Nature Reviews Gastroenterology & Hepatology **10**, 567 (2013); published online 3 Septmeber 2013; doi:10.1038/nrgastro.2013.172

GENETICS

Global role for *CPA1* variants in the pathogenesis of chronic pancreatitis

Genetic susceptibility is an accepted risk factor for chronic pancreatitis, particularly early-onset disease. However, *PRSS1*, *SPINK1* and *CTRC* mutations, which lead to intrapancreatic trypsin activity, are not found in numerous patients.

Heiko Witt, Miklós Sahin-Tóth and colleagues report that variants in *CPA1* (which encodes carboxypeptidase A1, a digestive carboxypeptidase in pancreatic juice) increase the chronic pancreatitis risk independent of trypsin activity.

Of 34 *CPA1* variants identified in a German discovery set, 17 were functionally defective (reducing CPA1 activity to <20%). Defective variants were significantly over-represented in cases (3.1%) versus controls (0.1%). "*CPA1* mutations were strong risk factors, stronger than *CTRC* or *SPINK1* mutations and closer to *PRSS1* mutations," explains Sahin-Tóth. In this cohort, the odds ratio was 24.9, increasing to 84 in those <10 years of age. "Carrying a defective *CPA1* mutation increases the risk for pancreatitis 84-fold, that is close to 100-fold, in children." The association between functionally defective variants and chronic pancreatitis was confirmed in replication sets from Europe, India and Japan.

Further work suggests limited interaction between *CPA1* variants and variants in known susceptibility genes. "It is unclear why loss of CPA1 function might lead to pancreatitis," says Sahin-Tóth. In the future, the team will investigate whether misfolding-induced endoplasmic reticulum stress is responsible, but "our immediate plans are to extend these studies to CPA2 and CPB1, the two other pancreatic carboxypeptidases expressed in humans."

Natalie J. Wood

Original article Witt, H. *et al.* Variants in *CPA1* are strongly associated with early onset chronic pancreatitis. *Nat. Genet.* doi:10.1038/ng.2730

© 2013 Macmillan Publishers Limited. All rights reserved