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Genome-wide Association Study of Obsessive-Compulsive Disorder

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Abstract

Obsessive-compulsive disorder (OCD) is a common, debilitating neuropsychiatric illness with complex genetic etiology. The International OCD Foundation Genetics Collaborative (IOCDF-GC) is a multi-national collaboration established to discover the genetic variation predisposing to OCD. A set of individuals affected with DSM-IV OCD, a subset of their parents, and unselected controls, were genotyped with several different Illumina SNP microarrays. After extensive data cleaning, 1,465 cases, 5,557 ancestry-matched controls and 400 complete trios remained, with a common set of 469,410 autosomal and 9,657 X-chromosome SNPs. Ancestry-stratified case-control association analyses were conducted for three genetically-defined subpopulations and combined in two meta-analyses, with and without the trio-based analysis. In the case-control analysis, the lowest two p-values were located within *DLGAP1* ($p=2.49\times10^{-6}$ and $p=3.44\times10^{-6}$), a member of the neuronal postsynaptic density complex. In the trio analysis, rs6131295, near *BTBD3*, exceeded the genome-wide significance threshold with a p-value=3.84×10^{-8}. However, when trios were meta-analyzed with the combined case-control samples, the p-value for this variant was 3.62×10^{-5}, losing genome-wide significance. Although no SNPs were identified to be associated with OCD at a genome-wide significant level in the combined trio-case-control sample, a significant enrichment of methylation-QTLs ($p<0.001$) and frontal lobe eQTLs ($p=0.001$) was observed within the top-ranked SNPs ($p<0.01$) from the trio-case-control analysis, suggesting these top signals may have a broad role in gene expression in the brain, and possibly in the etiology of OCD.

Keywords

Obsessive-compulsive disorder; GWAS; Genetic; Genomic; Neurodevelopmental disorder; DLGAP

Introduction

Obsessive-compulsive disorder (OCD) is a neuropsychiatric disorder characterized by obsessions and/or compulsions that are distressing, time consuming or significantly impairing. It is the fourth most common psychiatric illness[1] with a lifetime prevalence of

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1-3%.[2, 3] OCD was identified as the anxiety disorder with the highest proportion (50.6%) of serious cases by the National Comorbidity Study Replication[4] and as a leading global cause of non-fatal illness burden by the World Health Organization (WHO) in 2006.[5]

Genetic studies have demonstrated that both biological and environmental factors are important in the etiology of OCD. A multitude of OCD family studies published since the 1930's provide strong evidence for an approximate four to ten-fold OCD risk increase among first-degree relatives of OCD-affected children and adults, respectively, as compared to relatives of controls.[6-14] A review of twin studies concluded that obsessive-compulsive (OC) symptoms are heritable, with greater genetic influences in child-onset (45-65%), than in adult-onset OCD cases (27- 47%).[15] This finding has been supported by subsequent twin studies[16-18]. Linkage study results have been somewhat encouraging,[19] identifying peaks on chromosomes 3q,[20] 9p,[21] 10p,[22, 23] 15q[20, 24] and 19q[19] for OCD and on chromosome 14 for compulsive hoarding.[25] Unfortunately, none of these peaks exceeded the threshold for genome-wide significance, and only the 9p peak has reached suggestive significance in more than one sample.[19-21]

In addition, more than 80 positional and functional candidate gene studies of OCD have been reported, predominantly for variants within genes in the serotonin, dopamine and glutamate[26, 27] pathways and within those involved in immune and white matter pathways.[28] *SLC1A1,* which encodes a neuronal glutamate transporter and which is located within the linkage peak on chromosome 9p, is the only candidate gene observed to be associated in multiple independent samples, although the specific associated variant has varied.[29-32]

Excessive grooming and anxiety-like behaviors have been observed in mice lacking expression of *SAPAP3*, a post-synaptic scaffolding protein located at excitatory synapses. This finding, coupled with high *SAPAP3* expression levels in the striatum, identify its human ortholog (*DLGAP3)* as an appealing candidate gene in OCD.[33] Human studies have provided some support for a possible role of *DLGAP3* in OCD-related disorders, suggesting increased rare non-synonymous variant frequencies in OCD/trichotillomania subjects[34] and association of common *DLGAP3* variants with pathologic grooming in a family-based study,[35] albeit with some inconsistencies.[36]

In recent years, the genome-wide association study (GWAS) approach has led to the identification of many genetic associations for common complex traits.[37] This model-free approach to gene discovery has led to a greater pathophysiologic understanding of many disorders, although only small proportions of the total genetic variance have so far been explained, and many of the identified variants have not brought new biological understanding.[38] To address the latter concern, functional support for GWAS findings has been sought by determining their effects on gene expression (expression quantitative trait loci- eQTLs) and methylation level (methylation quantitative trait loci-mQTLs).[38] Top single nucleotide polymorphisms (SNPs) have also been examined for potential enrichment of eQTLs and mQTLs, compared to expected rates. Moreover, examination for over-representation of micro-RNA (miRNA) binding sites has also been adopted as an informative approach,[39] given the role of miRNA in regulating gene expression. In addition,

pathway analyses have been conducted to determine whether specific gene pathways are enriched among the strongest associated variants.[40]

The International OCD Foundation Genetic Collaborative (IOCDF-GC), consisting of more than 20 research groups, has performed a GWAS to search for common SNPs predisposing to OCD. We present our findings from an analysis of the genetic association between OCD and a genome-wide set of common SNPs among case-control and trio samples and their combined trio-case-control results. We also present analyses of top GWAS findings with respect to their biological function in OCD-related and other brain regions.

Materials and Methods

Subjects and Genotyping

Our initial sample consisted of 1,817 DSM-IV[41] OCD cases, 504 controls and 663 complete trios, genotyped using the Illumina Human610-Quadv1_B SNP array. This work was approved by the relevant IRBs at all participating sites, and all participants provided written informed consent. The majority of the control subjects genotyped as a part of this project were not screened for the absence of OCD. We also used data from 5,654 unscreened controls, previously genotyped on two different Illumina SNP arrays (Table S1).

Quality Control

The data for this study underwent QC and data cleaning with a concurrent GWAS of Tourette Syndrome (Scharf et al., Molecular Psychiatry, submitted),[42] using PLINK,[43] to exclude samples and SNPs for each array type (Figure S1).

Statistical analyses

To control for Type I error due to residual population stratification, case and control samples were separated into subpopulations of European (EU), South African Afrikaner (SA) and Ashkenazi Jewish (AJ) ancestry, using Multi-Dimensional Scaling (MDS) analysis (Supplementary Figures S2-4). Population stratification outliers and those lacking genomically-matched controls or cases were excluded, as were samples with excessive low-level relatedness to many others within each subpopulation. Separate association analyses were conducted for each of the case-control subsamples (EU, SA and AJ) and for the trio samples. For the former, logistic regression was employed using an additive test model (1 df), with diagnostic status as the dependent variable and each single SNP as the predictor, including specific ancestry-informative MDS axes as covariates (EU= 4 factors, SA= 2 factors, and AJ=1 factor). For the latter, the Transmission Disequilibrium Test (TDT) was used.

Two meta-analyses were conducted using METAL[44] by combining the three case-control sub-populations, and by combining the three case-control subgroups and the trio group, weighting by the number of cases or trios (Supplementary materials). Each SNP was tested separately, defining a genome-wide significance threshold at $p<5\times10^{-8}$, based on a 5% Type I error rate.[37] Using the PLINK retrieval interface,[43] SNP annotations were created using the TAMAL database[45]based chiefly on UCSC genome browser files,[46] HapMap[47] and

dbSNP.[48] Further annotation was conducted using SCAN[49] and SPOT[50] and top SNPs ($p<0.001$) were also manually annotated using the UCSC genome browser.[51] For analysis of sex chromosome SNPs, males and females were assessed separately for each subgroup, with adjustment by MDS factors as described above, and subsequent combination via meta-analysis, using the number of cases or trios as a weighting factor. A sign test was conducted to examine for increased consistent directionality of effect for the most strongly associated SNPs between the case-control and trio samples. Analyses of potential enrichment of SNPs from: a) 22 previously identified candidate genes, b) pre-defined gene pathways, and c) target gene intervals containing micro-RNA (miRNA) binding sites[52], among the top hits from the trio, case-control, or trio-case-control GWAS results were performed using INRICH.[40]

eQTL and mQTL annotation and enrichment tests

Functional support for the SNPs with the strongest evidence of association in the trio-case-control meta-analysis was sought by determining effects of the most significantly associated SNPs ($p<0.001$) on both gene expression (expression quantitative trait loci- eQTLs) and on methylation level (methylation quantitative trait loci-mQTLs). This was done with eQTLs from frontal lobes,[53] parietal lobes,[53] lymphoblastoid cell lines (LCL),[54] and the cerebellum,[54] and with mQTLs[54] from cerebellum, using previously collected data.[54] To test whether the SNPs with the strongest observed associations were enriched for eQTLS or mQTLs, the LD-independent SNPs from the trio-case-control analyses with $p<0.001$ and with $p<0.01$ were compared to 1,000 random sets of the same size, conditioning on allele frequency, to yield an empirical distribution. An enrichment p-value was then calculated as the proportion of randomized sets in which the eQTL (or mQTL) count matched or exceeded the actual observed count in the list of top SNP associations, as previously described[53] (see Supplementary materials).

Imputation of SNPs

Imputation of SNPs was conducted proximal to any SNPs with genome-wide significance from the trio, case-control or trio-case-control samples. This was completed using the 1000 Genomes Project via IMPUTE2,[55] and haplotypes from the 1,092 individuals in a 1000 Genomes Data Release[56] as a reference dataset. Post-imputation QC and allelic dosage analysis were conducted in PLINK (see Supplementary materials).

Results

Multidimensional scaling analyses identified three distinct genetic subpopulations within the case-control sample, which corresponded to: European (EU), South African (SA) and Ashkenazi Jewish (AJ) ancestries (Supplementary materials). After QC, a total of 1,465 cases (1,279 EU, 93 SA and 93 AJ), 5,557 controls (5,139 EU, 260 AJ and 158 SA) and 400 complete trios (299 EU) remained and each had genotypes for a common set of 469,410 autosomal and 9,657 X-chromosome SNPs (Table S1). Quantile-quantile (QQ) plots of the observed versus expected log(p) values under the null hypothesis were used to calculate genomic control lambda values for the trio ($\lambda=1.015$), case-control ($\lambda=1.002$), and trio-case-control samples ($\lambda=1.011$) (Figure 1). QQ plots for EU ($\lambda=1.009$), SA ($\lambda=0.969$) and AJ

(λ=0.982) case-control subpopulations were also constructed (Supplementary Figure S7). There was no evidence for significant residual stratification effects in any of the comparisons.

Trio Sample Results

An overview of the p-values for the trio analysis plotted against genomic location is illustrated in Figure 2a. Of the top 4 OCD-associated SNPs in the trio sample with p-values< 1×10^{-5}, one SNP, rs6131295 (11,996,267bp (hg19) on 20p12.1-2), exceeded the threshold for genome-wide significance of $p<5\times10^{-8}$ with a $p=3.84\times10^{-8}$.[57] This SNP is located ~90 kb 3′ to *BTBD3* (Figure 3). None of the other 442 SNPs with p-values<0.001 were in LD ($r^2>0.2$) with this SNP (Supplementary Table S2).

Case-Control Sample Results

In the case-control sample, no SNPs exceeded the genome-wide threshold for significance (Table 1, Figure 2). Nine OCD-associated SNPs had p-values<1×10^{-5} (Table 1). The lowest two p-values were for SNPs rs11081062 ($p=2.49\times10^{-6}$) and rs11663827 ($p=3.44\times10^{-6}$), located at chromosome 18 within an intron of *DLGAP1* (Figure 3). *DLGAP1* (also known as *SAPAP1*) encodes the discs, large (Drosophila) homolog-associated protein a member of the neuronal postsynaptic density complex. The third lowest p-value was for the SNP rs26728 ($p=4.75\times10^{-6}$), located within an intron of *EFNA5*, encoding Ephrin-A5 (Supplementary Figure S12). Ephrins are important for development of the neocortex through regulation of axonal inhibition or repulsion,[58] and *EFNA5* was also among top hits in an Alzheimer's disease GWAS.[59] The fourth lowest p-value=5.40×10^{-6}, was for rs4868342, lying within an intron of *HMP19*, encoding the brain-specific HMP19 protein (Supplementary Figure S12), which is expressed in the Golgi complex.[60] The fifth lowest p-value=5.81×10^{-6}, was for rs297941, which is located approximately 21 kb 5′ to the gene encoding *FAIM2* (also known as *LFG)* and about 25 kb from a cluster of genes encoding a group of aquaporins (*AQP5*, *AQP6*, *AQP2*), and lies within a putative coding region of mRNA BC034605, isolated from testis (Supplementary Figure S12).

Trio-Case-Control Meta-Analysis Results

None of the SNPs exceeded the genome-wide threshold for significance, although several of the top hits were also identified among top hits in either the trio analysis or in the case-control analysis (Figure S12). Using the sign test with 3616 LD-pruned SNPs with p<0.01, there was evidence for increased consistent directionality (1907/3616=0.52; $p=5.25\times10^{-4}$ for 1-sided binomial test) between the trios and the combined case-controls. The top 38 OCD-associated SNPs in this meta-analysis, with p-values<5×10^{-5}, are presented in Table 1. For example, the top signal ($p=4.99\times10^{-7}$), rs297941 near *FAIM2,* (LFG), was also the fifth ranked SNP in the case-control analysis. *FAIM2* is highly expressed in the central nervous system and plays a role in Fas-mediated cell death.[61] When rs6131295 (the SNP with significant genome-wide association in the trio sample) was meta-analyzed along with the case-control sample, the combined p-value significance decreased to 3.62×10^{-5}.

Examination of prior OCD linkage regions and candidate genes

There was no evidence found for genome-wide significant association with OCD in either previously identified putative linkage regions (Supplementary Table S3) or in 22 previously identified candidate genes when examining the trio, case-control and trio-case-control groups. The Q-Q plot of candidate gene SNPs for the case-control group showed little inflation (λ=1.085, Supplementary Figure S8), suggesting no evidence for over-representation within these genes. While the Q-Q plot of the combined trio-case-control sample indicated small inflation (λ=1.168, Supplementary Figure S8), the follow-up enrichment test demonstrated no over-representation of top hits ($p<0.001$ and $p<0.01$) within previously identified candidate genes (p=0.15 and p=0.10, respectively). For the 22 OCD candidate genes examined, the lowest SNP p-values are reported in Supplementary Table S4. The strongest finding was observed for *ADARB2*[22], with a p-value=1.6×10^{-4}, which did not survive correction for multiple testing of candidate gene SNPs (corrected p=0.53).

eQTL and mQTL annotation and enrichment analyses

Support for the SNPs with the strongest evidence of association in the combined trio-case-control sample was sought by determining functional effects of the most significantly associated autosomal SNPs. These top SNPs were annotated with expression QTL (eQTL) data from frontal, parietal and cerebellar brain regions (Table 1), along with lymphoblastoid cell lines (LCLs) (Supplementary Table S2) and methylation levels (mQTLs) in cerebellum (Table 1).

SNPs with association p-values < 0.01 (n=3,521) were then examined for enrichment of eQTLs and mQTLs. Significant enrichment was observed for frontal eQTLs (p=0.001) as well as for cerebellar eQTLs (p=0.033) and parietal eQTLs (p=0.003) (Figure 4a-c). Furthermore, enrichment of cerebellar mQTLs was observed ($p<0.001$) with an enrichment p-value of $p<0.001$ (Figure 4d), suggesting that these SNPs are more likely to influence the methylation state than expected by chance. No significant enrichment for either genic (p=0.54) or missense variants (0.34) was observed. A similar analysis examining only the top SNPs with association p-values <0.001 (n=415) demonstrated no significant enrichment for mQTLs or for eQTLs ($p>0.05$).

miRNA and pathway analyses

After correction for multiple hypothesis testing, there was no evidence for enrichment of specific miRNA binding sites among the LD-blocks containing top SNPs compared to the genes matched by size and marker density (see Supplementary Table S5). The strongest enrichment was found in 49 high-confidence (TargetScan probability>0.9) predicted miRNA-219-5p/508/508-3p/4782-3p targets, two of which have at least one SNP with $p<0.001$ (empirical p=0.011, corrected p=0.060) in the case-control GWAS result. A similar level of enrichment was also found in 89 high-confidence predicted miR-130ac/301ab/301b/301b-3p/454/721/4295/3666 targets, two of which have at least one SNP with $p<0.001$ in the trio TDT result. In the pathway analyses, no results achieved significance at the corrected p-value (lowest corrected p=0.55) (see Supplementary Table S6).

Discussion

We report results from the first genome-wide association study (GWAS) to search for common DNA sequence variation predisposing individuals to OCD. After removing low performing SNP assays and DNA samples, we analyzed 400 trios, 1,465 cases and 5,557 controls for 469,410 autosomal and 9,657 X-chromosome SNPs. The trio and case-control subsamples were analyzed individually, and then these results were combined in both case-control and trio-case-control meta-analyses. One SNP, rs6131295, located on chromosome 20p12.1-p12.2, approximately ~90 kb from the *BTBD3* gene, achieved genome-wide significance in the trio analysis ($p=3.84\times10^{-8}$), but not in the combined trio case-control meta-analysis, suggesting that further examination will be required using independent samples. *BTBD3* is a member of a large family of transcription factors, which includes *BTBD9,* a gene that has been associated with Tourette Syndrome, a disorder frequently co-morbid with OCD.[62] *BTBD3* participates in multiple cellular functions including transcriptional regulation, cytoskeleton dynamics, ion channel assembly and gating, protein ubiquitination and degradation[63] and has also been associated with primary open-angle glaucoma.[64] *BTBD3* is expressed in the brain, with the highest observed levels in childhood and adolescence (www.BrainSpan.org, Release 3),[63] when OCD frequently emerges.[65] rs6131295 is a cis-eQTL for *BTBD3* in the frontal cortex (p=0.028), a region that has repeatedly been implicated in OCD. This SNP is also a parietal cis-eQTL for *ISM1* (20p12;p=0.0036) and an LCL trans-eQTL for *DHRS11* (17q11.2;p=0.0001).

Interestingly, the brain-wide expression pattern of *DHRS11* and *ISM1* are highly correlated with the expression of several of the other genes found among the top hits of both the case-control and the trio-case-control meta-analyses (www.BrainSpan.org, Release 3) (Supplementary Figure S12).[66] Furthermore, many of these genes have been implicated in glutamate signaling. Specifically, *ISM1 (C20orf82)* is correlated with expression of pre-synaptically-located *ADCY8* (0.61, rank 11 of 22,328 transcripts), the gene with the seventh strongest OCD-association in the trio-case-control meta-analysis, which has also been associated with bipolar disorder[67] and with fear memory.[68] *ISM1* is also correlated with brain-wide expression of numerous glutamate-related genes including *GRIK4* (0.565, rank 66), *DLGAP3* (0.576,rank 44), *GRIK1* (0.595,rank 22), *SHANK3* (0.598,rank 21) as well as *ADARB2* (0.600,rank 19), which contains the SNP with the best p-value in this study among previously reported candidate genes (Supplementary Table S4), and lies within a childhood-onset OCD linkage peak.[22] Similarly, the expression of *DHRS11 (MGC4172)* is strongly correlated (0.847, rank 25 of 22,328 transcripts) with that of *FAIM2*, which is located in the same LD block as the best SNP (rs297941) in the trio-case-control, and fifth best in the case-control meta-analyses. *FAIM2* has been associated with neuroprotection following transient brain ischemia.[68] The rat homologue of *FAIM2*, neural membrane protein 35 (*NMP35)*, is expressed at the post-synaptic membrane in a subset of synapses and in dendrites, and co-localizes with the glutamate receptor *GluR2*.[61] Thus, there is a potential relationship between rs6131295 (trio analysis), and *FAIM2* and *ADCY8* (tagged by the SNPs ranked numbers 1 and 7 in the trio-case-control analysis).

The top two SNPs associated in the case-control meta-analysis (both with $p<3\times10^{-5}$ in the trio-case-control meta-analysis) are located in *DLGAP1*, another gene which influences

glutamate signaling. *DLGAP1* encodes a Shank-associated protein and has been associated with schizophrenia and with a smoking cessation phenotype[69] and *DLGAP1* deletions have also been observed (2 in schizophrenia cases versus 1 in controls).[70] Another member of this gene family, *DLGAP3,* has been implicated in compulsive-like behavior in a mouse model (*SAPAP3*). Specifically, knockout mice for the striatum-expressed *SAPAP3* gene (which codes for a post-synaptic protein at cortico-striatal glutamatergic excitatory synapses) developed repetitive grooming behaviors and anxiety that were reversed with an SSRI and with gene replacement.[24]

Several of the top associations in the combined trio-case-control meta-analysis are in or near genes that have been implicated in other studies of psychiatric disorders, including ADCY8[59, 71, 72], ARHGAP18[47] and JMJD2C [62] in bipolar disorder, schizophrenia and autism spectrum disorders, respectively. Enrichment for eQTLs was observed among the top associated GWAS SNPs (N=5,321; $p<0.01$), with empirical p-values of 0.001 for frontal cortex, 0.003 for parietal tissue and 0.033 for cerebellum. Marked enrichment was also observed for methylation QTLs ($p<0.001$). This is consistent with the finding by Nicolae et al. (2010),[54] who reported that disease-associated SNPs from GWAS were significantly more likely to be eQTL, than other random sets of SNPs with similar minor-allele-frequencies (MAF).

It remains unclear whether the finding at rs6131295, which exceeded genome-wide significance with $p=3.84\times10^{-8}$ in the trio sample, is a false positive or not. Certainly the decrease in significance of the p-value to 3.62×10^{-5} when the trio data is meta-analyzed with the much larger case-control sample data suggests so. On the other hand, our attempts to determine whether this finding was spurious did not find any evidence of such, as detailed here: 1) The intensity plot for this SNP has three tight, separated, clusters (Figure S10a); 2) There were no missing genotypes in the trio sample and there were no Mendelian errors; 3) Two nearby directly genotyped SNPs with low r^2 values (0.2-0.4) had p-values within the 10^{-2} range, demonstrating very low statistical significance (Figure S10b); and 4) Imputation of the trio sample provided additional results that are not inconsistent with a true positive finding. Of the 40 regional SNPs examined, those with large r^2 values (>0.90) and similar minor allele frequencies to rs6131295 had strong p-values in the range of 10^{-6} and 10^{-7} (Table S7 and Figure S11). Moreover, the surrounding SNPs in low r^2 with rs6131295 all have an opposite direction of risk effect, which may partially explain why they have much less significant p-values. Although these imputed data and the above noted facts cannot prove that rs6131295 is a true positive, they do not support the hypothesis that it is a false positive. Replication with additional samples will be required to provide further clarification.

