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An Association of Myelin Oligodendrocyte Glycoprotein (MOG) Gene Variants with White Matter Volume in Pediatric Obsessive-Compulsive Disorder

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Abstract

An increasing number of neuroimaging studies have implicated alterations of white matter in obsessive-compulsive disorder (OCD). The myelin oligodendrocyte glycoprotein (MOG) gene plays a major role in myelination, and has previously demonstrated significant association with

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6. Contributions:

Dr. Zai performed the genetic experiment and statistical analyses for this study in addition to drafting and finalizing the manuscript. Drs. Arnold, Richter, Hanna, Rosenberg, and Kennedy conceptualized the design of the study in addition to providing mentorship to Dr. Zai. Dr. Rosenberg provided the sample and clinical demographics for this study. Dr. Hanna conducted the imaging part of the study. Dr. Arnold extracted the imaging data and assisted with the statistical analyses. Dr. Kennedy provided oversight of the genotyping and genetic analyses. All authors contributed to the writing and review of the manuscript.

7. Conflict of Interest:

The other authors have no conflict of interest to declare.

this disorder, thus variations in this gene may contribute to observed white matter alterations. The purpose of this study is to examine the relationship between white matter volume in OCD and genetic variations in the MOG gene. Two polymorphisms in the MOG gene, MOG(C1334T) and MOG(C10991T), were investigated for association with total white matter volume as measured using volumetric magnetic resonance imaging in 37 pediatric OCD patients. We compared white matter volumes between allele and genotype groups for each polymorphism using ANCOVA. A significant relationship was detected between genotype C/C of MOG(C10991T) and decreased total white matter volume (P=0.016). Our results showed an association between a MOG genetic variant and white matter volume. This finding is intriguing in light of the posited role of white matter alteration in the etiology of at least some cases of childhood-onset OCD. Further investigation with larger samples and sub-regional white matter volume phenotypes is warranted.

Keywords

Pediatric obsessive-compulsive disorder (OCD); genetics; myelin oligodendrocyte glycoprotein (MOG) gene; magnetic resonance imaging (MRI); white matter volume

1. Introduction:

Obsessive-compulsive disorder (OCD) is a common and severe neuropsychiatric disorder with a prevalence of 2–3% in the general population (Ruscio et al., 2010; Sasson et al., 1997). As many as 50% of cases of OCD have their onset in childhood and adolescence (Kessler et al., 2005). There is broad support for the involvement of genetic factors in OCD, primarily based on family, twin, and segregation analyses (Hettema et al., 2001; Nicolini et al., 2009). Evidence from family studies (do Rosario-Campos et al., 2005; Hanna et al., 2005) and twin studies (Katerberg et al., 2008; Mathews et al., 2007; van Grootheest et al., 2005) suggests a stronger genetic component in pediatric OCD given that OCD aggregates to a greater degree in families of early onset probands and that estimates of genetic contribution to obsessive-compulsive symptoms range from 45% to 65% in children, and only 27% to 47% in adults.

One of the more striking findings in neuropsychiatry is the repeated observation of cortico-striatal-thalamo-cortical alterations in OCD (Kwon et al., 2009; MacMaster and Rosenberg, 2010; Saxena and Rauch, 2000). Several early neuroimaging studies also reported decreased white matter volume in OCD when compared with healthy controls (Breiter et al., 1994; Jenike et al., 1996; MacMaster et al., 1999; Rosenberg et al., 1997), which has led to questions regarding possible white matter dysfunction. Jenike and colleagues (1996) reported significantly less total white matter volumes in OCD when compared with normal controls. However, Atmaca et al. (2006) reported significantly increased white matter volume in OCD patients when compared to healthy controls. It has also been suggested that there is a greater relative proportion of water in frontal white matter based on several MRI studies (Garber et al., 1989; Jenike et al., 1996). A meta-analysis of neuroimaging in OCD using multimodal voxel-based methodology by Radua et al. (2014) reported widespread white matter abnormalities with the most robust finding of an increase in white matter volume and reduction in fractional anisotropy (FA) in the anterior midline tracts between the

anterior parts of the cingulum bundle and body of the corpus callosum. A recent study using tract-profiles rather than the conventional diffusion imaging approach also detected lower FA in the bilateral cingulum bundle in OCD when compared to controls (Versace et al., 2019). Another similar meta-analytical study observed abnormal diffusivity in major white matter regions in the cortico-striato-thalamo-cortical circuit in OCD samples compared to controls (Eng et al., 2015).

The majority of diffusion tensor imaging (DTI) studies in OCD have showed decreased FA in OCD patients when compared to healthy controls, with the most consistent white matter connectivity alterations in the cingulate bundle, corpus callosum, and the anterior limb of the internal capsule (Koch et al., 2014). More importantly, white matter changes have been observed in un-medicated patients with OCD and their unaffected siblings, implicating the unaffected relatives as an intermediate group between patients with OCD and healthy controls (Fan et al., 2016). Thus, based on this literature, researchers have hypothesized that impairment in the development or maintenance of myelination might play a role in the etiology of OCD in addition to providing a rationale for altered white matter as an endophenotype of OCD.

This white matter hypothesis has received some additional support from preliminary genetic studies implicating two myelination genes, the oligodendrocyte lineage transcription factor 2 (OLIG2; Stewart et al., 2007) and the myelin oligodendrocyte glycoprotein (MOG; Zai et al., 2004), in OCD. Our team has previously reported biased transmission of alleles of the myelin oligodendrocyte glycoprotein gene [MOG; allele 2 of (TAAA)n with P=0.022 and 4-marker haplotype with P=0.011; Zai et al., 2004] in a family study of OCD. Moreover, an association of MOG and white matter in OCD was reported (Atmaca et al., 2010), with larger total white matter volume in OCD patients with the Val/Val genotype of MOG G511C (Val142Leu; P<0.01).

Thus, we examined genetic variations in the MOG gene, which is associated with white matter. MOG, which has been implicated in autoimmune demyelinating diseases such as multiple sclerosis (Hartung and Rieckmann, 1997), is a member of the immunoglobulin super family and a component of the myelin sheath. It has been proposed that MOG might function as a cellular adhesion molecule, a regulator of oligodendrocyte microtubule stability, and/or as a mediator of interactions between myelin and the immune system, in particular, as an activator of the complement cascade (Johns and Bernard, 1997). Variations or mutations in this gene may, therefore, contribute to the development or progression of autoimmune disorders by various mechanisms, including altered gene expression, amino acid substitutions increasing the possibility of interactions between MOG and environmental factors, or loss of function rendering myelin more susceptible to autoimmune attack.

We examined two polymorphisms, two intronic C to T base-exchange polymorphisms located at position 1334 and 10991, entitled C1334T (rs2252711) and C10991T (rs2071653), across the MOG gene. We genotyped these two polymorphisms in a sample of 37 patients affected with OCD. We examined the distribution of MRI white matter volumes with genotype frequencies of these two polymorphisms for evidence of association between the MOG gene variants and white matter distribution.

2. Methods:

2.1. Clinical diagnostic criteria and sample.

Thirty-seven psychotropic-naïve children and adolescents (20 male and 17 female) with OCD were collected for this study at the Wayne State University pediatric anxiety disorders clinic. The age range was from 7 to 18 years (mean of 11.7 years and standard deviation of 2.9). Written informed consent was obtained from all parents, and all participants provided written assent prior to the study being conducted. All patients were administered the present and lifetime versions of the Schedule for Affective Disorders and Schizophrenia – School-Age Children (Kaufman et al., 1997) in addition to the following clinician-administered instruments: the Children's Yale-Brown Obsessive-Compulsive Scale (CYBOCS, Scahill et al., 1997) (mean of 25.3 and standard deviation of 7.1), Hamilton Anxiety Rating Scale (HAM-A, Hamilton, 1959) (mean of 7.15 and standard deviation of 4.66), Hamilton Depression Scale (HAM-D, Hamilton, 1967) (mean of 7.50 and standard deviation of 5.65), and the Yale Global Tic Severity Scale (YGTSS, Leckman et al., 1989) (mean of 3.30 and standard deviation of 8.56). Subscales within the Wechsler Intelligence Scale for Children-III (WISC-III, Wechsler, 1991) including Block Design and Vocabulary and Digit Span were administered to all patients and controls. An overall IQ of 80 or higher was required to be eligible for participation in the study. Additional exclusion criteria included: patients received cognitive-behavioural therapy prior to this study, patients with a history of significant debilitating medical or neurological conditions, or comorbidity with major depressive disorder, bipolar disorder, psychosis, substance use or dependence, eating disorders, attention deficit hyperactivity disorder, pervasive developmental disorder, learning disorders, or tic-related conditions. Local ethics approval has been obtained from participating sites.

