Gene Technology

Muthuswamy, et al., Gene Technology 2015, 4:1
DOI: 10.4172/2329-6682.1000116

Case Report Open Access

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

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Rec date: November 22, 2014; **Acc date:** February 14, 2015; **Pub date:** February 19, 2015

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 the both mutation p.N34S and G551D mutation 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, c.IVS3+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.DF508, p.G542X, p.G551D, p.R117H, p.S549N and IVS8 T 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 p.N34S and G551D mutations in heterozygous state as in the patient while rest of the family members were mutation free (Table 1).

Subject	Mutation status	Disease status
I.1	Deceased	Uncertain
I.2	Deceased	Uncertain
II.1 (Proband)	N34S, G551D carrier	Affected
II. 2	Negative	Unaffected
II.3	Deceased	Uncertain
III.1	Negative	Unaffected
III.2	N34S, G551D carrier	Asymptomatic

Table 1: Study subjects and their mutation status.

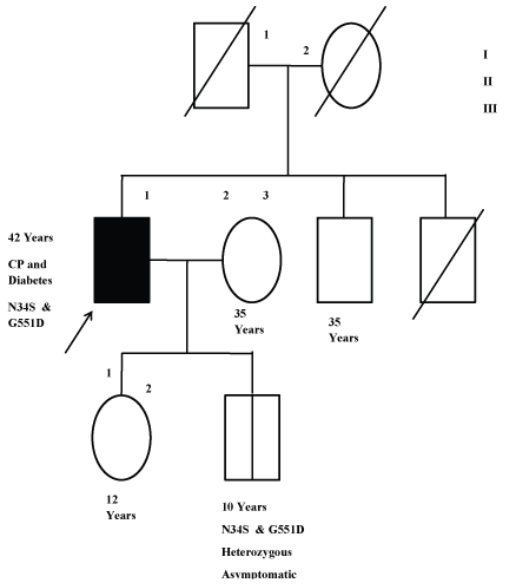

Figure 1: Family Pedigree of Patient. Square: Male; Circle: Female; Dark shade: Affected; Cross: Ceased; Vertical line: Carrier of both mutation and asymptomatic

Discussion

In this case report, we reported an idiopathic CP case with heterozygous mutations in *SPINK1* and *CFTR* gene and found one of his son to carry the same mutation. The co-existence of these two mutations supports the multigenic nature of idiopathic CP and interaction of other external factors that could predispose the mutation carrier to CP. Though *SPINK1* gene mutations alone have been reported to be present in idiopathic CP, presence of *CFTR* gene mutation may led to earlier onset of disease or may increase its severity. The presence of *CFTR* gene mutation in idiopathic CP was reported in few studies [12-14].

The *SPINK1* gene encoded protein prevents premature activation of zymogen by trypsin by interacting with trypsin [15]. Polymorphisms of *SPINK1* gene result in loss of function and are weakly associated with CP, irrespective of heterozygous or homozygous state. N34S is the most common missense mutation reported in CP. The heterozygous state of this mutation lowers the enzyme level there by premature activation of zymogen results in irreversible damage to pancreases along with *CFTR* mutation that increases severity further [16].

CFTR channel performs movement of chloride and bicarbonate ions across the pancreatic duct cells there by regulating absorption and secretion of fluids/enzymes. *CFTR* mutations are hypothesized to result in loss of bicarbonate secretion and cause recurrent acute and chronic pancreatitis rather than cystic fibrosis [8-17]. The reported G551D missense mutation of *CFTR* falls under class III mutation. These mutations have <1% channel function and display a severe phenotype with pancreatic insufficiency [18] by forming thick mucus in cells. Thick mucus hampers the secreter function of duct cells. The presence of pancreatic exocrine insufficiency in our patient is consistent with the above hypothesis.

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.

Acknowledgement

Muthuswamy S is thankful to ICMR, New Delhi for fellowship, Singh S is thankful to DST for fellowship and all the authors are thankful for SGPGI, Lucknow for providing infrastructure.

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