In summary, although no SNPs were identified to be associated with OCD at a genome-wide significant level in the combined trio-case-control sample, a highly significant enrichment of methylation-QTLs ($p<0.001$) and frontal lobe eQTLs ($p=0.001$) was observed within the top-ranked SNPs ($p<0.01$). This suggests that these top signals may have a broad role in gene expression in the brain, and possibly in the etiology of OCD. In the trio sample, we observed a genome-wide significant result for rs6131295, which is located near *BTBD3*, and is an eQTL for *BTBD3*, *DHRS11* and *ISM1*. The expression of these latter two genes are

highly correlated with other top hits, many of which are related to glutamatergic neurotransmission and signaling. So, while no genome-wide significant associations were found in the entire sample, the convergence of results from both the trio and combined trio-case-control analyses suggest the possibility that our findings at *BTBD3*, *FAIM2* and *ADCY8* are genes involved in the pathogenesis of OCD. In the case-control sample, the two most significant p-values were located within *DLGAP1,* a member of the same gene family as *DLGAP3,* which is also expressed in the neuronal postsynaptic density complex and which has been implicated in a mouse model of OCD,[33] making these results intriguing. Future exploration and attempts to replicate these findings with additional independent samples is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of Interest

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Egberts, T Renner and S Walitza received sample collection funding by DFG WA168/1-1. SL Rauch has received research funding from Cyberonics and Medtronic. JA Knowles is a recipient of grant funding from NIH and from NARSAD; he sits on the Scientific Advisory Committee for Next-Generation Sequencing of Life Technologies, Inc. and is a technical advisor to SoftGenetics, Inc.; he is on the Scientific Advisory Committee for Next-Generation Sequencing of Life Technologies, Inc. and is a technical advisor to SoftGenetics, Inc. JF Leckman has been funded by the NIH, the TSA, Talecris Biotherapeutics, Klingenstein Third Generation Foundation, John Wiley and Sons, McGraw Hill, and Oxford University Press. V Coric works for Bristol Myers-Squibb, Inc. DW Black has received NIH funding and support from AstraZeneca and Psysadon in addition to royalties from American Psychiatric Publishing, Inc. and Oxford University Press. SE Stewart, D Yu, BM Neale, P Evans, E Gamazon, A Tikhomirov, A Pluzhnikov, A Konkashbaev, L Davis, C Sabatti, S Purcell, MR Cookson, JR Gibbs, J Hardy, C Liu, RA Ophoff, E Strengman, P Falkai, L Lennertz, W Maier, S Ruhrmann, L Bellodi, M Cavallini, JL Kennedy, SMJ Hemmings, C Lochner, EF Garcia, H Garrido, P Umana, DA Chavira, A Azzam, B Sheppard, DL Murphy, EH Cook, D Rosenberg, R Blom, D Deforce, F Van Nieuwerburgh, GM Westenberg, D Denys, C Illmann, MA Jenike, C Cappi, MC doRosario, AS Sampaio, H Vallada, EC Miguel, N Lanzagorta, B Camarena, H Nicolini, R Delorme, M Leboyer, E Voyiaziakis, DC Cath, JH Smit, P Heutink, OJ Bienvenu, B Cullen, MA Grados, MA Riddle, J Samuels, Y Wang, JT McCracken, AJ Fyer, BD Greenberg, G Nestadt, C Pittenger, M Bloch, V Eapen, R Ophoff, E Strengman, D Cusi, F Frau, M Turiel and F Macciardi declare no conflicts of interest.

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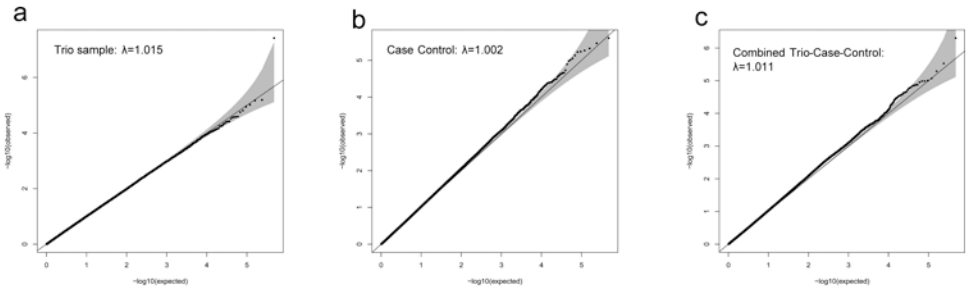

Figure 1. Quantile-quantile (QQ) Plots of Observed versus Expected −log(p) Statistics for: (a) Trio samples, (b) Case-Control samples and, (c) Combined Trio-Case-Control Samples

Quantile-quantile (Q-Q) plots of observed versus expected −log *(P)* test statistics for: (**a**) trio samples; (**b**) case-control samples; and (**c**) combined trio-case-control samples. The 95% confidence interval of expected values is indicated in grey. Corresponding genomic control lambda values are indicated within each plot.

