Hepcidin-regulating iron-metabolism genes and pancreatic cancer

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Background

Pancreatic ductal adenocarcinoma (PDAC) is among the most lethal cancers in the US.

Higher serum iron has been associated with PDAC and experimental studies of iron overload also support that iron accumulates in pancreatic islets.

Iron levels have been associated with diabetes mellitus, an established risk factor for PDAC.

Iron is tightly regulated by the peptide hormone hepcidin, and rare mutations in genes involving it regulation are known to cause hemochromatosis.

Objective

To determine whether the hepcidin-regulating gene pathway as characterized by common variants in hepcidin-regulating genes is associated with PDAC.

Methods

Pancreatic Cancer Cohort Consortium (PanScan) and Pancreatic Cancer-Case-Control Consortium (PANC4) previously conducted GWAS

9,253 PDAC cases and 12,525 controls of European ancestry

11 hepcidin-regulating genes (*BMP2*, *BMP6*, *FTH1*, *FTL*, *HAMP*, *HFE*, *HJV*, *NFR2*, *SLC40A1*, *TFR1*, and *TFR2*) and close genomic regions (20kb up- and downstream) with a total of 412 SNPs

Unconditional logistic regression adjusted for study, geographical region, age, sex, and principal components of population substructure

Meta-analyzed summary statistics from each GWAS study phase

Summary Adaptive Rank Truncated Product (sARTP)[1]

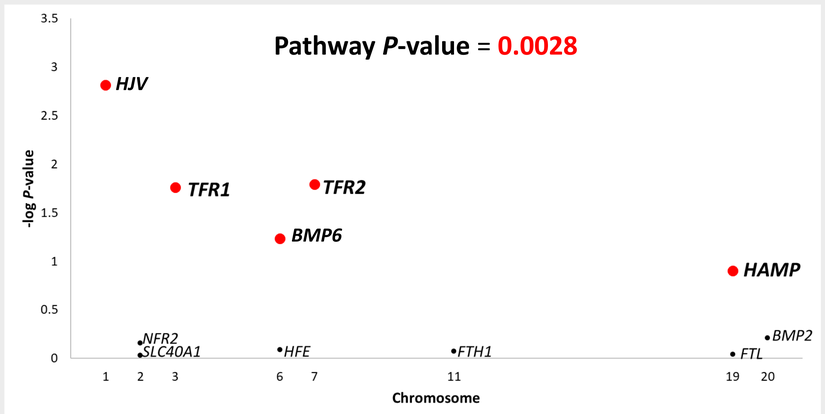
- Combines SNP-level signals across SNPs and genes in a pathway
- Up to 5 most significant SNP signals in a gene
- Adjusts by number of SNPs in a gene
- Adjusts by number of genes in a pathway through resampling procedure to control for false positives

P-value<0.05 is considered significant

Genes in iron-metabolism peptide hormone hepcidin are associated with PDAC

Results

Figure 1. Hepcidin-regulating gene pathway is associated with and PDAC risk in the PanScan and PANC4 studies[1]



[1]Pathway analysis was conducted using the sARTP as characterized by common variants in hepcidin-regulating genes-PDAC association, derived from 9,253 PDAC cases and 12,525 controls.

Strengths and Limitations

We were able to detect pathway-level associations that might not be detected in a single variant analysis in traditional GWAS studies.

No dietary data in all participants, most participants were older than 50 years old and study was only in European ancestry individuals.

Conclusions

Our study supports the hypothesis that hepcidin-regulating iron-metabolism gene pathway is associated with PDAC

The sARTP pathway analysis selected *HJV*, *TFR2*, *TFR1*, *BMP6*, and *HAMP* genes as the strongest signals

Potential role of iron metabolism in pancreatic carcinogenesis.

Future directions include:

- Replication in larger sample size and other ethnic groups
- Modifying effect of iron-rich foods with genetic susceptibility of this pathway
- Experimental models to confirm role of SNPs associated with PDAC

References

1. Zhang H et al. PLOS Genetics 2016;12(6).

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