

# Multi-Site Genetic Analysis of 1151 Diffusion MRI Scans from the ENIGMA-DTI Working Group

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<http://enigma.loni.ucla.edu/ongoing/dti-working-group/>

## Background

Human brain structure is genetically influenced, and many brain imaging measures are heritable, i.e., a proportion of their variance is due to differences in the human genome. Recently, the **Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA)** Consortium created a **Diffusion Tensor Imaging (DTI)** Working Group to study genetic influences on white matter micro-architecture and integrity. To make it efficient to analyze DTI on a large scale from many cohorts, we first set out to define reliable, and heritable, measures from DTI scans of cohorts of different ages and ethnicities, scanned with various acquisition protocols. We aimed to prioritize the most promising brain measures for genetic analysis, based on their consistently high heritability in different cohorts.

## Methods

### Making the target and Standardizing Protocols

From each of four independently collected datasets, we randomly selected 100 subjects (50 male, 50 female) to create a common template (i.e., **400 subjects total**). FA images from all subjects were aligned, using FSL's 'flirt' (Jenkinson et al., 2002), to the Johns Hopkins University (JHU) DTI atlas in ICBM space (ICBM-DTI-81 white matter labels atlas) (Mori et al., 2008).

A target was created as previously described (Kochunov et al., 2001; Kochunov et al., 2002) from these aligned images.

The target was then skeletonized with FSL's TBSS (Smith et al., 2006).

The mean FA in various ROIs were extracted.

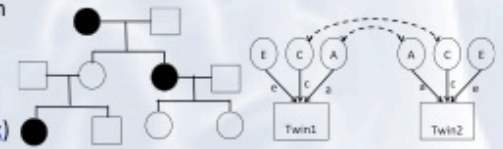


	QTIM	GOBS	BFS	UNCORIG	UMCU
Relatedness	Twins	Pedigree	Unrelated	Unrelated	Unrelated
Race/Ethnicity	Caucasian	Mexican American	Caucasian	Caucasian	Caucasian
#Subjects contributed	202	359	100	100	100
Sex	100M/102F	251M/108F	50M/50F	50M/50F	50M/50F
Age range (years)	21-29	18-85	18-20	71-74	18-45
Healthy	Yes	Yes	Yes	Yes	No
Scanner	Siemens	Siemens	GE	GE	Advent
Acquisitions	1	1	1	1	2
Field strength	4 T	3 T	1.5 T	1.5 T	1.5 T
Voxel size (mm)	1.8 x 1.8 x 2	1.7 x 1.7 x 3.0	2.5 x 2.5 x 2.5	2.0 x 2.0 x 2.0	2.5 x 2.5 x 2.5
N-gradients	64	53	64	64	52
N-f0	11	5	7	7	8
b-Value (s/mm <sup>2</sup> )	1159	700	1000	3000	1000
Reference	de Zubicaray et al. (2008)	Kochunov et al. (2011)	Sprooten et al. (2011)	Wardlaw et al. (2011)	Mandl et al. (2010)

### Calculating Heritability

Two ethnically different family-based datasets, QTIM and GOBS (the Queensland Twin Imaging and the Genetics of Brain Structure and Function Studies) with different imaging protocols were used to estimate heritability on a voxelwise and ROI level.

To calculate heritability across images, we used a variance components method, as implemented in the SOLAR software package ([http://www.nitrc.org/projects/se\\_linux](http://www.nitrc.org/projects/se_linux)) (Almasy and Blangero, 1998). Methods used to calculate heritability in SOLAR are detailed elsewhere (Kochunov et al., 2010; Winkler et al., 2010).



### Meta analysis

To obtain meta-analyzed heritability ( $h^2$ ), we used two alternative methods:

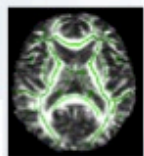
- 1) Weight the heritability from each study by its sample size ( $n$ ) (Sutton, 2000) as:
- 2) Weight by the heritability standard error ( $se$ ):

for  $v=1$  to  $N_v$  - the total number of voxels along the skeleton,

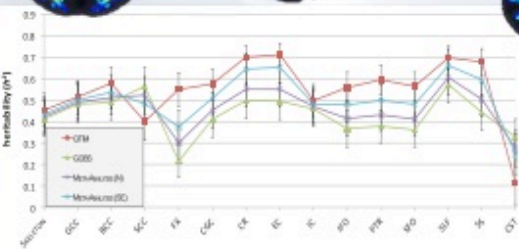
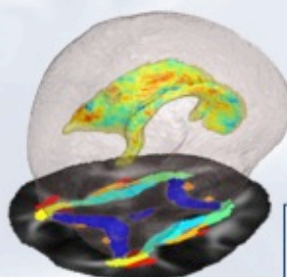
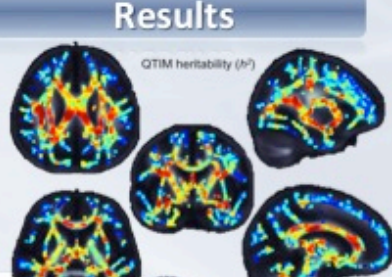
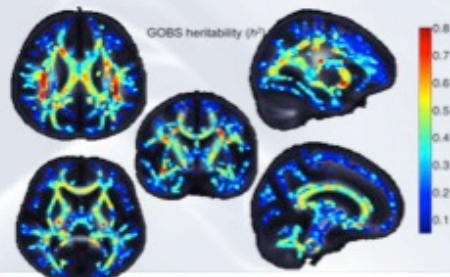
or the total number of ROIs; subscripts 1 and 2 refer to the two datasets used.

$$h_{MA}^2 = \frac{h_1^2(v) * n_1 + h_2^2(v) * n_2}{n_1 + n_2}$$

$$h_{MA}^2 = \frac{h_1^2(v) * se_1^{-2}(v) + h_2^2(v) * se_2^{-2}(v)}{se_1^{-2}(v) + se_2^{-2}(v)}$$



## Results



Publicly available processing and QC protocols: [enigma.loni.ucla.edu/ongoing/dti-working-group/](http://enigma.loni.ucla.edu/ongoing/dti-working-group/)

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