HHS Public Access

Author manuscript

Psychiatr Genet. Author manuscript; available in PMC 2024 August 01.

Published in final edited form as:

Psychiatr Genet. 2023 August 01; 33(4): 160–163. doi:10.1097/YPG.0000000000000343.

White Matter Volume and Myelin Oligodendrocyte Glycoprotein (MOG) Microsatellites in Pediatric Obsessive-Compulsive Disorder

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Abstract

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[6]Contributions:

Dr. G. Zai performed the statistical analyses for this study in addition to drafting and finalizing the manuscript. Dr. C. Zai contributed to the design and execution of the statistical analyses. Drs. Arnold, Richter, Hanna, Rosenberg, and Kennedy conceptualized the design of the study in addition to providing mentorship to Dr. G. 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.

Submission to: Psychiatric Genetics as a brief report

[7]Conflict of Interest:

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. The other authors have no conflict of interest to declare.

The myelin oligodendrocyte glycoprotein (*MOG*) gene plays an important role in myelination and has been implicated in the genetics of white matter changes in obsessive-compulsive disorder (OCD). We examined the association between variations of two microsatellite markers across *MOG* for association and total white matter volume as measured using volumetric magnetic resonance imaging in 37 pediatric OCD patients 7 to 18 years. We compared white matter volumes between microsatellite allele groups using ANCOVA with covariates of age, gender, and total intracranial volume. After controlling for multiple comparisons, a significant relationship was detected between *MOG* (TAAA)n and increased total white matter volume (P=0.018–0.028). Although preliminary, our findings provide further support for the involvement of *MOG* in OCD.

Keywords

Pediatric obsessive-compulsive disorder (OCD); myelin oligodendrocyte glycoprotein (*MOG*) gene; white matter volume

1. Introduction:

Obsessive-compulsive disorder (OCD) is a common and often debilitating psychiatric disorder with a prevalence of 2–3% in the general population (Ruscio et al., 2010; Sasson et al., 1997) and strong genetic component (Hettema et al., 2001; Nicolini et al., 2009).

Consistent findings have supported an alteration in cortico-striatal-thalamo-cortical (CSTC) circuitry in OCD (Kwon et al., 2009; MacMaster, 2010; Saxena and Rauch, 2000). Previously published neuroimaging studies from our group and others have also reported alterations in white matter in OCD when compared with healthy controls (Breiter et al., 1994; Jenike et al., 1996; MacMaster et al., 1999; Rosenberg et al., 1997). Two additional meta-analyses of neuroimaging in OCD using multimodal voxel-based methodology by Radua et al. (2014) reported white matter abnormalities in OCD patients compared to health controls (Eng et al., 2015). Thus, impairment in the development or maintenance of myelination may play a role in the etiology of OCD in addition to providing a rationale for altered white matter as an endophenotype of OCD. Our group previously reported preliminary genetic results implicating a myelination gene, 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). More recently, we also detected a significant relationship between genotype C/C of *MOG*(C10991T) and decreased total white matter volume (P=0.016; Zai et al., 2021). Therefore, given our previous findings of genetic association of *MOG* (TAAA)n and OCD, we examined genetic variations of two microsatellite markers, (TAAA)n and (CA)n, in *MOG*. We performed microsatellite genotyping of these two polymorphisms in a sample of 37 pediatric 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*

variants and total white matter volume and hypothesized that one of the microsatellite alleles is associated with a reduced white matter volume in our sample.

2. Methods:

Methodology regarding recruitment, demographic details, imaging protocol, genotyping, and statistical analyses have been previously described elsewhere (Barr et al., 2001; Zai et al., 2004; Zai et al., 2021). Thirty-seven pediatric subjects with OCD and an age range of 7–18 years were recruited for this study at the Wayne State University pediatric anxiety disorders clinic. Written informed consent was obtained from all parents, and all participants provided written assent prior to the study being conducted. Local ethics approval has been obtained from participating sites. In brief, all volumetric 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) according to the protocol previously described (Zai et al., 2021). 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 × 256 pixels, field of view = 24 cm, and flip angle = 40°.
The (CA)n polymorphism was genotyped according to procedures described in Barr et al. (2001). In brief, the (CA)n polymorphism was genotyped using the primers *MOG* 2 forward (5'-GAAATGTGAGAATAAAGGAGA) labeled with the fluorescent dye HEX and *MOG* 2 reverse (5'-GATAAAGGGGAACTACTACA). The PCR reaction was performed in a total volume of 20 μl containing 20 ng of genomic DNA, 0.026 μg of each primer, 6.7 μl of H_2O, and 10 μl of 2X HS-Red Taq polymerase mix (Wisent Inc.). The PCR reaction included an initial denaturing step at 95°C for 2 minutes, followed by 37 cycles at 95°C for 15 seconds, 55°C for 15 seconds, and 72°C for 15 seconds.

