmacogenet. Genom. 27, 7–18.
Lusis, A.J., Strom, S.C., Guengerich, F.P., Mehrabian, M., Molony, C., Millstein, J., Kruger, M.J., Chudin, E., Schadt, E.E., Sieberts, S., Hao, K., Yang, X., Zhu, J., Lamb, J., Kasarskis, A., Suver, C., Johnson, J.M., Wang, S., Lum, P.Y., Rushmore, T.H., Rohl, C.A., van Nas, A., GuhaThakurta, D., Schuetz, E., Avila-Campillo, I., Ulrich, R., Smith, R.C., Drake, T.A., Zhang, B., Derry, J., Storey, J.D., 2008. Mapping the genetic architecture of gene expression in human liver. PLoS Biol. 6, e107. https://doi.org/10.1371/journal.pbio.0060107.
Machiela, M.J., Chanock, S.J., 2018. LDassoc: an online tool for interactively exploring genome-wide association study results and prioritizing variants for functional investigation. Bioinformatics 34, 887–889. https://doi.org/10.1093/bioinformatics/btx561.
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, 3555–3557. https://doi.org/10.1093/bioinformatics/btv402.
Manczak, M., Reddy, P.H., 2013. RNA silencing of genes involved in Alzheimer's disease enhances mitochondrial function and synaptic activity. Biochim. Biophys. Acta. https://doi.org/10.1016/j.bbadis.2013.09.008.
Manczak, M., Sheiko, T., Craigen, W.J., Reddy, P.H., 2013. Reduced VDAC1 protects against alzheimer's disease, mitochondria, and synaptic deficiencies. J. Alzheimer's Dis. https://doi.org/10.3233/JAD-130761.
Marees, A.T., de Kluiver, H., Stringer, S., Vorspan, F., Curis, E., Marie-Claire, C., Derks, E.M., 2018. A tutorial on conducting genome-wide association studies: quality control and statistical analysis. Int. J. Methods Psychiatr. Res. https://doi.org/10.1002/mpr.1608.
Mataix-Cols, D., Fernández De La Cruz, L., Monzani, B., Rosenfield, D., Andersson, E., Pérez-Vigil, A., Frumento, P., De Kleine, R.A., Difede, J., Boadie Dunlop, W., Farrell, L.J., Geller, D., Gerardi, M., Guastella, A.J., Hofmann, S.G., Hendriks, G.-J., Kushner, M.G., Lee, F.S., Lenze, E.J., Levinson, C.A., Mcconnell, H., Otto, M.W., Plag, J., Pollack, M.H., Ressler, K.J., Rodebaugh, T.L., Rothbaum, B.O., Scheeringa, M.S., Siewert-Siegmund, A., Smits, J.A.J., Storch, E.A., Ströhle, A., Tart, C.D., Tolin, D.F., Van Minnen, A., Waters, A.M., Weems, C.F., Wilhelm, S., Wyka, K., Davis, M., Rück, C., 2017. D-cycloserine augmentation of exposure-based cognitive behavior therapy for anxiety, obsessive-compulsive, and posttraumatic stress disorders a systematic review and meta-analysis of individual participant data supplemental content. JAMA Psychiatry 74, 501–510. https://doi.org/10.1001/jamapsychiatry.2016.3955.
Mattheisen, M., Samuels, J.F., Wang, Y., Greenberg, B.D., Fyer, A.J., Mccracken, J.T., Geller, D.A., Murphy, D.L., Knowles, J.A., Grados, M.A., Riddle, M.A., Rasmussen, S.A., Mclaughlin, N.C., Nurmi, E.L., Askland, K.D., Qin, H.D., Cullen, B.A., Piacentini, J., Pauls, D.L., Bienvenu, O.J., Stewart, S.E., Liang, K.Y., Goes, F.S., Maher, B., Pulver, A.E., Shugart, Y.Y., Valle, D., Lange, C., Nestadt, G., 2015. Genome-wide association study in obsessive-compulsive disorder: results from the OCGAS. Mol. Psychiatry 20, 337–344. https://doi.org/10.1038/mp.2014.43.
Maurya, P.K., Rizzo, L.B., Xavier, G., Tempaku, P.F., Ota, V.K., Santoro, M.L., Spíndola, L.M., Moretti, P.S., Mazzotti, D.R., Gadelha, A., Gouvea, E.S., Noto, C., Maes, M., Cordeiro, Q., Bressan, R.A., Brietzke, E., Belangero, S.I., 2018. Leukocyte telomere length variation in different stages of schizophrenia. J. Psychiatr. Res. 96, 218–223. https://doi.org/10.1016/j.jpsychires.2017.10.016.
Min, R., van der Knaap, M.S., 2018. Genetic defects disrupting glial ion and water homeostasis in the brain. Brain Pathol. https://doi.org/10.1111/bpa.12602.
Moons, T., De Hert, M., Gellens, E., Gielen, L., Sweers, K., Jacqmaert, S., Van Winkel, R., Vandekerckhove, P., Claes, S., 2016. Genetic evaluation of schizophrenia using the Illumina HumanExome chip. PLoS One. https://doi.org/10.1371/journal.pone.0150464.
Murray, M., Zhou, F., 2017. Trafficking and other regulatory mechanisms for organic anion transporting polypeptides and organic anion transporters that modulate cellular drug and xenobiotic influx and that are dysregulated in disease. Br. J. Pharmacol. https://doi.org/10.1111/bph.13785.
Pérez-Escuredo, J., Van Hée, V.F., Sboarina, M., Falces, J., Payen, V.L., Pellerin, L., Sonveaux, P., 2016. Monocarboxylate transporters in the brain and in cancer. Biochim. Biophys. Acta 1863, 2481–2497. https://doi.org/10.1016/j.bbamcr.2016.03.013.
Pruim, R., Welch, R., Sanna, S., Teslovich, T., Chines, P., Gliedt, T., Boehnke, M., Abecasis, G., Willer, C., 2010. LocusZoom: regional visualization of genome-wide association scan results. Bioinformatics. https://doi.org/10.1093/bioinformatics/btq419.
Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M.A., Bender, D., Maller, J., Sklar, P., de Baker, P.I.W., Daly, M.J., Sham, P.C., 2007. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am. J. Hum. Genet. https://doi.org/10.1086/519795.
Real, E., Gratacòs, M., Labad, J., Alonso, P., Escaramís, G., Segalàs, C., Subirà, M., López-Solà, C., Estivill, X., Menchón, J.M., 2013. Interaction of SLC1A1 gene variants and life stress on pharmacological resistance in obsessive–compulsive disorder. Pharmacogenomics J. 13, 470–475. https://doi.org/10.1038/tpj.2012.30.
Real, E., Gratacòs, M., Soria, V., Escaramís, G., Alonso, P., Segalàs, C., Bayés, M., de Cid, R., Menchón, J.M., Estivill, X., 2009. A brain-derived neurotrophic factor haplotype is associated with therapeutic response in obsessive-compulsive disorder. Biol. Psychiatry 66, 674–680. https://doi.org/10.1016/j.biopsych.2009.05.017.
Renna, M.E., O'Toole, M.S., Spaeth, P.E., Lekander, M., Mennin, D.S., 2018. The association between anxiety, traumatic stress, and obsessive-compulsive disorders and chronic inflammation: a systematic review and meta-analysis. Depress. Anxiety 35, 1081–1094. https://doi.org/10.1002/da.22790.
Richter, P., Ramos, R., 2018. Obsessive-compulsive disorder. Continuum (Minneap. Minn) 24, 828–844. https://doi.org/10.1007/978-1-4899-7497-6_13.
Rodríguez, N., Morer, A., González-Navarro, E.A., Serra-Pages, C., Boloc, D., Torres, T., García-Cerro, S., Mas, S., Gassó, P., Lázaro, L., 2017. Inflammatory dysregulation of monocytes in pediatric patients with obsessive-compulsive disorder. J. Neuroinflammation 40, 261. https://doi.org/10.1186/s12974-017-1042-z.
Ruscio, AM, Stein, DJ, C.W., et al., 2010. Cross-sectional comparison of the clinical characteristics of adults with early-onset and late-onset obsessive compulsive disorder. Mol. Psychiatry 15, 53–63. https://doi.org/10.1038/mp.2008.94.The.
Samuels, J., Wang, Y., Riddle, M.A., Greenberg, B.D., Fyer, A.J., McCracken, J.T., Rauch, S.L., Murphy, D.L., Grados, M.A., Knowles, J.A., Piacentini, J., Cullen, B., Bienvenu, O.J., Rasmussen, S.A., Geller, D., Pauls, D.L., Liang, K.-Y., Shugart, Y.Y., Nestadt, G., 2011. Comprehensive family-based association study of the glutamate transporter gene SLC1A1 in obsessive-compulsive disorder. Am. J. Med. Genet. Part B Neuropsychiatr. Genet. 156, 472–477. https://doi.org/10.1002/ajmg.b.31184.
Schennach, R., Obermeier, M., Meyer, S., Jäger, M., Schmauss, M., Laux, G., Pfeiffer, H., Naber, D., Schmidt, L.G., Gaebel, W., Klosterkötter, J., Heuser, I., Maier, W., Lemke, M.R., Rüther, E., Klingberg, S., Gastpar, M., Seemüller, F., Möller, H.-J., Riedel, M., 2012. Predictors of relapse in the year after hospital discharge among patients with schizophrenia. Psychiatr. Serv. 63, 87–90. https://doi.org/10.1176/appi.ps.201100084.
Schumacher, T., Krohn, M., Hofrichter, J., Lange, C., Stenzel, J., Steffen, J., Dunkelmann, T., Paarmann, K., Fröhlich, C., Uecker, A., Plath, A.S., Sommer, A., Brüning, T., Heinze, H.J., Pahnke, J., 2012. ABC transporters B1, C1 and G2 differentially regulate neuroregeneration in mice. PLoS ONE. https://doi.org/10.1371/journal.pone.0035613.
Singh, T., Walters, J.T.R., Johnstone, M., Curtis, D., Suvisaari, J., Torniainen, M., Rees, E., Iyegbe, C., Blackwood, D., McIntosh, A.M., Kirov, G., Geschwind, D., Murray, R.M., Di Forti, M., Bramon, E., Gandal, M., Hultman, C.M., Sklar, P., Palotie, A., Sullivan, P.F., O'Donovan, M.C., Owen, M.J., Barrett, J.C., 2017. The contribution of rare variants to risk of schizophrenia in individuals with and without intellectual disability. Nat. Genet. https://doi.org/10.1038/ng.3903.

