C282Y and H63D mutations in the hemochromatosis gene, HFE, jointly affect white matter structure in 509 young adults scanned with diffusion tensor imaging

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Introduction

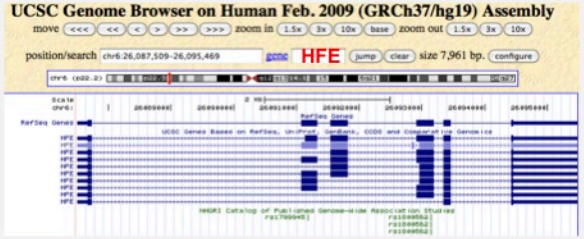
Two missense polymorphisms in the ***HFE* gene** on chromosome 6
(1) C282Y at rs1800562 (2) H63D at rs1799945
have been repeatedly associated with *hereditary hemochromatosis*, a disorder in which iron regulation is disrupted and too much iron is absorbed from the diet.

Brain **iron overload** implicated in several neurological disorders including Alzheimer's and Parkinson's diseases.

Most of the brain's iron is found in oligodendrocytes, where it supports myelination. Oligodendrocytes also maintain iron homeostasis in the brain.[1]

C282Y and **H63D** have also been implicated in interactions with AD [2,3]

We predict that genes regulating iron metabolism may individually and jointly influence white matter microstructure as measured through imaging.



Subjects and Imaging

509 *healthy* young adult twins and siblings of European ancestry
mean age: 23.5 ± 2.1 years
4-Tesla diffusion tensor imaging (DTI).

The most widely accepted DTI measure, fractional anisotropy (FA), evaluates the extent to which water diffusion is directionally constrained.
•Higher FA generally reflects preferential diffusion along more intact, heavily myelinated axons.

Statistical Association Methods

•The number of minor alleles for each *HFE* SNP of interest was regressed against the FA at each voxel within the white matter, after adjusting for sex and age.
•Family structure was taken into account with mixed effects modeling [4].
•Single-SNP models, considering each *HFE* SNP's effect independently, were fit to the data at each voxel of the brain
•A multi-SNP model, using multiple linear regression to estimate the *joint* effect of both SNPs on the brain was conducted using an F-test.
•In this analysis we again controlled for the effects of sex, age, and total serum iron levels.
•To correct for multiple comparisons across voxels, we used a searchlight method to control the false discovery rate (FDR) regionally [5]

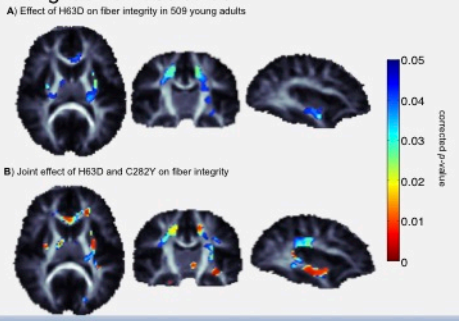
Results: Association of *HFE* with FA

H63D polymorphism (minor allele frequency of 0.17 in our dataset) showed significant associations with white matter fiber integrity (measured by FA), in the superior longitudinal fasciculus and the external capsule.

C282Y mutation was undetectable on its own (perhaps due to its low minor allele frequency of 0.075)

C282Y & **H63D**, the two SNPs were broadly associated white matter integrity (Figure 1B) in the callosal genu and temporal lobes.

2-SNP associations were stronger, versus the 1-SNP model, in the external capsules (lower corrected *p*-values), and weaker in the superior longitudinal fasciculus



Conclusions

The C282Y mutation is the most commonly associated mutation, with a minor allele frequency (MAF) of about 5% (HapMap CEU). The second mutation, H63D (Tomatsu et al., 2003), is more prevalent - with a MAF of about 0.2. By including both SNPs from the *HFE* gene, we were able to boost power in the association of this gene to microstructural variance. The joint effect of C282Y and H63D – the two most prevalent genetic polymorphisms involved in hereditary iron overload – was more extensive and showed more widespread effects on FA maps than either polymorphism alone. This analysis allowed us to map white matter variations associated with a severe mutation whose independent effect was not detectable on its own.

References & Acknowledgements

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* Denotes equal contribution

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