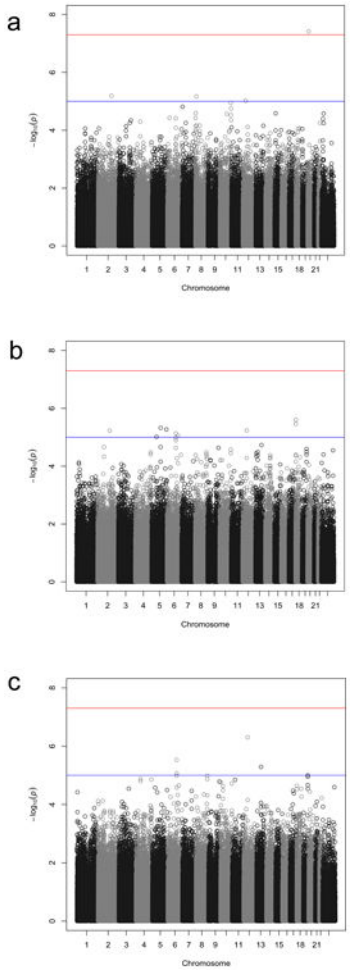

Figure 2. Manhattan Plots for: (a) Trio, (b) Case-Control and, (c) Combined Trio-Case-Control Samples

Manhattan plots of all genotyped single-nucleotide polymorphisms (SNPs) for (**a**) trio samples; (**b**) case-control samples; and (**c**) combined trio-case-control samples. Red and blue lines indicate significance thresholds of 5×10^{-8} and 1×10^{-5}, respectively.

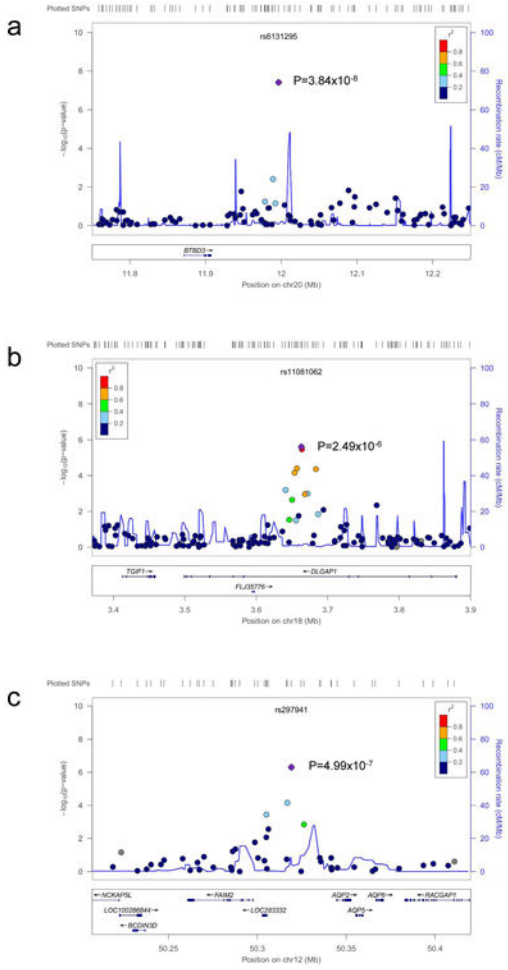

Figure 3. Locus Plots for SNPs rs6131295 (near *BTBD3*), rs11081062 (within *DLGAP1*) and rs297941 (near *FAIM2*)

Regional association plots of the best supported SNPs from the a) Trio, b) Case-Control and c) Trio-Case-Control analyses. Locations and observed -log (p-values) for genotyped SNPs are shown with circles. LD, in r^2, to the lowest p-value SNP in each plot is indicated using shading (dark blue, low LD, red-high LD). Light blue lines indicate the estimated recombination rate from HapMap release 22.

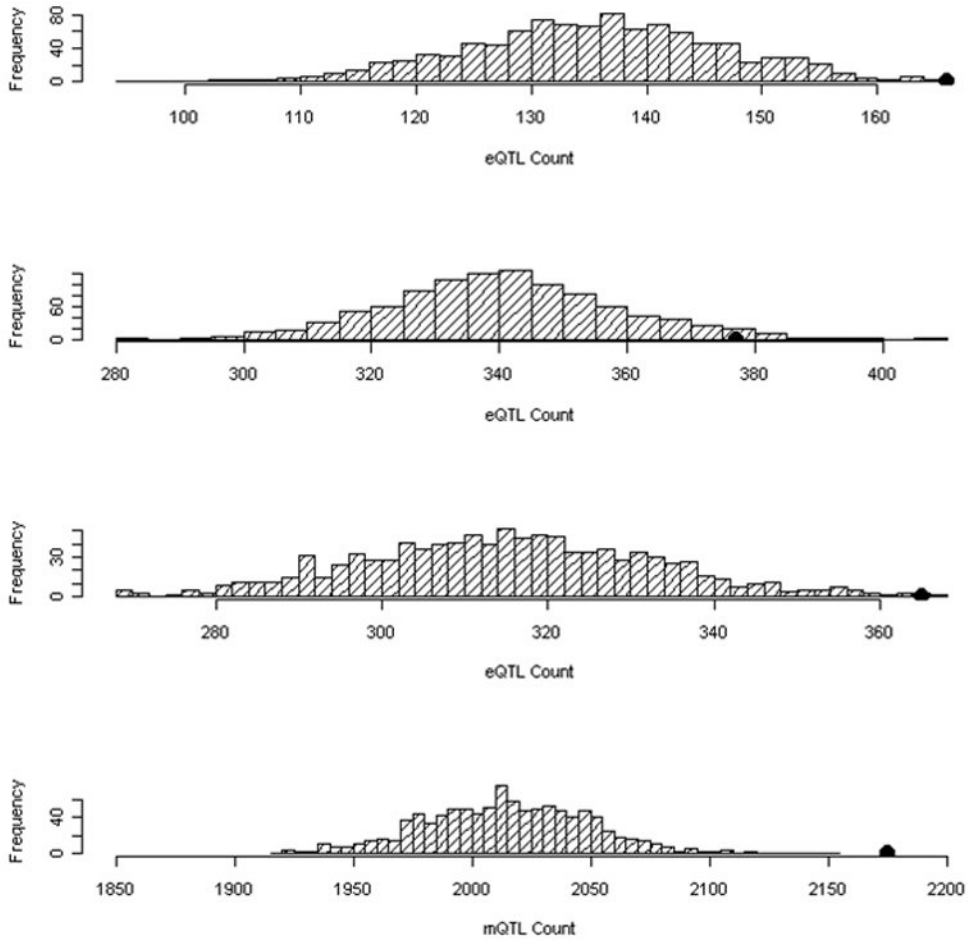

Figure 4. Enrichment analyses for Quantitative Trait Loci (QTLs) among GWAS Variants with p<0.01

Enrichment of (**a**) frontal lobe expression QTLs (p=0.001), (**b**) cerebellum expression QTLs (p=0.033), (**c**) parietal lobe expression QTLs (p=0.003), and (**d**) methylation QTLs (p<0.001) among GWAS SNPs with p<0.01 (N=5321). Distribution of the count of QTLs in 1,000 simulations are displayed, each matching the MAF distribution of the OCD–associated SNPs. The black dot identifies the observed eQTL or mQTL count in the OCD susceptibility–associated SNPs.

