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Risk Variant of Oligodendrocyte Lineage Transcription Factor 2 Is Associated With Reduced White Matter Integrity

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Abstract: The *oligodendrocyte lineage transcription factor 2* (OLIG2) regulates the genesis of oligodendrocytes, the brain cells responsible for axonal myelination. Although it has been associated with psychiatric and neurological disorders, the impact of this gene on white matter integrity has never been investigated in humans. Using diffusion tensor imaging, we examined the effect of a single nucleotide polymorphism (rs1059004) in OLIG2 previously associated with reduced gene expression, and with psychiatric disorders on fractional anisotropy in 78 healthy subjects. We found that the risk allele (A) was associated with reduced white matter integrity in the corona radiata bilaterally. This is consistent with evidence that it is a schizophrenia susceptibility gene, and suggests that it may confer increased risk through an effect on neuroanatomical connectivity. *Hum Brain Mapp 34:2025–2031, 2013.* © 2012 Wiley Periodicals, Inc.

Key words: fractional anisotropy; diffusion tensor imaging; genetics; schizophrenia; myelin

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INTRODUCTION

Oligodendrocyte lineage transcription factor 2 (*Olig2*) is a transcription factor regulating neuronal cell specification and the genesis of motor neurons and oligodendrocytes [Ono et al., 2009]. It is widely expressed throughout the central nervous system during development and throughout adulthood, as well as during glial scar formation after injury [Ono et al., 2009]. Oligodendrocytes are responsible for the myelination and integrity of brain axons [Ono et al., 2009]. As a fatty acid, myelin provides electric insulation around axonal fibers allowing for fast neuronal signal transmission [Bjartmar et al., 1999]. Myelin development is correlated with the level of general intelligence, reading ability and visual spatial information processing [Whitaker et al., 2008].The degree of myelination around neuronal axons can substantially modulate the anisotropy of water diffusing through them, and a measure of this, the fractional anisotropy (FA), is usually taken as a proxy for the integrity of the axonal fibres [Beaulieu, 2002]. Accordingly, increases in FA, have been shown to parallel the development of higher cognitive functions and have been associated with better performance on a wide range of tasks including reading ability, working memory capacity, reaction time, bimanual coordination and memory retrieval [Ullen, 2009]. Abnormal myelination contributes to synaptic destabilization and impaired anatomical and functional neural connectivity [Bjartmar et al., 1999].

Schizophrenia is thought to involve a disruption of cerebral connectivity, as evidenced by neuroimaging findings of functional dysconnectivity, reductions in the integrity and volume of white matter, and neuropsychological impairments and symptoms that may arise through impaired integration of cognitive processes [Davis et al., 2003]. Tractography studies, which refine the location of white matter abnormalities, have identified reduced integrity in most major tracts [Kanaan et al., 2009]. The neural basis of this putative dysconnectivity is unclear. An effect on axonal myelination may underlie dysconnectivity in schizophrenia, perhaps through loss and/or altered spatial distribution of oligodendrocytes [Davis et al., 2003]. Independent of its potential influence on myelination, OLIG2 is a prime candidate for hosting susceptibility variants for schizophrenia because it maps to 21q22.11, a region deleted in some individuals with schizophrenia [Georgieva et al., 2006]; conversely, individuals with trisomy 21 may have a reduced incidence of psychotic illness [Georgieva et al., 2006]. Indeed, genes involved in myelination and oligodendrocyte function have shown altered expression in patients with schizophrenia [Georgieva et al., 2006] and OLIG2 expression, in particular, is reduced in the disorder [Georgieva et al., 2006; Mitkus et al., 2008]. This is consistent with the strong evidence for a genetic component in schizophrenia [Georgieva et al., 2006]. Lower frontal FA has also been reported in nonaffected relatives and monozygotic cotwins of patients with schizophrenia [Camchong et al., 2009], indicating it may be a heritable trait.

