Complete cystic fibrosis transmembrane conductance regulator gene sequencing in patients with idiopathic chronic pancreatitis and controls

F U Weiss, P Simon, N Bogdanova, J Mayerle, B Dworniczak, J Horst, M M Lerch

Background: Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene—many of which cause cystic fibrosis—have also been reported in patients with chronic pancreatitis. The authors examine whether mild or severe CFTR mutations, homozygous or compound heterozygous CFTR mutations, or even simple cystic fibrosis carrier status alone increases the risk of developing pancreatitis.

Methods: After exclusion of patients with trypsinogen (PRSS1) mutations, cystic fibrosis, or pulmonary disease, and with known risk factors for pancreatitis, 67 patients with idiopathic chronic pancreatitis (ICP) from northwest Germany and 60 geographically and ethnically matched controls were recruited. The entire coding region of the CFTR gene was sequenced in all patients and controls. ICP patients were also analysed for serine protease inhibitor Kazal type 1 (SPINK1) gene mutations.

Results: Abnormal CFTR alleles were found to be twice as frequent in ICP patients as in controls (25/134 vs 11/120; p < 0.05). Three of four severe CFTR mutations detected in patients were compound heterozygous with another abnormal CFTR allele, whereas among controls three severe CFTR mutations were found in heterozygous cystic fibrosis carriers. In ICP patients 19 uncommon/mild mutations, including combinations of the T allele with 12TG repeats, were identified compared with only five in controls (p = 0.012). Heterozygous SPINK1 mutations were detected in eight ICP patients (15% vs 1% in controls) but only one also carried an additional mild CFTR mutation.

Conclusions: These data show that not only compound heterozygosity, but also cystic fibrosis carrier status for different types of CFTR mutations, including uncommon/mild mutations, significantly increase the risk of developing pancreatitis. Although 45% of the study’s ICP patients carried predisposing genetic risk factors (for example, mutations in CFTR or SPINK1), the authors found no evidence that the risk conveyed by CFTR mutations depends on co-inherited SPINK1 mutations.
the relevant mutations for other disorders such as pancreatitis seems doubtful and, in view of the mutations reported in, for example, CBAVD, also unlikely. In addition unusual lesions, detectable exclusively by sequencing analysis, might also be present in pancreatitis patients and would not have been identified.

Many studies further compared their observed changes with published historical cohorts rather than using geographically and ethnically matched control groups for their analyses.

This is mostly inappropriate for two reasons: (1) cystic fibrosis mutations are not equally distributed among different populations and carrier frequencies vary from 1/30 among White to 1/90 in Asian cohorts and (2) most historical control cohorts were investigated using commercial mutation panels rather than sequencing techniques and are therefore inappropriate controls for rare or uncommon mutations.

It is therefore not surprising that the question of whether only compound heterozygous CFTR mutations or also an otherwise harmless, heterozygous cystic fibrosis carrier status represents a risk factor for idiopathic pancreatitis remains unresolved. Moreover, it is still unknown whether only severe cystic fibrosis mutations must be regarded as pancreatitis associated mutations or mild and/or variable changes in the CFTR gene convey the same pancreatitis risk.

In order to determine whether or not different types of CFTR mutations affect the risk of developing chronic pancreatitis, and how high that risk may be, we recruited 67 patients with idiopathic chronic pancreatitis (ICP) and 60 geographically and ethnically matched controls. All patients and control subjects were White and from the same, narrowly confined area in northwest Germany. We sequenced the entire coding region of the CFTR gene in all subjects and could firmly determine that compound heterozygous mutation carriers, as well as heterozygotes with mild and uncommon mutations (previously regarded as unaffected cystic fibrosis carriers) have an increased risk of developing chronic pancreatitis. Two thirds of these patients would not have been identified by the commercially available screening panels for the common cystic fibrosis mutations. In combination with an independent population of patients who carry SPINK1 mutations (15%) a total of 45% of our patients with idiopathic chronic pancreatitis ultimately carried identifiable genetic risk factors for the disease.

MATERIALS AND METHODS

Patients and recruitment

Patients and controls were recruited over a five year period at a tertiary referral centre with a large population of outpatients suffering from chronic pancreatitis. The study was performed following a research protocol approved by the local ethics committee and after informed consent was obtained from each patient. All individuals included were White and originated from North-Rhine Westfalia, a populous province in northwest Germany. In order to limit the patient cohort to those with idiopathic chronic pancreatitis, participants were chosen based on unequivocal CT and/or endoscopic retrograde cholangiopancreatography (ERCP) criteria rather than on clinical history or laboratory findings. Patients who reported any known risk factor for pancreatitis, such as a history of nutritive (including alcohol consumption of more than two drinks a day (20 g)), biliary, metabolic, or endocrine disorders, as well as subjects with any evidence of pulmonary diseases or cystic fibrosis, were excluded from the study. Patients identified as mutation carriers in the cationic trypsinogen (PRSS1) gene—as evaluated by complete sequencing of the coding region of the PRSS1 gene—were also excluded, because hereditary pancreatitis caused by PRSS1 mutations is endemic in that region of Germany and cannot be safely ruled out, based on a negative family history alone.

The remaining panel of ICP patients consisted of 67 people (aged 3–68 years, 40 male and 27 female). The healthy control population consisted of 60 unrelated and unaffected partners of healthy cystic fibrosis carriers (aged 18–50 years, 16 male and 45 female) with an ethnic and geographical background identical to that of the ICP patients. In this control group pancreatic disease and immoderate ethanol consumption had been excluded by structured medical history taking.

Genetic studies

Genomic DNA was extracted from peripheral blood lymphocytes by standard isolation procedures using QiAmp DNA blood mini kit (Qiagen, Hilden, Germany). PCR-Amplification of all 27 CFTR exons, including flanking intronic regions, was performed using gene specific primers. Amplicons were sequenced in both directions using the ABI PRISM Dye terminator cycle sequencing reaction kit (Applied Biosystems, Foster City, CA, USA) and electrophoresis was performed on an ABI-3700 Genetic Analyzer (Applied Biosystems). Similarly, the entire coding region (exons 1 to 4) of the SPINK1 gene was amplified by PCR using gene specific primers and each exon was sequenced in both directions in all ICP patients.

Data management and statistical analysis

Statistical analysis was performed using SigmaStat software. Groups were compared using χ² test or the Fisher’s exact test (when at least one expected cell value in 2x2 table was less than 5). p values of below 0.05 were considered statistically significant. Tables were created using Microsoft Excel.

RESULTS AND DISCUSSION

A number of factors have impeded comprehensive investigations of the role of CFTR mutations in idiopathic chronic pancreatitis in the past. These include: (1) the large size of the 27 exon-spanning CFTR gene, (2) the high number of previously reported mutations in patients with cystic fibrosis, (3) the limited number of cystic fibrosis causing mutations that are included in the presently used screening panels for the diagnosis of cystic fibrosis, (4) existence of geographical and ethnic variations in CFTR mutation carrier frequencies, and (5) the lack of reliable data on the frequency of uncommon CFTR mutations in healthy control populations.

To settle the question of whether CFTR mutations convey an increased risk for developing chronic pancreatitis, we started a comprehensive sequencing study involving a cohort of 67 patients with idiopathic chronic pancreatitis as well as a geographically and ethnically matched control group.