Table 1

Strongest Associated GWAS Variants in Trio, Case-Control and Combined Trio-Case-Control Samples

Single nucleotide polymorphisms (SNP) listed by rs number include those with association P-values<10^{-5} for the trio and case-control samples, and those with P-values <5×10^{-5} for the combined trio-case-control sample association results. The chromosome (Chr) and base pair location for each SNP are listed in columns to the right of the SNP column. SNPs are listed separately for the analyses of trios (top section of table, with box around results), case-control samples including combined EU, SA and AJ MDS-defined ancestry subgroups (middle section and box), and for combined trio-case-control samples (lower section and box). SNPs with p<10^{-3} for any of the following are available in online Supplementary Table S2: EU, AJ and SA case-control subgroups individually and combined, trios, and combined case-control-trios). OR indicates the odds ratio for the tested allele in the trio sample. Direction indicates whether the direction of association between OCD and the A1 allele is either positive (+) or negative (-) for individual subgroups within the combined (EU, AJ, SA, trios) samples. The left gene and right gene columns lists the closest genes in the SNP region, either located within the gene (no distance given) or as right and left flanking genes (distance in kilobases). For SNPs located within genes, other functional elements in the region are as noted. QTL columns list genes whose expression (eQTL) or methylation

levels (m) are associated (P-value) with the specified SNP in that row, specifically as identified previously in EU-ancestry frontal (F), parietal (P) or cerebellar (C) tissue. mQTL and F eQTL data were unavailable for X chromosome SNPs.

SNP	Location		Trio		Case-Ctrl	Trio-Case-Ctrl		Left Gene (kb)	Right Gene	QTL
rs#	Chr	base pair (HG19)	OR	P	P	P	Direction	Intragenic (location)		
rs6131295	20	11996267	0.51	3.84E-08	0.0738	3.63E-05	---+	BTBD3 (89)	SPTLC3 (993)	F:BTBD3; P:ISM1; m:NOS1
rs10165908	2	158315629	2.05	6.43E-06	0.735	0.0169	+++-	CYTIP (15)	ACVR1C (68)	
rs6531002	8	12722703	1.63	6.84E-06	0.477	0.00665	-++-	LONRF1 (110)	KIAA1456 (80)	C:C8orf12; m:NOMO1,GNAL
rs11611761	12	33025612	0.56	9.58E-06	0.593	0.115	--+-	PKP2 (intronic)		m:TRIM31
rs11081062	18	3662879	1	1	2.49E-06	2.92E-05	+0++	DLGAP1 (intronic)		C:DLGAP1
rs11663827	18	3663631	1.03	0.799	3.44E-06	2.31E-05	++++	DLGAP1 (intronic)		C:TYMS, DLGAP1
rs26728	5	106946056	0.96	0.718	4.75E-06	0.000101	-++-	EFNA5 (intronic)		
rs4868342	5	173504522	1.03	0.783	5.40E-06	3.20E-05	++++	HMP19 (intronic)		C:CPEB4; F:CPEB4
rs297941	12	50319086	0.81	0.0294	5.81E-06	4.99E-07	----	FAIM2 (21)	AQP2 (25)	F:BCDIN3D
rs11898020	2	144282078	1.1	0.44	5.93E-06	0.000256	+-+-	ARHGAP15 (intronic)		m:CXCL9
rs2205748	6	104462555	1.11	0.301	7.38E-06	8.52E-06	++++	GRIK2 (1944)	HACE1 (713)	
rs182320	6	130073291	1.07	0.516	8.87E-06	2.25E-05	++++	ARHGAP18 (42)	C6orf191 (79)	P:TAAR5
rs1838733	5	58533392	0.96	0.669	9.71E-06	3.82E-05	----	PDE4D (intronic)		C:ELOVL; P:PLK2; m:TTYH1
rs297941	12	50319086	0.81	0.0294	5.81E-06	4.99E-07	----	FAIM2 (21)	AQP2 (25)	C:C12orf62,LASS5,TUBA1A; F:CDIN3D
rs9499708	6	104445367	0.83	0.0818	1.28E-05	2.96E-06	--+-	GRIK2 (1927)	HACE1 (731)	
rs9652236	13	72688774	1.4	0.0101	0.0001445	5.14E-06	++++	DACH1 (247)	MZT1 (594)	
rs2205748	6	104462555	1.11	0.301	7.38E-06	8.52E-06	++++	GRIK2 (1944)	HACE1 (713)	
rs485186	19	49207206	1.16	0.138	2.54E-05	9.94E-06	++++	FUT2 (coding-synon T (ACA)--> T (ACG))		C:SNORD33; F:SNAR-A1; m:HAS1,RASIP1, IZUMO1,FGF21, FUT1,M-RIP
rs6919215	6	104475419	1.12	0.277	1.04E-05	1.03E-05	++++	GRIK2 (1957)	HACE1 (701)	m:C9orf24,SYN1
rs7459733	8	131936877	0.84	0.114	3.32E-05	1.03E-05	----	ADCY8 (intronic)		P:ADCY8; m:MS4A12
rs602662	19	49206985	1.17	0.126	3.21E-05	1.11E-05	++++	FUT2 (missense G (GGT) --> S (AGT))		F:PRMT1,RASIP1, SNAR-A1,FCGRT, RPS11,NOSIP; m:HAS1, RASIP1, IZUMO1,FGF21, FUT1,M-
rs759082	4	55491904	1.24	0.0309	0.0001535	1.33E-05	++++	PDGFRA (327)	KIT (32)	
rs7461923	8	131936279	0.85	0.127	3.91E-05	1.35E-05	----	ADCY8 (intronic)		P: ADCY8
rs17070275	4	181813489	0.86	0.151	3.34E-05	1.41E-05	----	LOC285501 (2902)	LINC00290 (171)	P: HELT; m:PIWIL2
rs7124427	11	36089700	1.29	0.0348	0.0001482	1.42E-05	++-+	LDLRAD3 (intronic)		
rs7675203	4	55486182	1.26	0.0215	0.0002427	1.57E-05	+++-	PDGFRA (322)	KIT (38)	
rs1874777	9	129601002	1.17	0.227	2.33E-05	1.64E-05	++++	ZBTB43 (4)	ZBTB34 (22)	C:LRSAM1,RPL12,STXBP1,NA,ZBTB34; F:FAM129B
rs11252374	10	4186228	2.3	0.00137	0.001496	1.73E-05	++++	AK055803 (55)	LOC100216001 (506)	