Assessing the role of Olig2 on myelination may thus yield valuable insights into the etiology of a range of central nervous system disorders. To date there has been no examination of the impact of genetic variation in OLIG2 on the white matter in humans. The A allele of one of the single nucleotide polymorphisms (SNPs) in the OLIG2 gene, rs1059004, has been found to predict lower postmortem mRNA levels in the dorsolateral prefrontal cortex [Mitkus et al., 2008]. The same allele is significantly associated with schizophrenia in Caucasian [Georgieva et al., 2006] [but not Japanese (Usui et al., 2006)] populations, and with obsessive-compulsive disorder in Caucasians [Stewart et al., 2007]. As this SNP is located in the 3′UTR intronic region, it may either be in strong linkage with unknown functional variants, or may alter expression by affecting, for example, mRNA structure/stability [Georgieva et al., 2006]. Other variations in OLIG2 have also been associated with psychosis in patients with Alzheimer's disease [Sims et al., 2009].

We used diffusion tensor imaging (DTI) on a 1.5T MRI scanner to examine the influence of the OLIG2 polymorphism rs1059004 on white matter integrity. FA and mean diffusivity (MD) were measured in the whole brain of 78 Caucasian healthy individuals (15 C-homozygotes, 44 heterozygotes, and 19 A-homozygotes), with the data analyzed using a voxel-based approach. We predicted that the risk allele (allele A) would be associated with reduced FA in the major fasciculi of the white matter.

MATERIALS AND METHODS

Subjects

All 78 healthy volunteers gave written informed consent in accordance with protocols approved by the Local or Multicentre Research Ethics Committee (L/MREC); had no history of mental illness and no first degree relatives with a psychotic disorder, as assessed using the Family Interview for Genetic Studies [FIGS (Maxwell, 1992)]. Subjects who met DSM-IV criteria for a substance misuse disorder were excluded.

All subjects were genotyped for the OLIG2 SNP rs1059004 which yielded 15 CC, 44 CA, and 19 AA subjects (below). All subjects were Caucasian, with no significant differences ($P < 0.05$) between genotype groups in age, gender, handedness, IQ, and years in education at the time of scanning (Table I).

Genetics

DNA was extracted from blood or cheek swabs using standard methodology [Freeman et al., 2003]. Samples were genotyped as previously described [Georgieva et al., 2006] blind to the diagnostic characteristics of the sample. Genotype frequencies did not deviate from Hardy-Weinberg equilibrium ($\chi^2 = 1.34$; $P = 0.24$].

TABLE I. Demographic features of the sample, subdivided according to the OLIG2 genotype

OLIG2 rs1059004 Genotype	CC	CA	AA
N	15	44	19
Age (mean (sd), range)	34.3 (14.6), 18–63	33.5 (11.5), 17–62	32.4 (11.5), 19–57
Years of education [mean (sd)]	15.8 (3.1)	15.1 (3.1)	14.7 (2.6)
IQ [*z*-scores (sd)]	−0.80 (1.04)	−0.15 (1.09)	−0.37 (1.20)
Handedness (right/left/mixed)	13/1/1	40/1/3	18/1/0
Gender (male/female)	8/7	25/19	13/6

IQ was assessed using the WASI-FSIQ-4 (Wechsler Abbreviated Scale of Intelligence – Full Scale IQ) [Wechsler D, 1999] or the NART [National Adult Reading Test (Nelson, 1982)]. The proportion of subjects assessed with each tool was matched between OLIG2 genotype groups and ANOVA was performed with standardized scores (*z*-scores) based on the mean and standard deviation of the control group for each tool.

Data Acquisition

Data were acquired using a 1.5T GE Signa LX system (General Electric, Milwaukee, WI), with actively shielded magnetic field gradients (maximum amplitude 40 mT m^{-1}). A standard quadrature birdcage head coil was used for both radio-frequency transmission and nuclear magnetic resonance signal reception. Localizer scans were used to allow DTI data to be axially aligned to the anterior commissure–posterior commissure line. Diffusion weighted and reference volumes were acquired with a multislice, peripherally gated echo-planar imaging sequence, optimized for precise measurement of the diffusion tensor in the parenchyma of healthy volunteers, over 60 contiguous 2.5-mm-thick near-axial slice locations. Data were acquired with a 96 × 96 matrix over a 24-cm field of view, yielding isotropic (2.5 × 2.5 × 2.5 mm^3) voxels, and during reconstruction the data were zero-filled to 128 × 128, giving an apparent in-plane voxel size of 1.875 × 1.875 mm^2. The echo time was 107 ms; repetition time was 15 R–R intervals. The duration of the diffusion encoding gradients (δ) was 17.3 ms, giving a maximum diffusion weighting of 1,300 s mm^{-2}. Seven images without diffusion gradients and 64 diffusion-weighted images with gradient directions uniformly distributed in space were acquired at each slice location. Full details are given elsewhere [Jones et al., 2002].

Image Processing

The diffusion-weighted images were first corrected for eddy-current distortion using a mutual information-based registration scheme [Studholme et al., 1997], as previously described [Catani et al., 2002], and then masked, using locally written software plus the Brain Extraction Tool in the Functional Software Library package (Oxford Centre for Functional Magnetic Resonance Imaging of the Brain, Oxford University, Oxford, UK) [Jones et al., 2002]. The diffusion tensor was then calculated at each voxel using multivariate linear regression after logarithmic transformation of the signal intensities [Basser et al., 1994], and the FA and MD calculated at each voxel. Normalization used a two-stage process. First, a study-specific template was created and the FA and MD images were then registered to it as follows: the mean $b = 0$ (nondiffusion-weighted) image from every participant was registered using SPM2 (Wellcome Department of Imaging Neuroscience, London, UK) to the SPM2 echo-planar imaging template. The mapping parameters derived for each participant were then applied to that person's (inherently coregistered) FA and MD images. These normalized images were themselves averaged and smoothed with an 8 mm FWHM (full width at half maximum) Gaussian kernel to create a study-specific template. The second stage involved a new registration, as the original FA and MD images were then registered to this template, again using SPM2. The registered images were also segmented, using the default tissue probability information ("priors") in SPM2, and these probabilistic maps were thresholded at 10% probability to generate a liberal white/rest-of-brain mask. Finally, the FA and MD images were smoothed with a 5-mm FWHM kernel, before applying the white matter mask to create white-matter-only FA and MD maps. Note that the smoothing was not done to comply with the statistical requirements of parametric analysis, since the analysis was performed with nonparametric methods, but to increase signal-to-noise ratio and minimize the effects of residual anatomical differences between subjects—although this also served to sensitize the analysis to structures with spatial extents of this size [Jones et al., 2005].

Statistical Analysis

The principal analysis was a voxel-based (i.e., tested our null hypothesis independently at a large number of spatial locations), and utilized an analysis of variance (ANOVA) approach, modeling the white matter FA with genotype AA, AC, or CC) as the independent factor. This was carried out using XBAM version 4 (Institute of Psychiatry, London, UK), which employs a permutation rather than normal theory based inference [Bullmore et al., 1999]. An ANOVA, using medians instead of means, was fitted to each voxel of the normalized, segmented FA maps using diagnostic and genotype status as grouping variables. To

avoid regions where (due to differences in the white matter boundary between subjects) the masking procedure would lead to a large number of voxels with zero values, the ANOVA was only fitted at voxels where at least half the participants contributed data. By allowing less than full representation but also weighting the data, we permit voxels that have incomplete occupancy to be analyzed but reduce their weight. After fitting the ANOVA model to the real observed data, the participant labels were randomly permuted between groups to achieve the null hypothesis of no effect of group membership on FA. A similar method was employed when calculating the main effect of genotype and the overall interaction, using in each case a relevant permutation strategy. This permutation was carried out 1,000 times at each voxel to allow the construction of a separate null distribution of FA differences for each voxel. Such an approach is particularly important for DTI data because in areas close to tissue boundaries, any normalization error will produce a strongly bimodal distribution of FA. The analysis was extended from the voxel to the cluster level, as that potentially increases sensitivity, and the underlying statistical thresholds can be chosen so as to give precise control over the false positive rate [Rabe-Hesketh et al., 1997]. After determination of voxels showing significant effects at a threshold of $P < 0.05$, sets of spatially contiguous suprathreshold voxels were identified, and the sum of the suprathreshold voxel-wise test statistics (or "mass") of each three-dimensional cluster was calculated. The mass of each cluster was then tested against the masses of clusters present in the permutation distribution, an approach for which there is no parametric equivalent owing to the lack of appropriate theoretical distributions [Poline et al., 1997]. Cluster-wise significance thresholds were chosen so as to expect less than one false positive cluster over the whole brain. The identification of clusters with white matter tracts and their anatomical context were made by reference to Mori et al [2005]. All images are shown in radiological convention in which the left side of the image is the right side of the brain; coordinates are in MNI space. To characterize the monotonicity of the effects of genotypein the areas they were found, we extracted the mean FA of each identified cluster for each participant from XBAM to build boxplots and perform a post hoc nonparametric monotonic trend test, the Jonckheere-Terpstra test, in SPSS (version 15.0 for Windows). We chose a monotonicity test in order to encompass in our search both a codominant and a dominant/recessive allelic effect. Genotypes were inserted here in the CC<CA<AA order and two-tailed significance was used ($P < 0.05$). We tested for a genotype-wise effect on MD, using the same statistical methodology as for FA, as a complementary analysis.

