

Abstract for ACMG 2015

Title:

“Penetrance of hemochromatosis in HFE C282Y homozygotes and C282Y/H63D compound heterozygotes in the eMERGE Network”

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Abstract:

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Background:

Hereditary hemochromatosis (HH) is the most common genetic disorder identified in Caucasians. It may lead to iron-overload-related disease like liver cirrhosis and heart failure if left undiagnosed or untreated. Pathogenic variants in the *HFE* gene are associated with adult onset HH. The *HFE* C282Y (rs1800562) and H63D (rs1799945) missense variants account for more than 95% of the cases. While newborn screening for HH has not been adopted due to its adult onset and incomplete penetrance, the utility of examining whole exome or whole genome tests for HH has not been addressed. Such recommendations are informed by the penetrance and rate of diagnosis of HH in an unselected sample. The primary objective of this study is to determine the penetrance of *HFE* related HH in Electronic Medical Records and Genomics (eMERGE) Network participants who are unselected for this diagnosis.

Methods:

We conducted a retrospective study using the eMERGE Network, a consortium of seven adult and two pediatric U.S. cohorts with DNA biorepositories linked to electronic medical records data for large-scale, high-throughput genetic research. We selected patients that were either homozygous for the C282Y variant or compound heterozygous for C282Y/H63D. Clinical data was obtained using standardized chart abstraction and included medical history of hemochromatosis or iron-overload related conditions, iron studies, imaging studies, and physical findings consistent with HH. Comparisons of penetrance between groups were done using Chi-square test, and logistic regression was used to assess associations between diagnosis and genotype.

Results:

A total of 532 adults at risk for HH were considered, 106 were C282Y/C282Y and 426 were C282Y/H63D genotype, all were of European ancestry, mean age was 66.4 (± 15.8) years old. The proportion of C282Y homozygotes with a hemochromatosis diagnosis was 27.7% (13/47) for males and 13.7% for females (7/51). The proportion in C282Y/H63D compound heterozygotes was 4.0% (7/175) for males and 2.7% (6/222) for females. As expected, the penetrance of HH increased with age in C282Y homozygotes. After adjusting for sex, logistic regression showed that congestive heart failure was present in 20.0% of C282Y homozygotes and 12.2% of C282Y/H63D compound heterozygotes, not significantly different ($p = 0.058$). Liver cirrhosis was present in 23.8% of C282Y homozygotes and 8.2% of the C282Y/H63D compound heterozygotes ($p = <0.05$).

Conclusion:

We found that around a quarter of male and one eighth of female *HFE* C282Y homozygotes had a diagnosis of HH. These estimates are consistent with for male penetrance, and are higher than that for females. The C282Y/H63D genotype is associated with a 3-4% risk HH diagnosis in these unselected samples. These penetrance estimates will inform the utility of adding HH-*HFE* to the gene disease pairs considered for incidental finding return for whole exome and whole genome sequence tests. Unlike newborn screening where *HFE* genotyping would be required, in this case the HH risk results can be extracted from existing data. Further studies modeling cost outcomes of returning *HFE* related HH when genomic tests are done are indicated.