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POSTER ABSTRACTS

102.IRON HOMEOSTASIS AND BIOLOGY

Phenotypes Associated with HFE p.C282Y Homozygosity, the Main Hereditary Hemochromatosis Genotype, in Four Large Genetic Cohorts

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Introduction
Hereditary hemochromatosis (HH) is the most common known recessive hereditary disease in people of northern European descent. HH is most commonly caused by the HFE-C282Y homozygosity. Disease penetrance is highly variable (1-20%). We have examined the association between C282Y homozygosity and multiple phenotypes, both case-control and quantitative, across 4 international cohorts (deCODE genetics, UK Biobank, Denmark (Copenhagen Hospital Biobank / Danish Blood Donor Study) and Intermountain Healthcare) in an effort to shed a new light on the pathophysiology of this common hereditary disease.
Methods
We preformed a phenome wide association study meta-analyses for C282Y homozygosity across the 4 beforementioned cohorts, comprising around 970.000 individuals, of those 5928 were homozygous for the C282Y mutation (746 in de-CODE/Iceland MAF 6.71%, 2865 in UK Biobank MAF 7.94%, 1703 in CHB MAF 5.6% and 614 in Intermountain Healthcare MAF 6.19%). The analyses comprised both case-control phenotypes (approximately 7000), cases being defined by ICD-10 codes, and continuous quantitative phenotypes (approximately 5500), both results from blood tests and proteome data from deCODE and UK Biobank.
Results
C282Y homozygotes had a higher prevalence of the following liver, hematological and rheumatic diseases compared to a control group with no copy of the C282Y variant. Diagnosed fibrosis and cirrhosis of liver (odds ratio 4.30, 95% confidence interval 3.35 to 5.51, $p=1.77x10^{-30}$), liver cell carcinoma (9.04, 6.01 to 13.58, $p=3.24x10^{-26}$) and fatty liver disease (1.75, 1.45 to 2.11, $p=5.42x10^{-09}$) were strikingly more common in C282Y homozygotes. Unsurprisingly C282Y homozygotes also had higher liver parameters. Notably C282Y homozygotes had a higher prevalence of diagnosed polycythemia vera (7.24, 4.93 to 10.62, $p=4.37x10^{-24}$) yet no association was found with clonal hematopoiesis (1.09, 0.88 to 1.34, $p=4.47x10^{-01}$). Strong association was found between C282Y homozygosity and increased hemoglobin (0.41 standard deviations, 95% confidence interval 0.38 to 0.45, $p=6.84x10^{-142}$), MCH (0.98, 0.93 to 1.03, $p=<1.00x10^{-300}$) and MCV (0.82, 0.78 to 0.86, $p=<1.00x10^{-300}$). Red blood cell count (RBC) was decreased (-0.27, -0.30 to -0.23, $p=1.06x10^{-50}$), while reticulocyte count (0.30, 0.26 to 0.34, $p=1.42x10^{-54}$) and percentage (0.36, 0.32 to 0.40, $p=7.91x10^{-79}$) were increased. Erythropoietin (EPO) measurements were markedly decreased in C282Y homozygotes (-0.31, -0.40 to -0.22, $p=1.77x10^{-11}$). Homozygous individuals had an increased risk of being diagnosed with osteoarthritis of hip (1.83, 1.63 to 2.07, $p=4.30x10^{-23}$) and were more likely to undergo total hip replacement (2.00, 1.69 to 2.29, $p=5.81x10^{-18}$).

In contrast to these risk enhancing effects C282Y homozygotes had a lower prevalence of cardiovascular disease (CVD). C282Y homozygotes had decreased risk of coronary artery disease (CAD) (0.79, 0.72 to 0.86, p=4.26x10 $^{-07}$) and angina pectoris (0.77, 0.69 to 0.86, p=4.28x10 $^{-06}$) and were less likely to undergo coronary artery bypass graft (0.60, 0.49 to 0.74, p=2.39x10 $^{-06}$). Pure hypercholesterolemia (0.76, 0.69 to 0.83, p=2.52x10 $^{-09}$) and disorders of lipoprotein metabolism (0.75, 0.66 to 0.85, p=8.41x10 $^{-06}$) was less commonly diagnosed. C282Y homozygotes were less likely to take cholesterol lowering statin drugs (0.74, 0.67 to 0.81, p=1.45x10 $^{-09}$). Unsurprisingly with regard to these results strong association was found with lower cholesterol measurements in C282Y homozygotes, the effects being most pronounced on LDL cholesterol (-0.38, -0.42 to -0.35, p=1.61x10 $^{-99}$). Total cholesterol was also markedly lowered (-0.35, -0.38 to -0.31, p=1.38x10 $^{-91}$), as well as non HDL cholesterol (-0.34, -0.37 to -0.30, p=2.36x10 $^{-81}$). No significant association was found with HDL cholesterol and triglyceride measurements.

Conclusions

C282Y homozygosity was associated with significantly increased risk of liver disease, liver cell carcinoma and osteoarthritis of hip. Homozygous individuals had increased risk of non-clonal primary polycythemia, association with polycythemia vera likely due to misdiagnosis or early diagnosis exacerbated by significantly increased hemoglobin. C282Y homozygotes had a significant decrease in LDL, non-HDL and total cholesterol measurements and were protected against cardiovascular disease.

Disclosures Geirsdottir: *deCODE Genetics/Amgen:* Current Employment. **Lund:** *deCODE Genetics/Amgen:* Current Employment. **Saevarsdottir:** *deCODE Genetics/Amgen:* Current Employment. **Holm:** *deCODE Genetics/Amgen:* Current Employment. **Sulem:** *deCODE Genetics/Amgen:* Current Employment. **Gudbjartsson:** *deCODE Genetics/Amgen:* Current Employment. **Magnusson:** *deCODE Genetics/Amgen:* Current Employment. **Stefansson:** *deCODE Genetics/Amgen:* Current Employment.

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