Stewart, S.E., Yu, D., Scharf, J.M., Neale, B.M., Fagerness, J.A., Mathews, C.A., Arnold, P.D., Evans, P.D., Gamazon, E.R., Osiecki, L., McGrath, L., Haddad, S., Crane, J., Hezel, D., Illman, C., Mayerfeld, C., Konkashbaev, A., Liu, C., Pluzhnikov, A., Tikhomirov, A., Edlund, C.K., Rauch, S.L., Moessner, R., Falkai, P., Maier, W., Ruhrmann, S., Grabe, H.J., Lennertz, L., Wagner, M., Bellodi, L., Cavallini, M.C., Richter, M.A., Cook, E.H., Kennedy, J.L., Rosenberg, D., Stein, D.J., Hemmings, S.M.J., Lochner, C., Azzam, A., Chavira, D.A., Fournier, E., Garrido, H., Sheppard, B., Umaña, P., Murphy, D.L., Wendland, J.R., Veenstra-Vanderweele, J., Denys, D., Blom, R., Deforce, D., Van Nieuwerburgh, F., Westenberg, H.G.M., Walitza, S., Egberts, K., Renner, T., Miguel, E.C., Cappi, C., Hounie, A.G., Conceição Do Rosário, M., Sampaio, A.S., Vallada, H., Nicolini, H., Lanzagorta, N., Camarena, B., Delorme, R., Leboyer, M., Pato, C.N., Pato, M.T., Voyiaziakis, E., Heutink, P., Cath, D.C., Posthuma, D., Smit, J.H., Samuels, J., Bienvenu, O.J., Cullen, B., Fyer, A.J., Grados, M.A., Greenberg, B.D., McCracken, J.T., Riddle, M.A., Wang, Y., Coric, V., Leckman, J.F., Bloch, M., Pittenger, C., Eapen, V., Black, D.W., Ophoff, R.A., Strengman, E., Cusi, D., Turiel, M., Frau, F., MacCiardi, F., Gibbs, J.R., Cookson, M.R., Singleton, A., Arepalli, S., Cookson, M.R., Dillman, A., Ferrucci, L., Gibbs, J.R., Hernandez, D.G., Johnson, R., Longo, D.L., Nalls, M.A., O'Brien, R., Singleton, A., Traynor, B., Troncoso, J., Van Der Brug, M., Zielke, H.R., Zonderman, A., Hardy, J., Crenshaw, A.T., Parkin, M.A., Mirel, D.B., Conti, D.V., Purcell, S., Nestadt, G., Hanna, G.L., Jenike, M.A., Knowles, J.A., Cox, N., Pauls, D.L., Hardy, J.A., Ryten, M., Smith, C., Trabzuni, D., Walker, R., Weale, M., 2013. Genome-wide association study of obsessive-compulsive disorder. Mol. Psychiatry 18, 788–798. https://doi.org/10.1038/mp.2012.85.

