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Pancreatitis

The SPINK in chronic pancreatitis: similar finds, different minds

H Witt

SPINK mutations are strongly associated with chronic pancreatitis but may not cause the disease

Student ''Yet in each word some concept there must be.''
Mephistopheles ''Quite true! But don't torment yourself too anxiously;
For at the point where concepts fail,
At the right time a word is thrust in there.
With words we fitly can our foes assail,
With words a system we prepare,
Words we quite fitly can believe,
Nor from a word a mere iota thieve.''

Johann Wolfgang Goethe; Faust I

Approximately five decades ago it was recognised for the first time that chronic pancreatitis (CP) may cluster in selected families suggesting an inherited disorder in these patients.[1] However, the underlying genetic defect remained obscure for a long time. The discovery of cationic trypsinogen (*PRSS1*) mutations in CP families provided a first clue to the underlying disease mechanisms.[2] Subsequent studies revealed that *PRSS1* mutations are also present in patients with idiopathic CP. Recently, mutations in the serine protease inhibitor, Kazal type 1 (*SPINK1*) gene, a pancreatic trypsin inhibitor, were identified as associated with idiopathic or hereditary CP: in 22 of 96 paediatric patients, a *SPINK1* mutation was detected. In 18 patients, a substitution of asparagine by serine at codon 34 in exon 3 was found (N34S). Six patients were homozygous for this mutation.[3] These findings suggest that pancreatitis may be the result of an imbalance of proteases and their inhibitors within the pancreatic parenchyma.

In this issue of *Gut*, Threadgold and coworkers[4] and Drenth and colleagues[5] describe mutational studies of *SPINK1* in two large series with different types of chronic pancreatitis **[see pages 675 and 682]**. Threadgold *et al* found the *SPINK1* N34S mutation in 4/108 (3.7%) patients with hereditary CP, in 6/7 (86%) cases of so-called ''familial idiopathic CP'', in 11/87 (13%) patients with so-called ''true idiopathic CP'', and in 4/67 (6%) patients with alcohol related CP.[4] Drenth *et al* detected an N34S mutation in 2/10 (20%) patients with hereditary CP, in 5/24 (21%) patients with idiopathic CP, in 4/72 (5.6%) cases with alcohol induced CP, and in 2/9 (22%) patients with a miscellaneous origin of CP.[5]

Both studies showed a strong association between N34S and various types of CP but the mutation frequencies reported in different CP groups and the interpretation of their data differ markedly. In hereditary CP patients, Drenth *et al* found the N34S mutation in 20% whereas Threadgold *et al* detected this mutation in only 3.9%. Previous studies showed an N34S frequency in hereditary CP patients of 9.1%[6] and 7.0%.[7] These considerable differences may be partially explained by the fact that in some studies the N34S frequency was calculated by counting several members of one family whereas in other studies the frequency was determined by counting unrelated patients only. Furthermore, each group used different definitions of hereditary and idiopathic CP. Drenth *et al* diagnosed hereditary CP on the basis of two or more affected family members whereas Threadgold *et al* made the diagnosis of hereditary CP on the basis of two affected first degree or three or more affected second degree relatives in two or more generations. Thus in the latter study several patients with a family history where classified as having ''familial'' idiopathic CP. The concept of ''familial'' and ''true'' idiopathic CP appears strange as the term idiopathic usually implies the absence of any predisposing factor, including heredity. The chosen *contradictio in adjecto* ''familial idiopathic'' throws light on different understandings of hereditary CP and reflects the lack of a uniform terminology. As the first description of inherited pancreatitis suggested an autosomal dominant inheritance,[1] hereditary CP was defined as a dominant inherited disease. Subsequently, the finding of familial clustering in one generation only, which indicates other inheritance patterns such as recessive or complex trait, was blinded out in the disease concept of hereditary CP.