Amplification of the region containing the (TAAA)n was achieved using a reaction mixture of 20 ng/ul of genomic DNA, 0.026 μg of each of the 6-FAM labeled primers *MOG*-(TAAA)n(F): 50-AGA TAC GAG TTT TGG CCG G-30 and MOG-(TAAA)n(R): 50-GCC TCT GGG GTA ATG AGG CT-30, 6.7 μl of H_2O,and 10 μl of 2X HS-Red Taq polymerase mix (Wisent Inc.). Amplification of the fragments by PCR was done as follows: an initial denaturation stage at 95°C for 2 minutes followed by 34 cycles of denaturing at 95°C for 15 seconds, annealing at 61°C for 15 seconds, and extension at 72°C for 15 seconds.

For each sample, 1 μl of the PCR product, 12 μl of Hi-Di formamide (Thermofisher Scientific), and 0.5 μl of GeneScan ROX 500 (Thermofisher Scientific) size standard per reaction was denatured at 95°C for 5 minutes and then, 1 μl of this reaction was genotyped using the ABI 3500 Genetic Analyzer (Applied Biosystems). Results were analyzed using the ABI Genemapper software (Applied Biosystems). In brief, for statistical analyses, we performed ANCOVA to analyze white matter volume, with age, gender, and total intracranial volume as covariates, using the Statistical Package for Social Sciences (SPSS, version 22.0). All of the statistical analyses in this study were based on $P<0.025$ as significant after Bonferroni correction for testing two genetic variants. Given the small sample size, we combined the low frequency microsatellite group based on size of repeat.

3. Results:

In this study, we investigated the possibility of an association between the genotypes of the (CA)n and (TAAA)n microsatellite polymorphisms across *MOG* and MRI white matter volume in pediatric OCD. Table 1 presented our results. We detected a significant relationship between the microsatellite repeat greater than 450 or the presence of only the microsatellite repeat 450 of *MOG*-(TAAA)n and an increased total white matter volume (P=0.018–0.028) with age, sex, and intracranial volume as covariates. We did not observe significant finding for the *MOG*-(CA)n. We also did not detect age or sex effects in our exploratory analysis.

4. Discussion/Conclusion:

These preliminary findings further support a potential role of *MOG*'s involvement in white matter disruption in the pathogenesis of OCD. Two previous significant findings of variants across *MOG*, predicting white matter volumes (P<0.01 [Atmaca et al., 2010]; P=0.016 [Zai et al., 2021]) have implicated this gene and white matter alterations in OCD. The main limitation of this study is the relatively small sample size, which did not provide us with enough statistical power to examine regional white matter volume, and limited our ability to investigate the effects of all individual repeat sizes. Future directions should include the investigation of additional myelin-related genes, which may be of interest to further explore the hypothesis of demyelination and white matter alterations in OCD.

Acknowledgements:

Dr. G. Zai was previously in the Clinician-Scientist Program of her psychiatry residency training program and the Clinician Investigator Program at the Faculty of Medicine, University of Toronto while working on this research project. This work was supported by research grants from the National Institute of Mental Health (R01MH59299; K24MH02037; Miriam L. Hamburger Endowed Chair of Child Psychiatry, Paul and Anita Strauss Endowment, Elliott Luby Endowed Professorship and Lycaki-Young Fund, State of Michigan) (DRR), Canadian Institutes of Health Research (CIHR: MOP-38077) (JLK, MAR), the Ontario Mental Health Foundation (MAR, JLK), the National Institutes of Health (NIH: RO1-MH085300) (PDA), and the Alberta Innovates Translational Health Chair in Child and Youth Mental Health.

We would like to thank the research participants, clinical and research staff at Wayne State University and the Neurogenetics Laboratory (Centre for Addiction and Mental Health) and the Hospital for Sick Children for their valuable time, help, and support.

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Table 1.

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

White Matter Volume	Gene	Polymorphism	Allele	*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	(CA)n	118 Yes	14	422.44 (44.77)	0.788	0.383	0.017	0.898	0.015	0.904
			118 No	16	426.02 (57.41)						
			125–135 Yes	24	420.56 (53.44)	0.737	0.398	0.006	0.940	0.006	0.939
			125–135 No	6	439.50 (40.43)						
			140–144 Yes	10	434.46 (46.13)	1.677	0.206	0.302	0.587	0.289	0.595
			140–144 No	20	419.29 (53.76)						
	MOG	(TAAA)n	458 Yes	9	452.29 (55.71)	4.490	**0.044**	2.343	0.139	2.166	0.155
			458 No	19	413.70 (47.27)						
			<450 Yes	12	395.38 (46.18)	9.660	**0.005**	6.641	**0.017**	6.553	**0.018**
			<450 No	16	449.15 (45.35)						
			450 Yes	16	444.65 (43.37)	9.311	**0.005**	5.681	**0.025**	5.532	**0.028**
			450 No	12	401.38 (54.85)						

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