Taylor, S., 2013. Molecular genetics of obsessive-compulsive disorder: a comprehensive meta-analysis of genetic association studies. Mol. Psychiatry 18, 799–805. https://doi.org/10.1038/mp.2012.76.

Teng, O, Chen, ST, Hsu, TL, Sia, SF, Cole, S, Valkenburg, SA, Hsu, TY, Zheng, JT, Tu, W, Bruzzone, R, Peiris, JS, Hsieh, SL, Yen, HL, 2016. CLEC5A-mediated enhancement of the inflammatory response in myeloid cells contributes to influenza virus pathogenicity in vivo. J. Virol. 91, e01813–e01816. https://doi.org/10.1128/jvi.01813-16.

Toritsuka, M., Kimoto, S., Muraki, K., Kitagawa, M., Kishimoto, T., Sawa, A., Tanigaki, K., 2017. Regulation of striatal dopamine responsiveness by Notch/RBP-J signaling. Transl. Psychiatry. https://doi.org/10.1038/tp.2017.21.

Tosto, G., Fu, H., Vardarajan, B.N., Lee, J.H., Cheng, R., Reyes-Dumeyer, D., Lantigua3, R., Medrano4, M., Jimenez-Velazquez, Z., I., Elkind, M.S.V., Wright7, C.B., Sacco, R.L., Pericak-Vance, M., Farrer, L., Rogaeva11, E., George-Hyslop, P.S., Reitz, C., Mayeux, R., 2015. F-box/LRR-repeat protein 7 is genetically associated with alzheimer's disease. Ann. Clin. Transl. Neurol. 2, 810–820. https://doi.org/10.1002/acn3.223.

Tükel, R., Bozkurt, O., Polat, A., Genç, A., Atli, H., 2006. Clinical predictors of response to pharmacotherapy with selective serotonin reuptake inhibitors in obsessive-compulsive disorder. Psychiatry Clin. Neurosci. 60, 404–409. https://doi.org/10.1097/SLA.0000000000000648.

Uhl, G.R., Martinez, M.J., 2019. PTPRD: neurobiology, genetics, and initial pharmacology of a pleiotropic contributor to brain phenotypes. Ann. N. Y. Acad. Sci. https://doi.org/10.1111/nyas.14002.

Vallipuram, J., Grenville, J., Crawford, D.A., 2010. The E646D-ATP13A4 mutation associated with autism reveals a defect in calcium regulation. Cell. Mol. Neurobiol. 30, 233–246. https://doi.org/10.1007/s10571-009-9445-8.

Vilboux, T., Malicdan, M.C.V., Chang, Y.M., Guo, J., Zerfas, P.M., Stephen, J., Cullinane, A.R., Bryant, J., Fischer, R., Brooks, B.P., Zein, W.M., Wiggs, E.A., Zalewski, C.K., Poretti, A., Bryan, M.M., Vemulapalli, M., Mullikin, J.C., Kirby, M., Anderson, S.M., Comparative, N., Program, S., Huizing, M., Toro, C., Gahl, W.A., Gunay-Aygun, M., 2016. Cystic cerebellar dysplasia and biallelic LAMA1 mutations: a lamininopathy associated with tics, obsessive compulsive traits and myopia due to cell adhesion and migration defects. Cognit. Behav. Genet. 53, 318–329. https://doi.org/10.1136/jmedgenet-2015-103416.

Voorman, A., Brody, J., Lumley, T., 2013. SkatMeta: An R Package for Meta Analyzing Region-Based Tests of Rare DNA Variants.

Wang, X., Cui, D., Wang, Z., Fan, Q., Xu, H., Qiu, J., Chen, J., Zhang, H., Jiang, K., Xiao, Z., 2012. Cross-sectional comparison of the clinical characteristics of adults with early-onset and late-onset obsessive compulsive disorder. J. Affect. Disord. 136, 498–504. https://doi.org/10.1016/j.jad.2011.11.001.

Worthey, E.A., Raca, G., Laffin, J.J., Wilk, B.M., Harris, J.M., Jakielski, K.J., Dimmock, D.P., Strand, E.A., Shriberg, L.D., 2013. Whole-exome sequencing supports genetic heterogeneity in childhood apraxia of speech. J. Neurodev. Disord. 5, 1. https://doi.org/10.1186/1866-1955-5-29.

Wu, M.C., Lee, S., Cai, T., Li, Y., Boehnke, M., Lin, X., 2011. Rare-variant association testing for sequencing data with the sequence kernel association test. Am. J. Hum. Genet. 89, 82–93. https://doi.org/10.1016/J.AJHG.2011.05.029.

Yoon, K.J., Lee, H.R., Jo, Y.S., An, K., Jung, S.Y., Jeong, M.W., Kwon, S.-K., Kim, N.-S., Jeong, H.-W., Ahn, S.-H., Kim, K.T., Lee, K., Kim, E., Kim, J.-H., Choi, J.-S., Kaang, B.-K., Kong, Y.-Y., 2012. Mind bomb-1 is an essential modulator of long-term memory and synaptic plasticity via the Notch signaling pathway. Mol. Brain 5, 40. https://doi.org/10.1186/1756-6606-5-40.

Zamanian-azodi, M., Rezaei-tavirani, M., Mahboubi, M., Hamidpour, M., Tavirani, M.R., Hamdieh, M., Rostami-nejad, M., Nejadi, N., Derakhshan, M.K., 2018. Research paper: serum proteomic study of women with obsessive-compulsive disorder. Wash. Subtype 9, 337–346.