Six patients were homozygous for this mutation in only 3.9%. Previous studies showed an N34S frequency in hereditary CP patients of 9.1% and 7.0%. 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. Dre nth 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 contradiction 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, 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%. In contrast with Dre nth 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, Dre nth et al also found SPINK1 mutations in individuals in which the cause of CP was attributed to metabolic disorders or anatomical

**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 flit, can our foes assail, With words a system we prepare, Words we quite flit can believe, Nor from a word a mere iota thrive.”

Johann Wolfgang Goethe; Faust I

In this issue of *Gut*, Threadgold and coworkers5 and Dre nth and colleagues1 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.6 Dre nth 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.

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, Dre nth et al found the N34S mutation in 20% whereas Threadgold et al detected this
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 should 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. 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, 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, PRSSI mutations are thought to be dominant. However, the PRSSI A16V mutation is mainly found in idiopathic CP.

As the majority of patients with idiopathic or hereditary CP do not show a SPINK1 or PRSSI mutation, 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. 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.

Gut 2002;50:590–591

**REFERENCES**


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

www.gutjnl.com