2.2. Imaging procedure.

All volumetric magnetic resonance imaging (MRI) data were collected at the Children's Hospital of Michigan Imaging Center using a Sigma 1.5-Tesla unit (Horizontal LX software, General Electric Medical Systems, Milwaukee, WI). Scanning methods, image acquisition, and analytical procedures utilized to obtain structural MRI have been described in detail elsewhere (Gilbert et al., 2000; Szeszko et al., 2004a; Szeszko et al., 2004b). In brief, a 3-dimensional spoiled gradient echo pulse sequence acquired 124 1.5-mm-thick contiguous coronal images. Parameters used for this study included: echo time = 5 milliseconds, repetition time = 25 milliseconds, acquisition matrix = 256 x 256 pixels, field of view = 24 cm, and flip angle = 40°. Experienced and trained reliable operators, blinded to the participants' study group and any identifying information, measured white matter volume in the coronal plane using a manual tracing technique in the MEDx program. All MRIs were reviewed by a board certified pediatric neuroradiologist to exclude magnetic field inhomogeneities and any clinical abnormalities.

2.3. DNA isolation, polymorphism detection, and genotyping.

Venous blood was drawn from the subjects in two 10cc EDTA tubes, and a high salt method was used to extract DNA from blood lymphocytes (Lahiri and Nurnberger, 1991). For the C1334T (rs2252711) and C10991T (rs2071653) markers, their polymorphic sites were

amplified as previously described by Zai et al. (2005) with ABI7000 Assay-By-Design (Applied Biosystems, Foster City, CA). Genotypes were assessed by the TaqMan allele specific assay method using the ABI Prism® 7000 Sequence Detection System according to the manufacturer's protocols (Applied Biosystems, Foster City, CA). All genotypes were determined with the allelic discrimination program using the ABI software and were confirmed by two experienced researchers.

2.4. Statistical analysis.

We chose ANCOVA to analyze white matter volume, with age, gender, and total intracranial volume as covariates, using the Statistical Package for Social Sciences (SPSS, version 15.0). As in our previous study (Arnold et al., 2009), we also analyzed our data separately with only age as a covariate in addition to using age and intracranial volume as covariates for ANCOVA. Levene's test of equality of error variances was performed for independent variables between genotype groups. All of the statistical analyses in this study were based on $P<0.025$ as significant after Bonferroni correction for testing 2 variants.

Given the small sample size and relatively low minor allele frequencies of the candidate polymorphisms examined, the homozygote groups fell below 10% of the sample. We combined the low frequency homozygote group with the heterozygote group in a dominant model, for example, 1/1 versus 1/2 or 2/2. This approach has previously been adopted and utilized by Arnold et al. (2009).

3. Results:

The results are presented in Table 1. We detected a significant relationship between genotype C/C of MOG(C10991T) and decreased total white matter volume ($F=6.551$, $P=0.016$) with age, sex, and intracranial volume as covariates. We did not observe significant finding for the MOG(C1334T). We did not detect age or sex effects in our exploratory analysis.

4. Discussion:

In this study, we investigated the possibility of a significant relationship between the genotypes of the C1334T and C10991T polymorphisms across the MOG gene and MRI white matter volume in pediatric OCD. We found a significant association between total white matter volume and the C10991T marker. The relationship we identified between a MOG genetic variant and white matter volume in pediatric OCD is consistent with our earlier finding of significant association between MOG genetic variation and OCD in adults based on a family-based association study (Zai et al., 2004). Taken together, these findings support a potential role of MOG for disruption in myelination in the etiopathophysiology of OCD. Our result is supported by another previous significant finding of a variant in MOG, predicting white matter volumes ($P<0.01$; Atmaca et al., 2010).