RESULTS

We found that the OLIG2 rs1059004 allele A was associated with lower FA in two regions of white matter, in the right and left superior and posterior corona radiata (MNI coordinates of peak effect: 28 −20 30; cluster size $k = 351$, $P = 0.002$; and −28 −36 38; $k = 336$ and $P = 0.002$, respectively; $P < 0.007$ was the cluster-wise threshold of less than one false positive cluster expected by chance, Fig. 1). In both homologous regions the effect was in a significant allele-load fashion, i.e., the FA in heterozygotes was intermediate relative to that in the homozygote groups: median FA(CC) > FA(CA) > FA(AA) (Jonckheere-Terpstra monotonicity test, R cluster: $P = 0.001$; L cluster: $P = 0.001$). In these regions, there was a reduction in FA of 8.75% and a 6.37% respectively in subjects with two copies of the A allele compared to those with none. There were no areas where the reverse effect was found (higher FA in the AA group compared with the other groups).

The MD analysis revealed significant effects in the left corpus callosum/anterior region of the corona radiata and in the left inferior longitudinal fasciculus/posterior region of the corona radiate (MNI coordinates of peak effect: −40, −32, −4; cluster size $k = 207$, $P = 0.009$; and −14 38 4; $k = 193$, and $P = 0.008$, respectively; $P < 0.01$ was the cluster-wise threshold of less than one false positive cluster expected by chance). However, inspection of the boxplots revealed no clear direction of effect (Jonckheere-Terpstra monotonicity test was nonsignificant, $P > 0.5$ for both clusters) (Supporting Information Fig. 2).

To ascertain that there were no gross structural differences between the three genotype groups, we visually inspected the mean normalized FA maps of each group and detected no visible variability (Supporting Information Fig. 1 shows this for three key slices corresponding to the 3rd column of Fig. 1). There was also no significant ($P < 0.05$) difference in total white matter volume between genotype groups ($F = 0.32$, $P < 0.73$).

DISCUSSION

The present association of the risk allele for OLIG2 rs1059004 (A) with lower regional white matter integrity is consistent with our prior hypothesis given that this allele also predicts lower mRNA levels in the dorsolateral prefrontal cortex [Mitkus et al., 2008] and an increased risk for schizophrenia [Georgieva et al., 2006] and obsessive-compulsive disorder [Stewart et al., 2007].The findings also consistent with previous evidence that schizophrenia is associated with reduced FA in the major white matter fasciculi [Kanaan et al., 2005] and that it involves a perturbation of brain connectivity [Liu et al., 2008], which suggests that this may be related to changes in axonal myelination. In addition, previous studies have independently shown that other psychosis-risk alleles, such as that for NRG1, are associated with reductions in white matter integrity in the internal capsule, which contains the continuation of the axons in the corona radiata as they descend between the caudate and lentiform nuclei and the thalamus [McIntosh et al., 2007]. Like OLIG2, NRG1 is involved in