Among 67 ICP patients we identified a total number of 25 abnormal CFTR alleles, which amounts to twice the allele frequency in healthy controls (11 abnormal CFTR alleles in 60 controls; 18.6% vs 9.2%, p<0.05; details in tables 1 and 2). Detected mutations in 60 control subjects included three heterozygous classical mutations ΔF508, four mild CFTR mutations, and the T5 allele in intron 8 of the CFTR gene in additional four subjects. In the ICP cohort on the other hand, four patients were compound heterozygous for two gene mutations, nine patients were carriers of a single sequence variation, and in an additional eight patients the T5 sequence variant was detected. Due to the four compound heterozygous ICP patients the overall number of patients carrying CFTR mutations was 21. Although this is nearly twice the prevalence in controls the difference misses statistical significance (21/67; 31% vs 11/60; 18.3%; p = 0.14, see also table 3).
also carriers of 12 TG repeats (located in close proximity in
of those eight ICP patients with a 5T allele in intron 8 were
frame shift) and eight mild/uncommon mutations (2
CFTR mutation one severe (2184insA, this insertion causes a
symptoms of cystic fibrosis or evidence for pulmonary disease
be expected from a cohort from which all individuals with
levels and function of CFTR. None of the patients, however,
CFTR alleles that may additively reduce the physiological
higher in the ICP patient group (4/67; 6%). This points to
combined genetic changes in the two
normal population and therefore appears about 18-fold
compound heterozygous subjects would be 0.34% in the
Two mild mutations (S1235R/R668C). Taking into account
three 5T alleles were not significantly increased in ICP
patients (8/134 v 3/120; p = 0.29). Interestingly however, six
of those eight ICP patients with a 5T allele in intron 8 were
also carriers of 12 TG repeats (located in close proximity in
Three of the four compound heterozygous ICP patients
carried one severe ΔF508 mutation (genotypes: ΔF508/
R117H, ΔF508/A1087P, ΔF508/D1152H) and one carried
two mild mutations (S1235R/R668C). Taking into account
the allele frequency of severe and mild alleles in our control population (7/120; 5.8%) the calculated frequency of
compound heterozygous subjects would be 0.34% in the
normal population and therefore appears about 18-fold
higher in the ICP patient group (4/67; 6%). This points to
an important role of combined genetic changes in the two
CFTR alleles that may additively reduce the physiological
levels and function of CFTR. None of the patients, however,
had a combination of two severe CFTR mutations, as would be expected from a cohort from which all individuals with
symptoms of cystic fibrosis or evidence for pulmonary disease
had been excluded.

In the group of ICP patients being heterozygous for a single
CFTR mutation one severe (2184insA, this insertion causes a frame shift) and eight mild/uncommon mutations (2 ×
S1235R, R31C, R75Q, R347P, G576A, M348V, and V754M) were identified. M348V and A1087P present novel molecular
alternatives of 5T–12TG were therefore 5.2
times more frequent in the patient group (6/134 v 1/120; p = 0.16) whereas combined allele frequencies of CFTR
mutations and 5T–12TG combinations, but excluding “benign” 5T alone, were increased to statistically significant
levels among ICP patients (23/134 v 8/120; p = 0.012). As we
had excluded patients with symptoms of cystic fibrosis or
evidence for pulmonary disease from the study, the number of severe CFTR mutations might have been biased towards a
low prevalence. This restriction, however, was necessary to
discriminate between pancreatic dysfunction as one possible symptom of cystic fibrosis as opposed to being caused by
idiopathic pancreatitis. If we therefore disregard severe
mutations and compare only mild CFTR mutations (which,
when heterozygous do not cause cystic fibrosis) we find that mild
CFTR mutations, including combination of 5T–12TG
repeats, are also increased to significant levels in ICP patients
when compared with controls (19/134 v 5/120; p = 0.012).
Therefore, in addition to compound heterozygous patients,
subjects who carry one mild CFTR mutation or a 5T–12TG
combination must now be considered to be at an increased
risk of developing idiopathic chronic pancreatitis.

Recently an analysis of CFTR mutations in four population
samples with a total of 191 individuals was reported that used a novel denaturing gradient gel electrophoresis (DGGE)
approach which is estimated to detect about 95% of all
mutations.18 This study is presently the largest analysis of
healthy controls and identified 30 CFTR mutations and 17 5T
alleles. However, the presence or absence of the more
functionally relevant combination of 5T alleles with 12TG
repeats had not been evaluated. Excluding 5T alleles and 5T–
12TG combinations the allele frequency of CFTR mutations in
that study was approximately 7.8%. The population samples
had been gathered from four different regions in southern
Europe and the observed mutation frequencies and their
distribution were not significantly different from those in our
control population (5.8%).

