

A Genetic Family-Based Association Study of *OLIG2* in Obsessive-compulsive Disorder

S. Evelyn Stewart, MD; Jill Platko, PhD; Jesen Fagerness, BS; Julie Birns, BA; Eric Jenike, BA; Jordan W. Smoller, MD; Roy Perlis, MD; Marion Leboyer, MD; Richard Delorme, PhD; Nadia Chabane, PhD; Scott L. Rauch, MD; Michael A. Jenike, MD; David L. Pauls, PhD

Context: Obsessive-compulsive disorder (OCD) is a debilitating familial psychiatric illness with associated brain abnormalities in the white matter. The gene for oligodendrocyte lineage transcription factor 2 (*OLIG2*) is an essential regulator in the development of cells that produce white matter (myelin). The *OLIG2* gene is also highly expressed in brain regions implicated in OCD.

Objectives: To examine *OLIG2* as a candidate gene for OCD susceptibility and to explore whether comorbidity subtypes of OCD have distinct associations with *OLIG2* and the functionally related *OLIG1* gene. It was hypothesized a priori that *OLIG2* and *OLIG1* were associated with OCD regardless of the presence of comorbid Tourette disorder (TD), but not with TD alone.

Design: Family-based association candidate gene study.

Setting: Participants and their family members were recruited from tertiary care OCD and TD specialty clinics.

Participants: Families of 66 probands with OCD with and without TD and 31 probands with TD without OCD.

Main Outcome Measures: Genotypes of single nucleotide polymorphism markers and related haplotypes.

Results: The following 3 single nucleotide polymorphism markers on *OLIG2* were associated with the OCD without TD phenotype: rs762178 (minor allele frequency, 35%; $P < .001$), rs1059004 (minor allele frequency, 44%; $P = .005$), and rs9653711 (minor allele frequency, 44%; $P = .004$). A 5-marker haplotype (A/C/T/T/G) constituting these single nucleotide polymorphisms and exonic single nucleotide polymorphisms rs6517137 and rs13046814 was undertransmitted (frequency, 32%; permuted $P = .004$), whereas the G/A/T/T/C haplotype (frequency, 22%; permuted $P = .02$) was overtransmitted to probands with OCD alone, with a significant global P value (permuted $P = .008$).

Conclusions: This is the first study reporting an association between *OLIG2* and OCD, specifically when TD comorbidity is absent. The findings support a role for white matter abnormalities in the etiology of the disorder.

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Author Affiliations: Psychiatric Neurodevelopmental and Genetics Unit (Drs Stewart, Platko, Jenike, Smoller, Perlis, and Pauls; Mr Fagerness; and Ms Birns), Psychiatric Neuroscience Research Division (Dr Rauch), and Obsessive-compulsive Disorder Clinic, Harvard Medical School (Drs Stewart and Jenike), Massachusetts General Hospital, Boston; and Departments of Psychiatry, Mondor-Chenevier Hospital, University of Paris (Dr Leboyer), and Robert Debré Hospital (Drs Delorme and Chabane), Paris, France.

OBSESSIVE-COMPULSIVE DISORDER (OCD) is a serious psychiatric condition with debilitating effects on adults and children.¹

Originally thought to be rare,² it is now known that OCD is a common disorder with lifetime prevalence rates ranging from 1.1% to 3.3% worldwide.^{3,4} Obsessive-compulsive disorder is a complex genetic disorder^{5,6}; however, the precise genetic mechanism is not known. Recent molecular studies provide evidence that specific genes play a role in the manifestation of OCD.⁷ Furthermore, OCD with and without tics or Tourette disorder (TD) may be associated with different candidate genes or regions of interest in the genome.^{5,6,8}

The biological nature of OCD is supported by neuroimaging findings. Struc-

tural and functional neuroimaging studies of OCD implicate defects in the frontal cortical-basal ganglia-thalamocortical circuit.⁹⁻¹⁴ Specifically, in addition to the orbitofrontal and anterior cingulate cortices, the caudate nuclei, amygdala, and thalamus have been implicated in the pathophysiology of OCD.¹²⁻¹⁵ The nodes of this circuit are interconnected via 2 principal white matter tracts—the cingulum bundle and the anterior limb of the internal capsule. Obsessive-compulsive disorder is also associated with decreased white matter volume, although the etiology of this finding is poorly understood.^{16,17} Moreover, the structure of white matter in OCD demonstrates abnormalities, as reflected by decreased fractional anisotropy in brain regions implicated with this illness.¹⁸ None of the imaging studies implicating white

matter abnormalities included subjects with comorbid TD.¹⁶⁻¹⁸ Consequently, the present study was undertaken to test the hypothesis that genes involved in the regulation of white matter development might be involved in conferring risk for OCD.