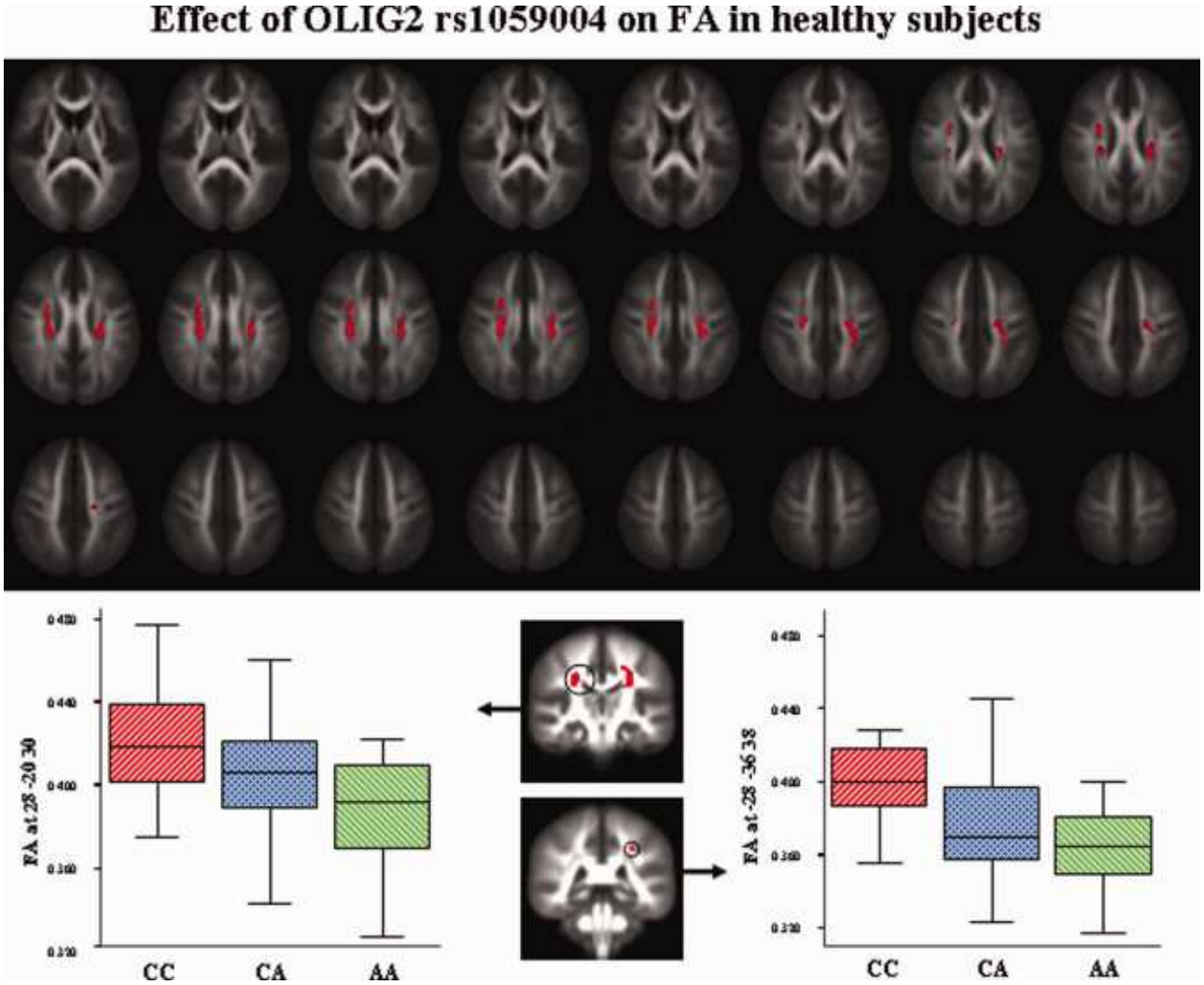

Figure 1.

A decrease of fractional anisotropy (FA, a proxy for white matter integrity) was associated with the A allele of OLIG2 rs1059004 in an allele-load fashion: FA(AA) < FA(AC) < FA(CC). Having two A alleles showed a FA decrease in 8.75% in the right and 6.37% in the left superior and posterior corona radiata, compared with having none. Median FA in the right cluster was 0.36 for AA, 0.37 for AC and 0.40 for CC and median FA in the left cluster was 0.39 for AA, 0.41 for AC and 0.42 for CC. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

myelination besides neuronal migration, axon guidance [McIntosh et al., 2007].