One of the limitations of this study is the relatively small sample size and therefore, there was not enough statistical power to examine regional white matter volume, which would be of significant interest in understanding the mechanisms of OCD. Previous morphology and diffusion-imaging studies have reported that structural changes in white matter have been

implicated in the pathophysiology of OCD; however, different methodological approaches and heterogeneity of the patient samples in addition to small sample sizes have resulted in inconsistency of results across studies. Thus, the significant findings reported among many regions of interest are still preliminary. For example, diffusion tensor imaging (DTI) studies comparing white matter of patients with OCD to healthy volunteers have reported lower FA in the left lingual (medial occiptotemporal) gyrus, right midbrain, right precuneus (Tao et al., 2016), corpus callosum, left anterior corona radiate, left superior corona radiate, left superior longitudinal fasciculus (Gan et al., 2017), forceps minor, interhemispheric fibers of the frontal cortex, and right uncinate fasciculus (He et al., 2018), in addition to bilaterally in the anterior cingulate gyrus (Szeszko et al., 2005), the rostrum (Szeszko et al., 2008) and genu and body (Zhou et al., 2018) of the corpus callosum, as well as the cingulum bundle (Saito et al., 2008). FA is reflective of the integrity of myelination and axonal function, with lower values reflecting disturbance in the unidirectional diffusion expected in normal axonal bundles. Cannistraro et al. (2007) reported greater left than right FA in the cingulum bundle and anterior limb of the internal capsule regions. Menzies et al. (2008) reported significantly reduced FA in a large region of right inferior parietal white matter and increased FA in the right medial frontal region in patients with OCD in addition to abnormal FA findings in their relatives. Another limitation of this study is the lack of control group since this study only investigated pediatric patients with OCD. Additionally, there are limited studies examining the role of MOG in the pathophysiology of OCD and therefore, further examination of the role of MOG and/or genetic variations in linkage disequilibrium of MOG(C10991T) in the etiology of OCD.

For future directions, genes encoding for other myelin-related proteins such as myelin-association glycoprotein (MAG) and myelin basic protein (MBP), and the enzyme cyclic nucleotide phosphodiesterase (CNPase), may also be of interest in order to expand the hypothesis of demyelination in OCD. In addition, future studies with sufficient sample sizes will hopefully be able to perform genome-wide analyses of white matter, given that many genes other than MOG are likely to influence white matter volume.

Since significant association of a MOG gene variant was observed with white matter volume in pediatric OCD, future studies combining imaging and genetics should replicate this result using larger samples in addition to investigating sub-regional white matter volume. We suggest further study of the function of MOG in the context of other known demyelinating disorders as well as identifying any additional functional polymorphisms within *MOG* and other myelination genes, or at remote regulatory sites. Ideally future studies should be conducted utilizing DTI in order to more accurately evaluate phenotypic expression and potential white matter dysfunction related to this putative susceptibility gene.

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Dr. Kennedy is a member of the Scientific Advisory Board of Myriad Neuroscience (unpaid) and holds several patents relating to pharmacogenetics tests for psychiatric medications. Dr. Richter has previously received speaker's honoraria from Lundbeck and Brainsway.

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Highlights:

- MOG(C10991T) C/C genotype is associated with a decrease in white matter volume.
- A trend was observed between genotype of MOG(C1334T) and total white matter volume.
- These results provide support of white matter alteration in the etiology of OCD.

Table 1.

Genetic association – ANCOVA results – between white matter volumes and MOG gene variants.

White Matter Volume	Gene	Polymorphism	Genotype	*N*	Mean Volume in cm^3 (SD)	*F* score	*P* value	*F* score	*P* value	*F* score	*P* value
						Controlled for age		Controlled for age & total ICV		Controlled for age, gender, & total ICV	
Total	MOG	C10991T	T/T or T/C	10	452.358 (43.241)	3.356	0.077	6.456	**0.017**	6.551	**0.016**
			C/C	23	412.667 (57.340)						
	MOG	C1334T	C/C	23	436.389 (54.116)	2.322	0.138	3.144	0.087	3.073	0.091
			C/T or T/T	10	397.797 (53.053)						