The gene for oligodendrocyte lineage transcription factor 2 (*OLIG2*) is an essential regulator in the development of human cells that produce white matter (myelin).¹⁹ This gene is located on the long arm of chromosome 21 and is involved with remyelination and neurogenesis in mice.^{19,20} The *OLIG2* gene is highly expressed in the amygdala, thalamus, and caudate nuclei²⁰—brain regions implicated in OCD.¹²⁻¹⁵ It also has a close functional association with *OLIG1*, an immediately adjacent gene on chromosome 21q that acts as a transcription factor in the differentiation of oligodendrocyte progenitor cells.²¹ In addition to functional support for examining *OLIG2* and *OLIG1* as candidate genes for OCD, there is some modest positional support. In a recent linkage scan conducted using the OCD Genetics Collaborative Study sample, a suggestive linkage peak was found on chromosome 21 by using a cutoff point of 0.05 in multipoint nonparametric analyses.²²

The *OLIG2* and *OLIG1* genes have not been studied to date as candidate genes for OCD or TD. The present study examined transmission of 26 single nucleotide polymorphism (SNP) markers from parents to offspring in nuclear families of OCD-affected probands with and without TD and TD-affected probands without OCD. We specifically hypothesized a priori that *OLIG2* is associated with OCD, regardless of the presence of comorbid TD, but not with TD alone. Furthermore, we hypothesized that *OLIG1* is also associated with OCD and that it acts with *OLIG2* in conferring susceptibility to OCD.

METHODS

SUBJECTS

We examined the families of 97 probands meeting *DSM-IV* criteria for OCD and/or TD.²³ Families were recruited from specialized OCD and TD clinics in New Haven, Conn; Boston, Mass; and Paris, France. The probands with OCD and TD and their family members underwent structured clinical interviews, which included the Structured Clinical Interview for *DSM-IV*–Non-Patient edition²⁴ for adults and the Kiddie Schedule for Affective Disorders and Schizophrenia–Present and Lifetime Version²⁵ for children and adolescents younger than 18 years. Diagnoses of OCD and TD also used information gathered from the Family Self-report Questionnaire.²⁶ This measure is derived from the Yale-Brown Obsessive Compulsive Scale²⁷ and the Yale Global Tic Severity Scale.²⁸ Interviewers from the Paris site were child psychiatrists with expertise in OCD and TD. Interviewers from the New Haven and Boston sites had at least a bachelor's degree and went through a rigorous training program for the conduct of structured interviews. At all sites, interviews were reviewed by 2 expert clinicians (including M.L. and D.L.P.), a best estimate diagnosis was assigned,²⁹ and diagnoses were confirmed by an expert clinician interview.

We recruited 97 families. Among the 84 families with both parents available, there were 22 in the OCD + TD group, 35 in the OCD-only group (OCD without TD), and 27 in the TD-only group (TD without OCD). Among the 13 families recruited with only 1 parent and at least 1 sibling, 3 were in the

OCD + TD group, 6 were in the OCD-only group, and 4 were in the TD-only group. Thus, the total numbers of families in the OCD + TD, OCD-only, and TD-only groups were 25, 41, and 31, respectively.

Furthermore, the numbers of affected male probands in the OCD + TD, OCD-only, and TD-only groups were 20 (80%), 28 (68%), and 27 (87%), respectively. There was no statistically significant difference in sex among the groups ($\chi^2=3.70$; $P=.16$). The mean ages of the probands in these 3 groups were 12.3, 15.8, and 13.6 years, respectively, and did not differ significantly (analysis of variance—adjusted $r^2=0.03$; $P=.09$). The mean age at OCD onset in the OCD + TD group was 6.7 years and in the OCD-only group was 10.5 years; these were significantly different from one another (analysis of variance—adjusted $r^2=0.11$; $P=.007$). Written informed consent was obtained from all adult participants, and written assent was obtained from children and adolescents younger than 18 years in the presence of their parents, who provided the written consent on their behalf.

