Co-existence of CFTR and SPINK1 Gene Mutations in an Idiopathic Chronic Pancreatitis Case

Srinivasan Muthuswamy1, Shweta Singh1, Gourdas Choudhuri2 and Sarita Agarwal∗
1Department of Medical Genetics, Sanjay Gandhi Postgraduate Institute of Medical Sciences, India
2Department of Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, India

Abstract

Familial aggregation of CP suggests genetic factors for disease without definitive mode of inheritance. The hypothesized primary putative gene for CP includes SPINK1, CTSB, CTRC, PRSS1 and CFTR. These genes interact with each other and exhibit a variable phenotype in patients. The present report describes a male adult aged 42 years with a complaint of severe recurrent pain in the abdomen and weight loss and the age of onset was 35 years. The family history of chronic pancreatitis was not found. The biochemical examination revealed the exocrine insufficiency. Abdominal CT identified a dilated main pancreatic duct with numerous stones in the pancreas head. Genetic studies identified the patient to be heterozygous for p.N34S and G551D in SPINK1 and CFTR gene. Extended family screening identified his son (10 years) to have both mutation p.N34S and G551D in heterozygous state. Present findings suggest the need of genetic diagnosis in familial CP cases thereby precaution can be taken to delay or avoid the disease onset.

Introduction

Cystic Fibrosis Transmembrane Regulator (CFTR) gene harbors over 1910 mutations till date (www.genet.sickkids.on.ca). These mutations result in cystic fibrosis or other disease like Congenital Bilateral Absence of Vas Deferens (CBAVD), obstructive azoospermia, bronchiectasis, asthma and Chronic Pancreatitis (CP) etc. [1]. Chronic pancreatitis is a disease of pancreas that is characterized by permanent destruction and fibrosis of the exocrine parenchyma, leading to exocrine pancreatic insufficiency and progressive endocrine failure leading to diabetes.

A familial aggregation nature of CP suggests genetic etiology without definitive mode of inheritance [2,3]. Extensive genetic studies on CP let to classification of hereditary CP and idiopathic CP. Hereditary CP has a penetrance of 70-80% with autosomal dominant inheritance [4]. Idiopathic CP too involves genetic factors but multigenic. The genetic loci reported to predispose CP includes: Serine Protease Inhibitor Kazal 1 (SPINK1), CFTR, CTRC, PRSS1 and cathepsin B (CTSB) [5]. In spite of definitive role of CFTR gene in CP pathogenesis, [6] there are contradictory reports that claim no association of CFTR gene [7,8]. However, recent studies have reported an increased occurrence of CFTR gene mutations in alcohol related CP patients [9,10]. In this case report, we have demonstrated the co-existence of CFTR and SPINK1 gene mutations in an Idiopathic CP cases.

Case Report

A male adult patient aged 42 years visited Gastroenterology OPD of Sanjay Gandhi Postgraduate Institute of Medical Sciences with a complaint of severe recurrent pain in the abdomen and weight loss. A detailed history revealed that the age of onset was 35 years and the patient had no habit of alcohol intake. The family history of CP was not evident. The patient underwent biochemical and radiological examination. Biochemical: Serum amylase test report was normal and pancreatic function test showed only 54.4% (normal value >70%) confirming the exocrine insufficiency. Abdominal CT identified a dilated main pancreatic duct with numerous stones in the pancreas head.

We carried out genetic test of SPINK1, CTSB and CFTR genes. The SPINK1 gene was studied for the most common variants, p.N34S, cIVS3+2T>C and IVS-37T>C, by PCR RFLP method [11,12]. The CTSB was analysed for p.L26V mutation by PCR RFLP method [13]. The CFTR gene was examined for p.D508, p.G542X, p.G551D, p.R117H, p.S549N and IVS8 polymorphism as described by Muthuswamy et al., [10]. The patient was found be heterozygous for p.N34S and G551D in SPINK1 and CFTR gene. Following the mutation identification we explored the mutation status in rest of the family members (Figure 1). We found his son of 10 years old to have both mutation p.N34S and G551D mutations in heterozygous state as in the patient while rest of the family members were mutation free (Table 1).

<table>
<thead>
<tr>
<th>Subject</th>
<th>Mutation status</th>
<th>Disease status</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.1</td>
<td>Deceased</td>
<td>Uncertain</td>
</tr>
<tr>
<td>I.2</td>
<td>Deceased</td>
<td>Uncertain</td>
</tr>
<tr>
<td>II.1 (Proband)</td>
<td>N34S, G551D carrier</td>
<td>Affected</td>
</tr>
<tr>
<td>II.2</td>
<td>Negative</td>
<td>Unaffected</td>
</tr>
<tr>
<td>II.3</td>
<td>Deceased</td>
<td>Uncertain</td>
</tr>
<tr>
<td>III.1</td>
<td>Negative</td>
<td>Unaffected</td>
</tr>
<tr>
<td>III.2</td>
<td>N34S, G551D carrier</td>
<td>Asymptomatic</td>
</tr>
</tbody>
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Table 1: Study subjects and their mutation status.
Molecular investigation of the family members identified his son as a carrier for both SPINK1 and CFTR mutation. During the study, he was at the age of 10 years and may be a prospective CP patient. The issues have been discussed with the family members about his predisposition for CP.

In conclusion, these data highlight the need of genetic testing in CP patients for effective treatment and family members can be screened to identify any prospective cases they by proper intervention can be started before the disease progresses.

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References


Figure 1: Family Pedigree of Patient. Square: Male; Circle: Female; Dark shade: Affected; Cross: Ceased; Vertical line: Carrier of both mutation and asymptomatic