

CASE REPORT

Chronic Pancreatitis Associated with the p.G208A Variant of *PRSS1* Gene in a European Patient

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ABSTRACT

Context The major etiologic factor of chronic pancreatitis in adults is excessive alcohol consumption, whereas among children structural anomalies, systemic and metabolic disorders, and genetic factors are prevalent. Mutations in the cationic trypsinogen gene (*PRSS1*) cause hereditary pancreatitis, while mutations in serine protease inhibitor Kazal type 1 (*SPINK1*), cystic fibrosis transmembrane conductance regulator (*CFTR*) and chymotrypsin C (*CTRC*) genes have been shown to associate with chronic pancreatitis as independent risk factors. **Case report** We present a case of 13-year-old boy with idiopathic chronic pancreatitis. Given the unexplained attacks of pancreatitis since early childhood and despite the negative family history, molecular-genetic analysis of four pancreatitis susceptibility genes (*PRSS1*, *SPINK1*, *CTRC* and *CFTR*) was performed. The boy was found to carry the c.623G>C (p.G208A) mutation of the *PRSS1* gene and the c.180C>T (p.G60G) mutation of the *CTRC* gene, both in heterozygous state. These mutations are considered as contributing risk factors for chronic pancreatitis. **Conclusions** In children with idiopathic chronic pancreatitis genetic causes should be considered, even in absence of positive family history. To the best of our knowledge, this is the first description of a European patient with chronic pancreatitis associated with the p.G208A mutation of *PRSS1* gene. This mutation was previously reported only in Asian subjects and is thought to be a unique genetic cause of pancreatitis in Asia.

INTRODUCTION

The major etiologic factor of chronic pancreatitis in adults is excessive alcohol consumption, whereas among children structural anomalies, systemic and metabolic disorders, and genetic factors are prevalent. Hereditary pancreatitis (OMIM #167800, Online Mendelian Inheritance in Man; www.omim.org) is an autosomal dominant disorder with about 80% penetrance caused by mutations in the cationic trypsinogen gene (*PRSS1*) [1]. The p.R122H and p.N29I mutations of *PRSS1* appear to be the most common world-wide. However, additional rare *PRSS1* variants have been reported, the majority of which were found in sporadic cases without a family history of chronic pancreatitis ([2],

www.pancreasgenetics.org). Mutations in other genes such as serine protease inhibitor Kazal type 1 (*SPINK1*) [3], cystic fibrosis transmembrane conductance regulator (*CFTR*) [4] and chymotrypsin C (*CTRC*) [5] have been shown to associate with chronic pancreatitis as independent risk factors.

Here we present a case of chronic pancreatitis associated with a rare heterozygous mutation of *PRSS1* in a Slovak child. This mutation was previously reported only in Asian subjects and is thought to be a unique genetic cause of pancreatitis in Asia [6].

CASE REPORT

The currently 13-year-old Caucasian boy was first examined at our department at the age of 11 on account of acute abdominal pain, intense nausea and vomiting. His prior history included several similar episodes (approximately 2 attacks per year), some managed at home and others with brief hospitalization. The first episode occurred at the age of 2.5 with same symptoms and elevated serum amylase and lipase levels. Over the next years further investigations have been performed to determine the root cause of patient's complaints

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Abbreviations *CTRC*: chymotrypsin C

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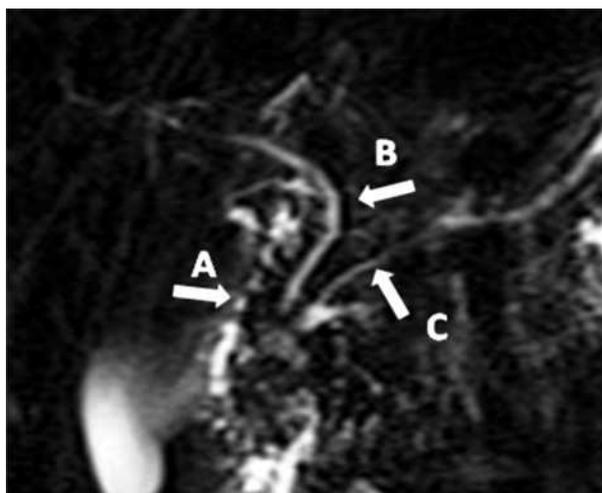


Figure 1. Magnetic resonance cholangiopancreatography (MRCP) image of the patient. By MRCP scan the diagnosis of chronic pancreatitis probably on the basis of pancreas divisum was suspected, but it was ruled out later by endoscopic retrograde cholangiopancreatography. A: duodenum; B: common bile duct; C: pancreatic duct

and abdominal trauma, cystic fibrosis, infectious, metabolic, autoimmune, drug and systemic causes were gradually excluded, by means of anamnestic investigations, clinical observations and by laboratory evaluations. Attempting to exclude any structural anomaly, magnetic resonance cholangiopancreatography (MRCP) (Figure 1) and endoscopic retrograde cholangiopancreatography (ERCP) were performed and the diagnosis of chronic pancreatitis probably on the basis of pancreas divisum was established. Note that this finding was also excluded later (see below).

When coming to our attention, the boy felt tired and presented epi- and meso-gastric tenderness. