Alpha 1 Antitrypsin MZ Information & Research

News & Research Update

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Website status and research update

Dear Subscribers,

This time a research update which explains why some Alpha1 patients develop more Liver issues than others. See the abstract below..

This type of research is really fascinating, because this enhances the understanding of the mechanisms involved in the Autophagy of the misfolded Z accumulation in the ER of the Hepatocyte.

Variants in autophagy genes MTMR12 and FAM134A are putative modifiers of the hepatic phenotype in α1-antitrypsin deficiency

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Abstract

Background and Aims:

In the classical form of α1-antitrypsin deficiency, a misfolded variant α1-antitrypsin Z accumulates in the endoplasmic reticulum of liver cells and causes liver cell injury by gain-of-function proteotoxicity in a sub-group of affected homozygotes but relatively little is known about putative modifiers. Here, we carried out genomic sequencing in a uniquely affected family with an index case of liver failure and 2 homozygous siblings with minimal or no liver disease. Their sequences were compared to sequences in well-characterized cohorts of homozygotes with or without liver disease, and then candidate sequence variants were tested for changes in the kinetics of α1-antitrypsin variant Z degradation in iPS-derived hepatocyte-like cells derived from the affected siblings themselves.

Approach and Results:

Specific variants in autophagy genes MTMR12 and FAM134A could each accelerate the degradation of α1-antitrypsin variant Z in cells from the index patient, but both MTMR12 and FAM134A variants

were needed to slow the degradation of α1-antitrypsin variant Z in cells from a protected sib, indicating that inheritance of both variants is needed to mediate the pathogenic effects of hepatic proteotoxicity at the cellular level. Analysis of homozygote cohorts showed that multiple patient-specific variants in proteostasis genes are likely to explain liver disease susceptibility at the population level.

Conclusions:

These results validate the concept that genetic variation in autophagy function can determine susceptibility to liver disease in α1-antitrypsin deficiency and provide evidence that polygenic mechanisms and multiple patient-specific variants are likely needed for proteotoxic pathology.