GWAS of the white matter micro-structure suggests multigenic architectures: a UKBiobank study

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Introduction:

Diffusion MRI (dMRI) tractography allows modeling of white matter fiber bundles giving clues on how brain areas are interconnected. The heritability of tract-based fractional anisotropy has been demonstrated recently [7]. In this work, we aim at identifying variants associated with brain tracts by conducting a Genome Wide Association Study on Tract-Based Spatial Statistics (TBSS) [6] of neurite orientation dispersion and density imaging (NODDI) [10] parameters: ICVF (intra-cellular volume fraction), ISOVF (isotropic volume fraction) and OD (orientation dispersion index). ICVF, ISOVF and OD maps are projected onto a white matter skeleton using the TBSS method. Then, average regional values of the parameters on the skeleton are obtained using the JHU parcellation [5].

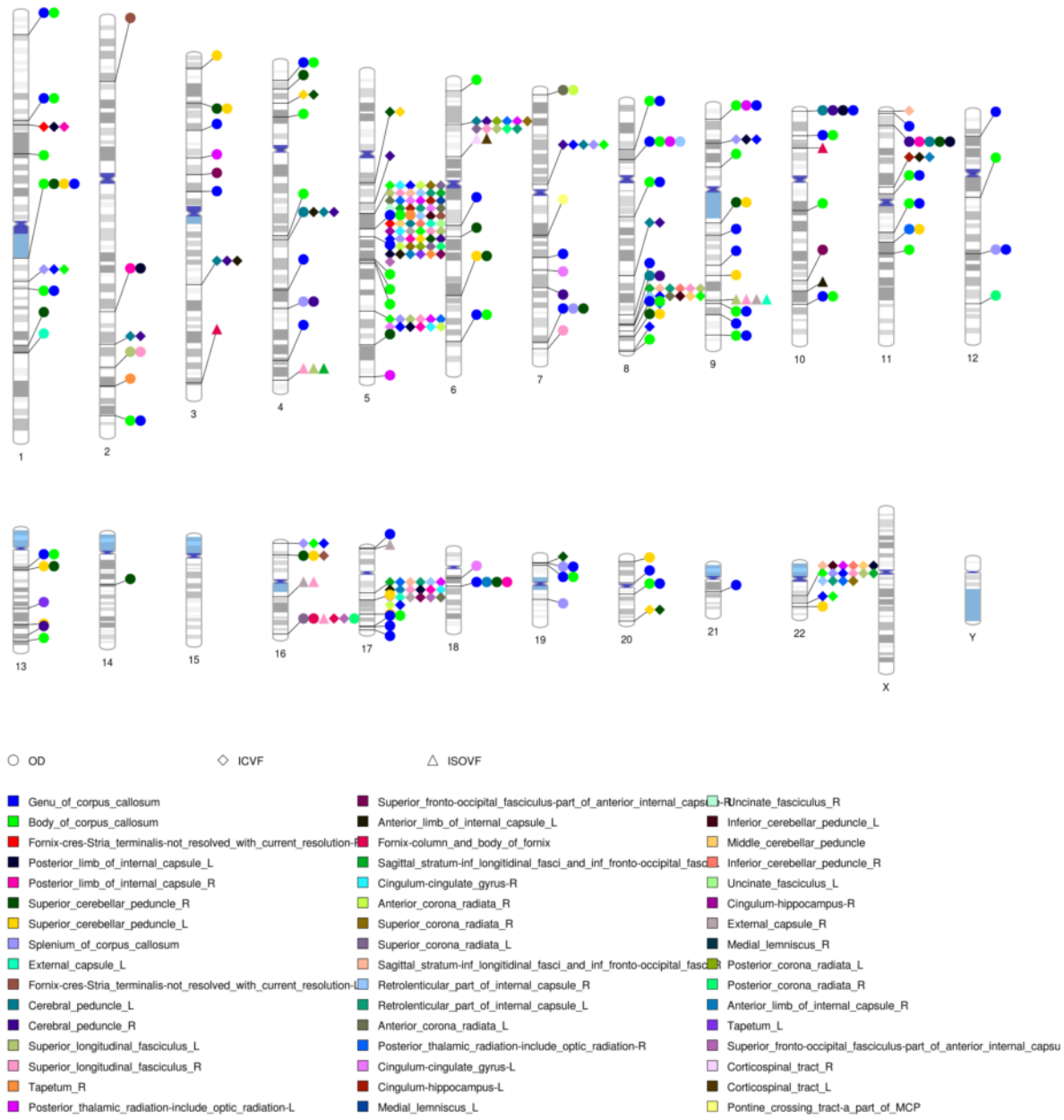
Methods:

We used the latest release of UKB imaging data [1] (October 2018, application #25251), which consists of 20,923 subjects with diffusion-weighted brain MRI and imputed genotyping data [2]. It contains 83,045,758 SNPs spanning across the 22 autosomal chromosomes. In our analysis we selected subjects identified by UKB as belonging to the main white British ancestry subset. In total, we retained 16,540 subjects with approximately 48% of males and 52% of females. From the UKB dataset, we selected the dMRI skeleton measurements generated by an image-processing pipeline developed and run by UKB. For our association study we selected the averaged values of TBSS-projected measures ICVF, ISOVF and OD across a set of 48 standard-space tract masks [5].
The genotype-phenotype association analyses were performed using PLINKv1.9, with the following thresholds: missing genotype = 10% , hwe = 10e−6, and maf = 1.0%. In total 9,376,730 variants passed the genetics QC. We included as covariates the sex, the genotyping array type and the age at the MRI session. From the association results, significant SNP hits were selected by applying a stringent

Bonferroni corrected genomic threshold to account for multiple testing (48 regional tracts * 3 measures, significant p < 1.736e-10).
The PhenoGram tool [9] was used to visualize SNP-phenotype associations on the chromosomes. To improve PhenoGram readability, SNPs in linkage disequilibrium with top SNPs (LD < 0.001) were removed and, SNPs in a region of 200k bp were summarized by the top SNP. ANNOVAR [8] was used for gene-based variant annotation and GTEx eQTL browser [9] for eQTL mapping.

Results:

Genomic loci that were significantly associated with ICVF, OD and ISOVF are illustrated in Figure 1. Table 1 summarizes the top association p-values for genomic locations that influence more than 6 white matter tracts. The variety of tracts associated to these genomic regions suggest a pleiotropic effect of the genes nearby.
In line with Elliott et al. [3], rs17205972, rs3776089, rs79220007 and rs34081316 have been found whereas rs55705857, rs9937293 and rs2267161 are new to our knowledge. These later loci were annotated in the vicinity of GAL3ST1 gene and CCDC26 lncRNA which interacts with ADAMTSL4, BANP and KRT40 proteins. These genes are known to be implicated respectively (i) in synthesis of galactosylceramide sulfate, a major lipid component of the myelin sheath and, (ii) in cellular adhesion and matrix attachment region binding.
While genetic loci associated with ICVF showed a clustered arrangement, the loci associated with OD were distributed across the genome and no large cluster of phenotypes emerged (Figure 1). The most represented tract regions were the body and genu of corpus callosum. This suggests a multigenic architecture of the OD in corpus callosum. We also noticed several associations of bilateral regions with the same loci suggesting a symmetric genetic control.



·Figure 1. Ideogram of genome-wide significant loci influencing NODDI measures OD, ICVF and ISOVF in 48 white matter tract regions.

chr	position	rsID	ref allele	non ref allele	MAF	gene annotation	locus	GTEx eQTL (V6,V7)	# phenotypes	p-value	top phenotype	measure type
5	82859065	rs17205972	G	T	0.197	intronic	VCAN		61	2.27E-051	Sagittal_stratum-inf_longitidinal_fasci_and_inf_fronto-occipital_fasci-L	ICVF
5	139727260	rs3776089	G	A	0.265	intergenic	HBEGF (dist=1072), SLC4A9 (dist=12527)	SRA1	12	1.19E-039	Genu_of_corpus_callosum	ICVF
6	26098474	rs79220007	T	C	0.073	intergenic	HFE (dist=3005), HIST1H4C (dist=5702)		11	2.33E-014	Cerebral_peduncle_L	ICVF
8	130645692	rs55705857	A	G	0.055	ncRNA intronic	CCDC26 (lncRNA)		14	1.88E-016	Sagittal_stratum-inf_longitidinal_fasci_and_inf_fronto-occipital_fasci-L	ICVF
16	87225101	rs9937293	G	A	0.389	intergenic	LINC02181 (dist=127504), LOC101928708 (dist=20620)	RP11-899L11.3	6	1.5E-016	Superior_corona_radiata_L	OD, ISOVF, ICVF
17	44338782	rs34081316	AT	A	0.19	intergenic	KANSL1 (dist=36043), LRRC37A (dist=33714)		20	1.14E-016	Superior_fronto-occipital_fasciculus-part_of_anterior_internal_capsule-R	ICVF
22	30953295	rs2267161	C	T	0.307	exonic (nonsynonymous SNV)	GAL3ST1	SEC14L6, SEC14L3, SEC14L4, TCN2, CCDC157, PES1	16	7.96E-018	Body_of_corpus_callosum	ICVF

·Table 1. Summary of most highly associated SNP-phenotype clusters (GRCh37).

Conclusions:

Our study identified new loci influencing neurite density of multiple white matter tracts indicating a pleiotropic effect. The loci influencing the orientation dispersion in corpus callosum are distributed across the genome, suggesting a multigenic architecture.

Genetics:

Genetic Association Studies [1]

Imaging Methods:

Diffusion MRI [2]

Keywords:

ADULTS
Data analysis
Statistical Methods
Tractography
Univariate
WHITE MATTER IMAGING - DTI, HARDI, DSI, ETC
Other - GWAS; dMRI ; TBSS; NODDI;

[1|2]Indicates the priority used for review