GENOTYPING

We extracted DNA from peripheral blood and buccal cell samples using the Gentra protocols,³⁰ and samples with low yields underwent whole-genome amplification via the REPLI-g protocol (Qiagen Inc, Valencia, Calif). The known call rates (SDs) for the SNPs used on DNA derived from blood, buccal cells, and whole-genome amplification were 84.9% (10.3%), 87.5% (6.1%), and 76.5% (16.3%), respectively.

The SNPs thought to be highly polymorphic were selected by downloading all available SNP information from the db-SNP (<http://www.ncbi.nlm.nih.gov/projects/SNP/celera>), Celera (<http://www.celera.com>), and HAPMAP (<http://www.hapmap.org/>) databases. Twenty-eight SNPs were chosen across a 105-kilobase (kb) region to create a linkage disequilibrium (LD) map in 93 CEPH (Centre d'Etude du Polymorphisme Humain) samples (12 families and 24 trios) for the region surrounding *OLIG2*. The resultant average spacing was 1 SNP every 3.75 kb. These data were then used to select an informative pairwise set of 13 tag SNPs using the program Tagger.³¹ Genotyping was performed on the Sequenom homogeneous MassEXTEND platform.³² Markers with genotyping success rates of less than 90% on our sample, with minor allele frequency of less than 5%, with more than 1 Mendel error, or with a Hardy-Weinberg P value of less than .01 were excluded, leaving a set of 12 of the 13 markers for analysis. Of these 12, 1 marker was excluded from the Family Based Association Test (FBAT) analysis owing to the presence of fewer than 10 informative families, leaving a set of 11 of the 13 markers. The resulting 11 SNPs in the preliminary analysis covered *OLIG2* and *OLIG1*, spanned 82.2 kb, and had a density of 7.5 kb/SNP. The average r^2 value between tested (eg, tag) SNPs and other known SNPs examined in our CEPH samples was 0.991.

After the 11 tag SNPs were genotyped in the preliminary analysis, the single-marker and haplotype associations were examined. Correction for multiple testing was conducted using Bonferroni correction for 11 independent markers and 3 phenotype groups (ie, correcting for 33 tests). Subsequently, haplotype analysis was completed for a 2-marker haplotype on *OLIG2* in the OCD-only group (including the marker that trended toward significance after correction for multiple testing). Bonferroni correction was completed for 3 haplotypes in the 1 phenotypic group.

We performed further genotyping to provide denser coverage of the area. Additional SNP markers were selected using SNPper.^{33,34} An additional 33 SNPs were tested in our original region and 27.9 kb in the 3' direction to capture more information about *OLIG2*, *OLIG1*, and the surrounding region. Fifteen

Table 1. Preliminary Single-Marker Associations for *OLIG2* in OCD + TD, TD-Only, and OCD-Only Groups Using FBAT

SNP Identification No.	hg17 Positions	Minor Allele Frequency, %	Major/Minor Alleles	Gene/Region*	OCD + TD Group		TD-Only Group		OCD-Only Group	
					χ^2 Test	P Value	χ^2 Test	P Value	χ^2 Test	P Value†
rs2834046	33281013	33	G/A	Between genes	0.24	.59	0.17	.68	0.27	.60
rs2834064	33301078	30	T/C	Between genes	1.92	.17	2.67	.10	0.31	.56
rs11701698	33315815	24	T/G	<i>OLIG2</i> promoter	NA	NA	0.05	.82	0.18	.67
rs1005573	33320586	22	T/C	<i>OLIG2</i> intron	2.84	.09	0	>.99	1.20	.27
rs6517137	33322649	8	T/C	<i>OLIG2</i> exon	NA	NA	NA	NA	0	>.99
rs9653711	33323819	44	C/G	<i>OLIG2</i> 3' UTR	2.67	.10	0.27	.60	8.53	.004
rs2834076	33338971	41	G/A	Between <i>OLIG2</i> and <i>OLIG1</i>	0.06	.83	0.04	.84	0.31	.58
rs2409469	33342690	31	C/T	Between genes	1.16	.28	0.39	.53	0.76	.38
rs2834079	33352040	11	A/G	Between genes	NA	NA	NA	NA	1	.32
rs2834083	33358843	35	A/G	<i>OLIG1</i> promoter	0.33	.57	0.86	.35	0	>.99
rs928736	33361759	22	T/C	<i>OLIG1</i> promoter	4.20	.04	0.04	.85	0.86	.35

Abbreviations: FBAT, Family Based Association Test^{36,37}; hg, human genome; NA, fewer than 10 informative families; OCD, obsessive-compulsive disorder; *OLIG2*, gene for oligodendrocyte lineage transcription factor 2; SNP, single nucleotide polymorphism; TD, Tourette disorder; UTR, untranslated region.

*From SNPper, version 123.³⁴

†Boldface type indicates statistical significance.

of these additional SNPs met criteria for data analytic inclusion. The average density for the total 26 SNPs (11 preliminary and 15 additional SNPs) in the entire 97-kb region was 1 SNP per 3.7 kb. Haplotype block structure of the SNPs was examined using the solid spine of LD as implemented in Haploview.³⁵

STATISTICAL ANALYSES

Analyses were completed with version 1.5.5 of the FBAT program^{36,37} and Haploview.³⁵ The biallelic mode of FBAT under an additive model was used. We used FBAT to conduct single-marker and haplotype analyses by calculating *P* values for individual SNPs and their associated haplotypes. A minimum of 10 informative families was used as a default threshold in FBAT. Haploview was used to define LD in the region. Bonferroni correction for multiple testing was applied for single markers (11 in 3 phenotypic groups) and for significant haplotypes (3 in the 1 phenotypic group with significant single-marker associations) in the preliminary analysis. Subsequent analyses of the 15 additional markers in the region were not subjected to Bonferroni correction, as these were not considered to be independent of the initially chosen markers and owing to the fact that this was a part of follow-up analyses based on initial findings (rather than being randomly selected SNPs). Using the FBAT program, we calculated haplotype-specific and global permuted *P* values for the haplotypes selected by Haploview. The χ^2 values were calculated by squaring the *z* score provided in the FBAT output.

RESULTS

There were 25, 41, and 31 families in the OCD + TD, OCD-only, and TD-only groups, respectively. In the preliminary analysis, the mean call rate for the 11 successful SNPs was 98.6%. The initial SNPs examined in the preliminary study are described in **Table 1**. A positive association was found for SNP rs9653711 in the OCD-only group ($\chi^2=8.53$; *P*=.004) (Table 1). The SNP rs9653711 is located in the 3' untranslated region (UTR) of *OLIG2*. It has a minor allele frequency of 44%, with the major and minor alleles being C and G, respectively. The C allele was overtransmitted and the G allele was undertransmitted in 29 informative families.

After Bonferroni correction for 11 markers and 3 phenotypes (33 "independent" tests), the *P* value only trended toward significance at .12. In subsequent analysis of the OCD-only phenotype, a 2-marker haplotype with the SNP described in the previous paragraph and rs6517137 was tested. The findings demonstrated overtransmission of the most frequent haplotype, TC (frequency, 49%; permuted *P*=.003) and undertransmission of haplotype TG (frequency, 34%; permuted *P*<.001) (global *P*=.002). These remained significant, even after Bonferroni correction for testing 3 haplotypes (3 independent tests on 1 phenotype; corrected *P*=.009 and corrected *P*=.002, respectively). There were no significant single-marker associations in the OCD + TD, the TD-only, or the combined OCD + TD and OCD-only groups before or after Bonferroni correction.

Subsequently analyzed SNPs included other markers on *OLIG2* and *OLIG1* and in the proximity, as described in **Table 2**. In the OCD-only group, significant differences between transmission and nontransmission of *OLIG2* alleles were determined for 2 single markers near rs9653711 (Table 2). The most significant of these was rs762178, a serine-serine synonymous coding SNP in amino acid position 77 in exon 2 of *OLIG2*, with overtransmission of the G allele (minor allele frequency, 35%; $\chi^2=13.33$; *P*<.001). The major and minor alleles for this SNP are G and A, respectively. The SNP rs1059004 (minor allele frequency, 44%; $\chi^2=7.81$; *P*=.005), located within exon 2 in a UTR, had significant overtransmission of the A allele. The major and minor alleles for this SNP are A and C, respectively. There were no significant associations for single markers in the TD-only or the OCD + TD groups, and there were no significant associations for the *OLIG1* markers in any of the groups on the follow-up single-marker analysis.

A 5-marker haplotype containing the markers described (rs9653711, rs762178, and rs1059004) and 2 exonic SNPs (rs6517137 and rs13046814) was associated with the OCD-only phenotype (permuted global *P*=.008) (**Figure**).³⁸ Haplotype-specific tests revealed undertrans-

Table 2. Follow-Up Single-Marker Associations for *OLIG2*, *OLIG1*, and Surrounding Regions in OCD + TD, TD-Only, and OCD-Only Groups Using FBAT

SNP Identification No.	hg17 Positions	Minor Allele Frequency, %	Major/Minor Alleles	Gene/Region*	OCD + TD Group		TD-Only Group		OCD-Only Group	
					χ^2 Test	P Value	χ^2 Test	P Value	χ^2 Test	P Value
rs2008980	33306458	28	G/A	Between genes	2.13	.14	0.43	.51	3.33	.07
rs743330	33306722	38	C/T	Between genes	0.17	.68	0.57	.45	0	>.99
rs2834070	33309322	33	G/T	<i>OLIG2</i> promoter	0.11	.74	0.17	.68	2.29	.13
rs16990063	33310603	10	G/T	<i>OLIG2</i> promoter	0.14	.71	0.07	.80	1.33	.25
rs762178	33321271	35	G/A	<i>OLIG2</i> exon†	2.579	.108	0.154	.695	13.33	<.001
rs1059004	33322333	44	A/C	<i>OLIG2</i> UTR	4.84	.03	0.04	.84	7.81	.005
rs13046814	33323247	37	T/G	<i>OLIG2</i> exon	0.08	.78	0.14	.71	1.69	.19
rs881666	33327136	45	C/G	<i>OLIG2</i> 3' UTR	3.27	.07	0.04	.84	0.80	.37
rs762237	33330047	31	C/T	<i>OLIG2</i> 3' UTR	2.91	.09	0.43	.51	0.13	.72
rs2834072	33332334	38	A/G	<i>OLIG2</i> 3' UTR	0.80	.37	0.67	.41	0.04	.85
rs2834074	33337172	31	C/T	Between <i>OLIG2</i> and <i>OLIG1</i>	1.09	.30	1.19	.28	0.15	.70
rs11554600	33366007	10	G/A	<i>OLIG1</i> exon	0.14	.71	0	>.99	1.47	.23
rs7278735	33366952	12	C/T	<i>OLIG1</i> 3' UTR	0.08	.78	0.05	.82	1.19	.28
rs8131457	33375767	39	T/C	<i>OLIG1</i> 3' UTR	0.62	.43	1.50	.22	0.12	.73
rs2834084	33378202	47	T/C	Between genes	0.04	.84	0.22	.64	1.40	.24

Abbreviations: See Table 1; *OLIG1*, gene for oligodendrocyte lineage transcription factor 1.

*From SNPper, version 123.³⁴

†Synonymous coding SNP.

mission of haplotype A/C/T/T/G (frequency, 32%; $\chi^2=8.35$; permuted $P=.004$) and overtransmission of haplotype G/A/T/T/C (frequency, 22%; $\chi^2=5.44$; permuted $P=.02$). This haplotype spans 2548 base pairs in exon 2 and in the 3' UTR of *OLIG2*. Despite testing of several additional markers on *OLIG1* and nearby regions, no evidence of single-marker association emerged outside the region of interest on *OLIG2* identified in preliminary analyses (Figure). There was one 6-marker haplotype (frequency, 7%) in the *OLIG1* region, which initially appeared to be significant ($P=.03$) but lost significance on permutation testing ($P=.06$).

COMMENT

To our knowledge, this is the first report of an association between the *OLIG2* gene and OCD. Given that *OLIG2* is required for the development of oligodendrocytes, that oligodendrocytes are responsible for the production of white matter (myelin), and that OCD has been associated with white matter abnormalities,¹⁶⁻¹⁸ this association suggests that there is a potential etiologic connection among the *OLIG2* gene, white matter abnormalities, and OCD.

Our findings are consistent with previous evidence suggestive of distinct genetic underpinnings for OCD subtypes.³⁹ An association with *OLIG2* was evident only in the OCD phenotype without TD. An association was not even present when OCD with and without TD comorbidity was combined (thus imparting greater power) as a part of the post hoc analyses. Similarly, previous OCD structural imaging studies reporting white matter abnormalities involved samples that were expressly limited to the diagnosis of OCD without comorbid TD.¹⁵⁻¹⁸ Thus, the subtype of OCD that appears to be associated with *OLIG2* and white matter abnormalities is that without comorbid TD.

