

## Voxelwise genome-wide association of Diffusion Tensor Images identifies putative novel variants influencing white matter integrity in 467 related young adults

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*Abstract:* The quest to identify genes that affect brain integrity will be greatly accelerated by diffusion tensor imaging (DTI) of large populations of subjects with genome-wide association scans (GWAS). Many studies relate genetic variants to imaging phenotypes, but few focus on white matter data and still fewer have used a voxel-by-voxel analysis to map associations in 3D. Here we present the first whole-brain voxel-wise Genome-wide Association Study (vGWAS) with DTI. We tested associations between 413,783 single nucleotide polymorphisms (SNPs) at each of 4,943 voxels from whole-brain 3D DTI scans in 467 healthy twin and sibling pairs from the Brisbane Adolescent/Young Adult Longitudinal Twins Study (BLTS) (mean±s.d., age: 23.8±2.2, 187 males). Association was tested using mixed-effects regression to account for family relatedness, assuming an additive genetic model, and controlling for age and sex. The most associated variant at each voxel was recorded and the top SNP significance map was corrected using an inverse Beta transform to control the false discovery rate (FDR) across voxels (Stein 2010). No SNPs survived the stringent correction, but many top SNPs were located in protein coding genes expressed in the brain, making them candidates to carry forward to a future hypothesis-driven study. For example, one of the most highly associated variants was in the MDGA1 gene; this codes for an anchor protein required in the radial migration of cortical neurons. Our top ten SNPs (Table 1) warrant further exploration in future neuroimaging genetic studies.

SNP Name	Base Pairs	Chromosome	Minor Allele Freq.	In Gene (±50kb)	Uncorrected P value
rs7585194	172120862	2	0.266	CYBRD1	6.91E-09
rs1934937	15809448	10	0.257	ITGA8	9.26E-09
rs10947686	37714783	6	0.203	MDGA1	1.07E-08
rs11116408	83365095	12	0.114	Intergenic	1.24E-08
rs1441263	78482459	13	0.234	Intergenic	1.38E-08
rs6915645	143882733	6	0.292	FUCA2	1.42E-08
rs2799403	130000458	10	0.200	AK124226	1.44E-08
rs9847467	102343265	3	0.308	Intergenic	1.50E-08
rs1109374	65406085	1	0.348	AK3L1	1.87E-08
rs1684583	4538559	16	0.276	C16orf5	1.95E-08