In a study by Ockenga et al., the authors analysed 20
German ICP patients using a cystic fibrosis screening panel
covering 32 frequent CFTR mutations.19 Six patients carrying
at least one abnormal CFTR gene were identified (30%) and
only one patient was compound heterozygote for two
mutations (1/20, 5%). Studies by other groups20–21 also
identified patients with idiopathic chronic pancreatitis that
were compound heterozygote for two mutations (3/14, 21%;
9/39, 23%; 4/39, 10%). The reason why numbers for
compound heterozygous ICP patients in these studies are
diverse (4/67 = 6% in our study) may be due to differences

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<td>10/11</td>
<td>--/-</td>
</tr>
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<td>7/9</td>
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<tr>
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<td>10/11</td>
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<tr>
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<td>7/9</td>
<td>10/11</td>
<td>N34S/-</td>
</tr>
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<td>7/7</td>
<td>11/11</td>
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</tr>
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<td>11/11</td>
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<tr>
<td>30</td>
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<td>--/-</td>
<td>7/7</td>
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<td>ΔF508/-</td>
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<tr>
<td>R117H/-</td>
<td>2</td>
</tr>
<tr>
<td>2184insA/-</td>
<td>1</td>
</tr>
<tr>
<td>597Y/-</td>
<td>1</td>
</tr>
<tr>
<td>5T/12TG</td>
<td>1</td>
</tr>
<tr>
<td>5T/11TG</td>
<td>3</td>
</tr>
</tbody>
</table>
in patient recruitment, the catchment populations, or the stringency with which cystic fibrosis patients were excluded. To date it remains unclear whether in these compound heterozygotes the impairment of CFTR function is not yet severe enough to cause the onset of classic cystic fibrosis or whether pancreatitis is an independent disease entity caused by diminished CFTR function. Affected patients could therefore suffer from either an atypical variety of cystic fibrosis or from a completely different disease—ICP—that is also associated with CFTR mutations.

Concerning the relevance of 5T alleles it is true that 5T alleles have never been shown to be in linkage disequilibrium with severe CFTR mutations like ΔF508. When found in trans position with a severe cystic fibrosis causing mutation some individuals, however, have been reported to develop non-classic cystic fibrosis, others were diagnosed with male infertility caused by CBAVD, while approximately 40% had no detectable phenotypic changes. In 91% of clinically affected individuals abnormal TG repeats were identified and the TG repeat number therefore seems to correlate closely with the pathogenicity of the 5T allele. 5T alleles in combination with a normal allele or a normal TG repeat number have not been considered as disease causing. The increased frequency of heterozygous uncommon/mild mutations, including the 5T–12TG combination, among patients with ICP may indicate that pathogenic processes affecting the exocrine pancreas may already be operative at levels of CFTR functional impairment that are still compatible with male fertility, normal pulmonary physiology, and absence of cystic fibrosis. How heterozygous CFTR mutations could predispose patients to developing ICP is not readily understood. One possible explanation would be the combination with defects in other gene products that could result in a synergistic pathogenetic effect on acinar cell function.

We sought to test this hypothesis for a possible interaction of CFTR mutations with mutations in the SPINK1 gene, for which an association with idiopathic and tropical pancreatitis has previously been reported. Sequencing analysis of the entire coding region of the SPINK1 gene revealed that 10 patients were found to carry SPINK1 mutations (8 × N345, 1 × P555, and 1 × IVS3+2TC). All SPINK1 mutation carriers had normal CFTR alleles with the exception of one patient who was heterozygous for the N345 mutation and a 5T–12TG combination. This result constitutes a 15% prevalence of SPINK1 mutations among our ICP patients—versus 1% in the ethnically matched controls of our catchment area according to one of our recent studies—and confirms the previous finding of an increased frequency of SPINK1 mutations in chronic pancreatitis. However, it also indicates that a co-occurrence of SPINK1 mutations is not required for CFTR mutations to confer their risk for developing pancreatitis. Similar findings were reported by Berndino et al who investigated 82 Brazilian ICP patients and 200 controls. They found that about 10% of the Brazilian patients carried CFTR mutations whereas only a single patient carried a SPINK1 mutation. It therefore appears that in Brazil, very unlike the Indian subcontinent, alterations in the SPINK1 gene play no role in the pathogenesis of pancreatitis. It also confirms our interpretation that CFTR mutations convey an increased risk for the development of pancreatitis that is independent of co-inherited mutations in the SPINK1 gene.