Obsessive-compulsive disorder without comorbid TD is also distinct from OCD with TD in other ways. It is

associated with a better treatment response to selective serotonin reuptake inhibitors⁴⁰ and with distinct symptomatology. Subjects with OCD without comorbid TD report fewer aggressive, religious, and sexual obsessions; fewer checking, ordering, counting, and touching compulsions⁴¹; and fewer touching behaviors.⁴² In comparing the symptoms of OCD and TD, Cath et al⁴³ also reported that patients with OCD and TD are phenomenologically less similar to OCD than to TD. It has been postulated that the differences between OCD with and without TD may relate to putative differences in pathophysiology or to genetic heterogeneity within OCD.⁴⁴ This would be consistent with our observation that OCD alone, but not OCD with TD, was associated with *OLIG2*.

Because 2 of the neuroimaging studies that reported white matter abnormalities analyzed samples of female patients only,^{16,17} it would be of interest for future studies to explore the potential of a sex effect for this gene. However, further subdividing this study's sample would deem the power to detect differences insufficient, especially among female subjects. Thus, if such post hoc analyses were conducted for the present sample, the results would be inconclusive and noncontributory to the study's findings.

Future candidate gene research should use more homogeneous samples of OCD-affected individuals to limit conflicting results between studies. Because *OLIG2* has not been reported as a candidate gene for OCD to date, this finding should also be replicated on independent samples with increased power. Ongoing work on the function of *OLIG2* is also required, which may begin to elaborate on the putative etiologic connection between *OLIG2* and neuropathology leading to OCD. The haplotypes and SNPs associated with the OCD-only phenotype in this study were in an exon and a 3' UTR of *OLIG2*. A non-validated SNP rs17854475 that is located 73 amino acids away from SNP rs762178 is a nonsynonymous SNP, coding for threonine and alanine. The mechanism by

