Investigating the Joint Effect of *HFE* mutations on White Matter Structure (N=544 DTI study)

Omid Kohannim[1], Neda Jahanshad[1], Derrek P. Hibar[1], Jason L. Stein[1], Katie L. McMahon[2], Greig I. de Zubicaray[3], Sarah E. Medland[4], Grant W. Montgomery[4], John B. Whitfield[4], Nicholas G. Martin[4], Margaret J. Wright[4], Arthur W. Toga[1], Paul M. Thompson[1]

[1]Laboratory of Neuro Imaging, Department of Neurology, UCLA School of Medicine, Los Angeles, CA, USA
[2]Univeristy of Queensland, Center for Advanced Imaging, Brisbane, Australia
[3]University of Queensland, School of Psychology, Brisbane, Australia
[4]Queensland Institute of Medical Research, Brisbane, Australia

Introduction:

Impaired iron homeostasis in the brain has been implicated in several neurodegenerative diseases including Alzheimer's disease. Two missense mutations (C282Y and H63D) of the *HFE* gene cause a majority of hereditary hemochromatosis (iron overload) cases. Iron transport occurs almost exclusively via the transferrin protein, which in the brain is most commonly expressed in white matter oligodendrocytes. We therefore examined the effects of these two *HFE* single nucleotide polymorphisms (SNPs) on white matter microstructure in a population of healthy young adult twins and siblings with diffusion tensor imaging (DTI).

Methods:

Subjects: 544 healthy young twins and siblings (mean age: 23.5 ± 2.1 years) were considered in this study, for whom DTI scan and genotyping information were available.

Diffusion Tensor Imaging: 4-Tesla images were acquired for the young adults. A mean deformation template was created for the images, and all subjects' maps were registered to the template.

Genetic variants: Two well-known, missense mutations in the hemochromatosis *HFE* gene were considered in this study. The subjects were previously genotyped, and genotypic imputation to HapMapII was additionally performed.

Statistics: The number of minor alleles for each SNP was regressed individually and jointly against voxelwise DTI-derived fractional anisotropy (FA) measures. Both single and multi-SNP regressions were adjusted for sex, age and iron levels. Relatedness was also taken into account using mixed-effects modeling. *P*-value maps were corrected for multiple comparisons using a regionoal false discovery rate (FDR) method.

Results:

Figure 1 displays the voxelwise effects of the H63D mutation in the *HFE* gene on voxelwise DTI-derived fractional anisotropy (FA) maps. Significant associations are seen in the external capsule and the superior longitudinal fasciculus. The regressions are adjusted for sex, age and iron levels, in addition to kinship structure of the subjects. *P*-values are corrected for multiple comparisons across voxels. The C282Y mutation did not show statistically significant effects on the FA maps (not displayed), most probably due to its low minor allele frequency; in fact, no subjects in our dataset had both copies of the C282Y minor allele.

Figure 1: H63D effects on white matter

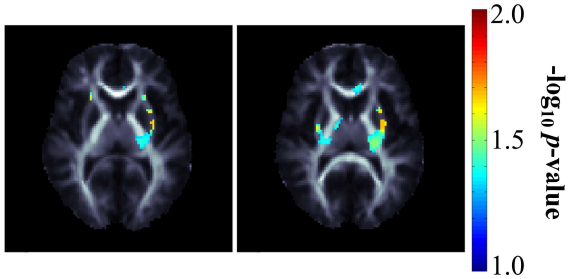

Figure 2: Joint H63D and C282Y effects on white matter

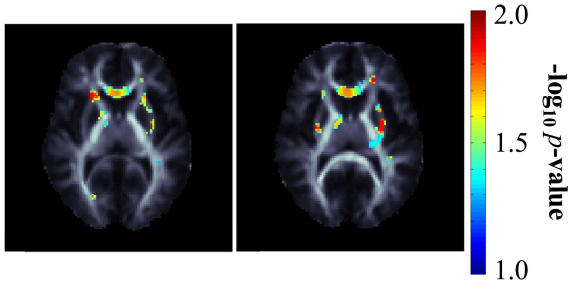

Figure 2 shows the combined influence of *HFE* C282Y and H63D mutations on white matter structure. The multi-SNP model shows more widespread effects on the FA maps, particularly in the genu of the corpus callosum, and temporal lobe white matter. The evidence for association was greater in the external capsules (lower corrected *p*-values), and less in the superior longitudinal fasciculus (smaller region of association). As above, sex, age, iron levels and kinship are adjusted for in the regressions, and *p*-values are corrected for multiple comparisons across voxels.

Conclusions:

We were able to find that the joint effect of C282Y and H63D – the two most prevalent genetic polymorphisms involved in hereditary iron overload – was extensive and showed more widespread effects on FA maps than either polymorphism alone. Our multilocus approach may be useful for neuroimaging studies assessing multiple genetic variants, with known disease associations. This voxelwise, multi-SNP method may also help accelerate the discovery and replication of gene effects on brain structure.

Financial Support: UCLA MSTP to OK, and R01 EB007813, R01 HD050735, P41 RR013642 to PT

kohannim@ucla.edu thompson@loni.ucla.edu