A disease modifier role of PRSS1 mutations on alterations in the CFTR gene was already ruled out by our exclusion criteria during patient recruitment.

If we had used commercially available screening panels to identify CFTR alterations, rather than DNA sequencing, we would have missed 16 of the 25 uncovered mutations. According to our study, the risk of developing chronic pancreatitis for a heterozygous carrier of a CFTR mutation (regardless of its severity) is increased approximately three- to fourfold over that of the normal population. The risk for a compound heterozygous individual whose mutations include a severe type, on the other hand, is presumably increased several 100-fold over that of the control population. From the latter group with the highest risk of developing chronic pancreatitis the majority would, after all, have been identified using commercially available cystic fibrosis screening panels although their compound heterozygous status would have been missed.

At present the routine testing of chronic pancreatitis patients for either CFTR or SPINK1 mutations—using mutation panels or full sequencing—outside of research protocol driven studies cannot be recommended and remains without clinical consequences.

Among White populations the healthy carriers of severe cystic fibrosis causing CFTR mutations (about 5%) are thought to be at an increased risk of developing chronic pancreatitis. Our study has determined that not only compound heterozygous carriers of CFTR mutations but also carriers of mild/uncommon CFTR mutations (about 8% of the population) carry an increased risk of developing chronic pancreatitis. The cellular mechanism through which a functionally impaired CFTR leads to the onset of pancreatitis still needs to be elucidated.

**ACKNOWLEDGEMENTS**

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**Table 3** CFTR allele frequencies in ICP patients and controls

<table>
<thead>
<tr>
<th></th>
<th>ICP patients</th>
<th>Controls</th>
<th>p Value</th>
</tr>
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<tbody>
<tr>
<td>Abnormal CFTR alleles (affected subjects)</td>
<td>25/134 (18.8%)</td>
<td>11/120 (9.16%)</td>
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</tr>
<tr>
<td>Compound heterozygous alleles</td>
<td>8/134</td>
<td>0/120</td>
<td>0.018*</td>
</tr>
<tr>
<td>Severe CFTR mutations</td>
<td>4/134</td>
<td>3/120</td>
<td>0.88</td>
</tr>
<tr>
<td>Mild/uncommon CFTR mutations (excluding 5T alleles)</td>
<td>13/134</td>
<td>4/120</td>
<td>0.08</td>
</tr>
<tr>
<td>Simple 5T alleles</td>
<td>8/134</td>
<td>4/120</td>
<td>0.49</td>
</tr>
<tr>
<td>ST-12TG combination</td>
<td>6/134</td>
<td>1/120</td>
<td>0.16</td>
</tr>
<tr>
<td>Mild/uncommon CFTR mutations including ST-12TG, excluding mere 5T alleles</td>
<td>19/134</td>
<td>5/120</td>
<td>0.012*</td>
</tr>
<tr>
<td>All CFTR mutations, including ST-12TG, excluding mere 5T alleles</td>
<td>23/134</td>
<td>8/120</td>
<td>0.018*</td>
</tr>
</tbody>
</table>

*p values below 0.05 are considered statistically significant.

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1. “Investigated 82 Brazilian ICP patients and 200 controls. 25 affected individuals abnormal TG repeats were identified.”

2. “They found that about 10% of the Brazilian patients carried pathogenetic effect on acinar cell function.”

3. “The cellular mechanism through which a functionally impaired CFTR leads to the onset of pancreatitis still needs to be elucidated.”

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**SPINK1 mutations among our ICP patients—versus 1% in the control population. From the latter group with the highest risk of developing chronic pancreatitis the majority would, after all, have been identified using commercially available cystic fibrosis screening panels although their compound heterozygous status would have been missed.**

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