rs3824760	10	131861906	2	0.197	2.66E-05	1.91E-05	++++	EBF3 (100)	LOC38772 (3236)	F:SNAR-A1, RASIP1,RPS11, PRMT1,FCGRT, NOSIP;C:PRMT1,PRMT1, GRWD1, SNORD33; m:FGF21,FUT1,HAS1,IZUMO1, RASIP1,M-RIP
rs504963	19	49208865	1.17	0.115	7.16E-05	2.15E-05	++++	FUT2 (UTR-3)		P: TAAR5 C: TYMS,DLGAP1 P: ARX; C: BAMBI
rs182320	6	130073291	1.07	0.516	8.87E-06	2.25E-05	++++	ARHGAP18 (42)	C6orf191 (79)	
rs11663827	18	3663631	1.03	0.799	3.44E-06	2.31E-05	++++	DLGAP1 (intronic)		
rs749631	10	29402289	0.78	0.0395	0.0002177	2.33E-05	----	LOC100507605 (317)	LYZL1 (176)	
rs5908139	X	141175215	1.21	0.2805	2.83E-05	2.54E-05	++-+	MAGEC1 (178)	MAGEC2 (115)	P: OPRD1 C: LIFR; m:DCAMKL1,FYB, KENAE C: QTRTD1 C: PRMT1,GRWD1; F:SNAR-A1,NUCB1,RASIP1,RPS11,PRMT1,F CGRT,NOSIP,NA3365; m:FGF21,FUT1,IZUMO1,RASIP1, TSKS
rs6919443	6	104493098	1.11	0.328	2.32E-05	2.63E-05	++++	GRIK2 (1975)	HACE1 (683)	
rs6897719	5	34795981	1.28	0.0668	0.0001558	2.66E-05	++++	RAI14 (intronic)		
rs1392261	3	115144685	0.79	0.0244	0.000393	2.86E-05	---+	ZBTB20 (279)	GAP43 (198)	
rs676388	19	49211969	1.13	0.242	3.97E-05	2.87E-05	++++	FUT2 (3)	FLJ36070 (4)	F: NARS C: DLGAP1 C: CPEB4; F: CPEB4 P: ARX; C:BAMBI F: DHX58 P:C7orf60; C:DLD,LOC401397 F: BTBD3; P:ISM1; m:NOS1 C: UBE4B; m:TNFRSF25 P:PLK2; C:ELOVL7; m:TTYH1 F: LUC7L3; C:SPAG9, NXPH3 C: DPY19L4, POP1; m:SAFB2,KIAA0802,EFCAB3 F: TSPYL1; m:C6orf78; BCAP31
rs1005419	18	54308996	1.16	0.207	4.94E-05	2.90E-05	++++	TXNL1 (intronic)		
rs11081062	18	3662879	1	1	2.49E-06	2.98E-05	0+++	DLGAP1 (intronic)		
rs4868342	5	173504522	1.03	0.783	5.40E-06	3.20E-05	++++	HMP19 (intronic)		
rs2793345	10	29409192	0.79	0.0466	0.000263	3.24E-05	----	LOC100507605 (324)	LYZL1 (169)	
rs2857254	17	39620034	1.21	0.0946	0.0001426	3.39E-05	++++	KRT32 (intronic)		
rs12705610	7	109161891	1.33	0.006065	0.001191	3.42E-05	+++-	DNAJB9 (947)	LRRN3 (1569)	
rs6131295	20	11996267	0.51	3.84E-08	0.07383	3.62E-05	---+	BTBD3 (89)	SPTLC3 (993)	
rs4908608	1	7292772	1.21	0.0655	0.0002276	3.79E-05	+++-	CAMTA1 (intronic)		
rs1838733	5	58533392	0.96	0.67	9.71E-06	3.82E-05	----	PDE4D (intronic)		
rs2586494	17	48273155	1.57	0.002075	0.002568	4.17E-05	++++	COL1A1 (intronic)		
rs2515144	8	95289326	1.23	0.0792	0.0002315	4.58E-05	+++-	GEM (15)	RAD54B (95)	
rs636252	6	117157774	1.12	0.2905	5.37E-05	4.72E-05	++++	GPRC6A (8)	RFX6 (41)	
rs12334868	8	131954652	0.76	0.0284	0.0005812	4.82E-05	----	ADCY8 (intronic)		