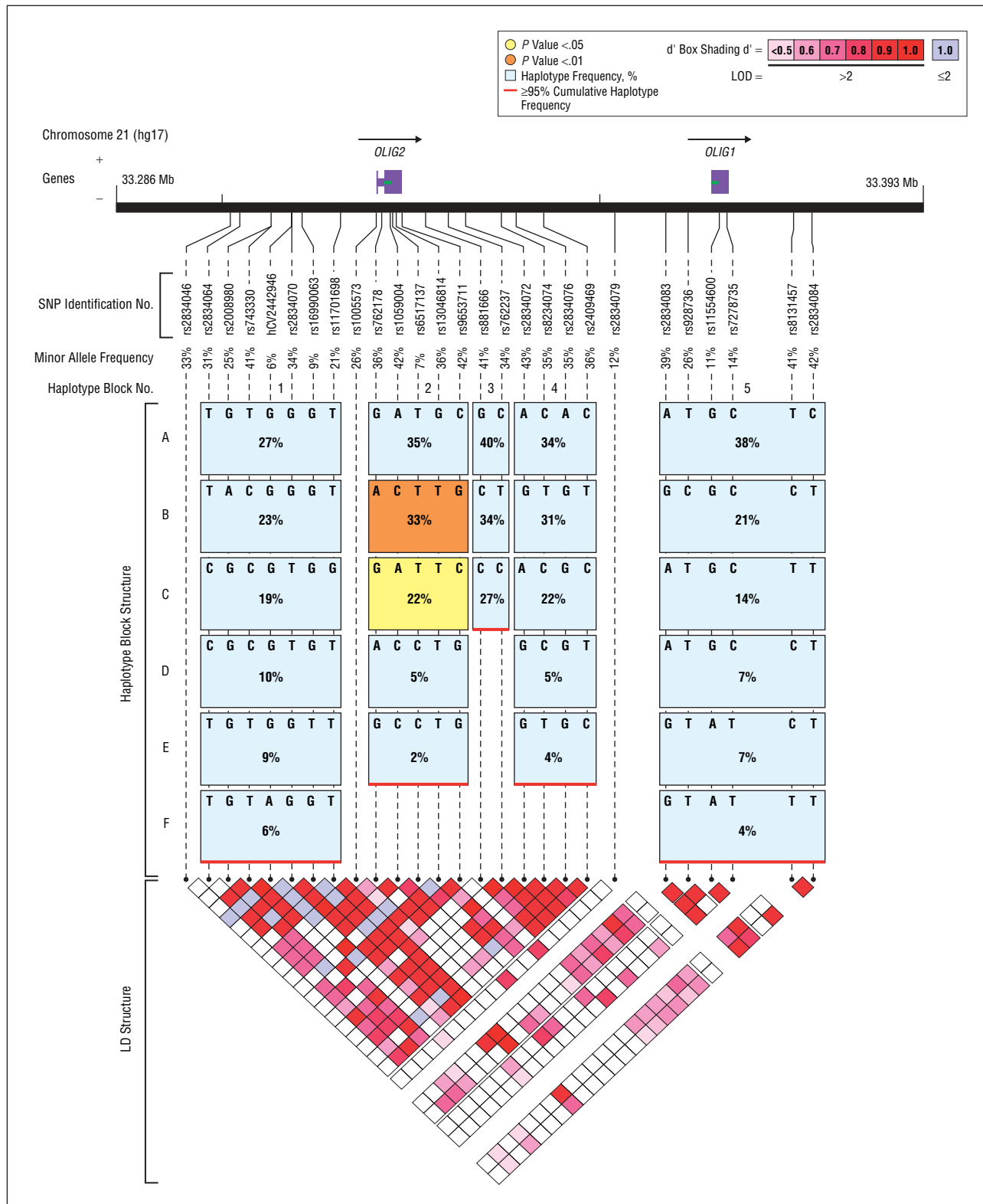


Figure. Single-marker associations and Haploview-selected haplotype blocks for the group with obsessive-compulsive disorder only.³⁸ hg, indicates human genome; LD, linkage disequilibrium; LOD, limit of detection; Mb, megabase; *OLIG*, genes for the oligodendrocyte lineage transcription factors; and SNP, single nucleotide polymorphism.

which certain genetic variants in this region may increase susceptibility for the OCD subtype without comorbid TD also requires further work. In this study, *OLIG1* was also examined, given that it is a nearby gene

with a known functional association to *OLIG2*. However, no association was found.

Bonferroni correction for multiple independent tests is considered to be overly conservative for single mark-

ers that may be in LD, as the presence of LD indicates that results are not independent of each other. Nevertheless, because the preliminary analyses involved the multiple testing of 11 markers and 3 phenotypic groups, this correction was applied. Although the *P* value for rs9653711 only trended toward significance after correction (*P*=.12), 2 of the 2-marker haplotypes in the preliminary analyses with the described SNP and rs6517137 (T/C and T/G) were found to be significant even after correction for 3 haplotypes (*P*=.009 and *P*=.002, respectively). This led us to believe that a causal gene for OCD may be in the region of rs9653711. Thus, a decision was made to conduct further study of this gene by genotyping additional SNPs based on these preliminary data. The additional analyses were not subjected to Bonferroni correction, as these tests were driven by earlier findings.

Limitations of the study must be acknowledged. These include power restrictions, as type II error may have been responsible for the lack of a significant association in the OCD + TD and the TD-only groups. Although we hypothesized that OCD with TD may be associated with different genes from those for OCD without TD, it is possible that the lack of significant findings in the OCD + TD group simply may be related to inadequate power. However, when the sample size was increased by combining the OCD + TD group with the OCD-only group (with known associations), no single-marker associations were present. Results from power calculations⁴⁵ indicate that our power was adequate (>80%) to detect moderate to large genetic effects (genotypic relative risks, >1.5), but not smaller effects. Nevertheless, we did find significant associations in the OCD-only group. In addition, we examined multiple SNPs and 3 phenotypes, raising the possibility of type I error. However, after Bonferroni correction, the haplotypes remained significant. Furthermore, markers with significant association (although they were not subjected to Bonferroni correction) in the follow-up genotyping of 15 SNPs were in the same region as rs9653711. This implies that significant findings were related to underlying causal SNPs rather than to type I error. Another limitation is that the association between the OCD-only phenotype and significant SNPs may not have been causal, but reflective of proximity to causal genes. Furthermore, the differing age at OCD onset between the OCD + TD and OCD-only groups may have been a source of confounding bias.

This study provides preliminary evidence that *OLIG2*, and thus oligodendrocytes, may play an etiologic role in the development of some cases of OCD. This work potentially suggests novel insights into the neurobiology of OCD.

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Correspondence: David L. Pauls, PhD, Psychiatric and Neurodevelopmental Genetics Unit, Harvard Medical School, 185 Cambridge St, 6th Floor, Boston, MA 02114 (dpauls@pngu.mgh.harvard.edu).

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