White matter integrity may influence cognitive performance by affecting the temporal coordination of neuronal activity [Ullen, 2009]. Such a mechanism is supported by reports of positive correlations between regional FA and performance on a wide range of cognitive tasks. The corona radiata is one of the tracts in the brain where myelin is most profuse [Counsell et al., 2002]. The corona radiata continues to develop throughout childhood until young adulthood, and its structural maturation is essential for the successful development of cognitive, motor, and sensory functions [Snook et al., 2005]. It provides various important connections between the frontal, parietal, temporal, and occipital lobes [Wakana et al., 2004], as well as reciprocal connections between cortex and thalamus, and descending projections to the midbrain and spinal cord [Mori et al., 2005]. The thalamic radiation is an important target of dopamine modulation and is involved in the processing of disparate sensory modalities, in motor behavior and, importantly, in planning, and abstract cognition [Rodriguez et al., 2004]. It consists of glutamatergic pathways projecting from the thalamus to the cortex and vice-versa, and thus is part of the cortico-thalamic-striato-cortical loop connecting the striatum to the cortex via the thalamus. It is thought that abnormalities in this pathway

affect prefrontal function, such as working memory, impairment of which is a major pathophysiological feature of schizophrenia [Grace, 2000]. Consistent with this, FA in the anterior corona radiata and working [Olesen et al., 2003] and visual [Bendlin et al., 2009] memory capacity have been positively associated and reduced FA in the corona radiata has been found in schizophrenia [Kanaan et al., 2009]. In addition, the projections to the brainstem and the spinal cord also pass through the internal capsule [Mori et al., 2005], which has been shown to have lower white matter integrity in schizophrenia [Mitelman et al., 2007]. Abnormal myelination in these tracts in schizophrenia is consistent with delayed motor development, and impaired motor skills [Walker et al., 1994] and coordination [Schiffman et al., 2009], in people who develop schizophrenia [Walker et al., 1994]. In addition to its role in oligodendrocyte genesis, Olig2 also regulates the generation of motor neurons [Ono et al., 2009].As cortical motor neurons' axons comprise a major part of the corona radiata, and since our differences included the pyramidal system, the effect of OLIG2 genetic variation we observed could also partly relate to OLIG2's effect on the genesis of motor neurons. The regional differences of our results are also consistent with OLIG2 impacting on the development of astrocytes, which promote the myelinating activity of oligodendrocytes, in a region-specific manner [Ono et al., 2008].

In respect to MD, inspection of the boxplots (Supporting Information Fig. 2) show greatly overlapping variance between genotype groups and no discernible difference in mean MD. This suggests that the genotype-wise effect we found was highly heterogeneous throughout the cluster (subregions within the clusters showing different effects, e.g., AA $<$ AC $=$ CC or AA $<$ AC $>$ CC, etc) and thus no simple genotype-dependent effect could be inferred. The absence of a colocation and consistent difference in MD and FA could be taken as evidence that the FA differences are to do with disorganization rather than myelination (though we cannot exclude the possibility that we have not found a clear MD difference due to lack of power). Since the corona radiate fibers are relatively simply organized, this might explain why they were singled out by our FA analysis. However, this needs to remain a tentative speculation.

Future studies are warranted that bridge the gap between known genetic susceptibility factors (namely, the recent genome-wide association findings) and complex neuronal network abnormalities in schizophrenia. A promising way forward would be the integration of genetic data (e.g., risk polymorphisms combined) and multimodal imaging (e.g., PET + fMRI + sMRI + DTI) the further our understanding of the underlying mechanisms of the observed abnormalities.

In conclusion, our data provide preliminary evidence of an effect of genetic variation of OLIG2 on the white matter integrity of the human brain plausibly by way of its effects on myelination; this effect is consistent with recent findings on OLIG2 gene expression and on schizophrenia susceptibility. This evidence adds to the understanding of the biological mechanisms underlying the illness and its clinical heterogeneity. If replicated, OLIG2 genotype together with white matter abnormalities may in the future serve as biomarkers to improve disease prevention, early detection, diagnostic specificity, and personalized therapeutics.

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