The observed N34S frequencies in alcohol related CP were similar in both studies published in this issue of *Gut* (6.0% and 5.6%, respectively) and are in line with the previously reported frequency of 5.8%.[8] In contrast with Drenth *et al* however, Threadgold *et al* failed to find a significant association between N34S and alcoholic CP due to the high N34S frequency in their control subjects from the Liverpool area (4/100).

Interestingly, Drenth *et al* also found *SPINK1* mutations in individuals in which the cause of CP was attributed to metabolic disorders or anatomical

anomalies. Although the number of investigated cases was small (n=9) and thus their results might be only preliminary, these data open exciting new research directions. Future investigations have to show whether genetic variations influence disease susceptibility or severity in patients with anatomical variations, abdominal trauma, or other factors. Probably future studies may show a complex relationship between multiple genetic and environmental factors with different weights of these factors depending on the type of CP.

Both articles in this issue of *Gut* reflect the ongoing controversy on the meaning and inheritance pattern of *SPINK1* mutations in CP. It was argued that patients with mutant *SPINK1* could not suffer from autosomal recessive disease because individuals who are heterozygous for N34S ought to be asymptomatic. However, in two previous studies, approximately 10% of patients with idiopathic CP were homozygous for N34S.[3 6] Assuming an N34S carrier frequency of about 1–2% in the general population, the observed frequency of N34S homozygotes was 1000–4000 times higher than expected. Although a recessive inheritance pattern does not explain the high frequency of observed N34S heterozygotes, refusing a recessive trait does not explain the strong accumulation of N34S homozygotes in CP.

There is now growing evidence that many inherited disorders of the gastrointestinal tract such as haemochromatosis, α_1 antitrypsin deficiency, or CP follow a more complex trait and not only simple mendelian inheritance patterns: for example, hereditary haemochromatosis is caused in most cases by a cysteine to tyrosine substitution at position 282 (C282Y) in the *HFE* gene. Several C282Y homozygotes however do not suffer from clinical apparent liver disease. Moreover, a significant percentage with symptomatic haemochromatosis are only heterozygous for C282Y or bear no *HFE* mutation, indicating that other genes are involved also. This is supported by the finding of transferrin receptor 2 mutations in haemochromatosis families. Furthermore, recent research showed that haemochromatosis may also follow an autosomal dominant trait caused by ferroportin mutations. In summary, haemochromatosis may be induced by different recessive, dominant, and complex mechanisms in different genes. The same is clearly true for CP. One may discuss if the terms dominant or recessive are appropriate for these diseases, however they may be helpful to navigate through the genetic sea, keeping in mind that all models are only coordinate systems but never image exactly the reality.

Discussion of the role of *SPINK1* in CP (disease inducer, per se, modifier) reflects the lack of sufficient knowledge of these as yet unidentified factors and does not contribute usefully to the understanding of inherited CP. Usually, the first step is to identify the disease causing gene or genes and later to isolate modifying genes. Different mutations in different genes may have different inheritance patterns. For example, *PRSS1* mutations are thought to be dominant. However, the *PRSS1* A16V mutation is mainly found in idiopathic CP.[7]

As the majority of patients with idiopathic or hereditary CP do not show a *SPINK1* or *PRSS1* mutation,[3] several other genes may be involved in the disease pathogenesis. Future research will identify more pancreatitis related genes and will also more precisely determine the meaning of mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene in CP.[9 10] Several studies found a *CFTR* mutation in up to 30% of patients with idiopathic CP. In contrast with Threadgold *et al* who proposed that *CFTR* is not a good candidate gene for the second gene in patients with SPINK1 mutations, we assume consistent with the opinion of Drenth *et al*, that *CFTR* mutations have a major impact on the disease pathogenesis. Possibly, in a more sophisticated way, three or more different genetic defects lead to CP. Future genetic studies on *CFTR* and other candidate genes will give important insights into the mechanisms of inherited pancreatitis and will probably lead to a complex genetic model.

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Author's affiliation
H Witt, Kinderklinik, Charité-Campus Virchow-Klinikum, Humboldt-Universität, Augustenburger Platz 1, D-13353 Berlin, Germany; heiko.witt@charite.de

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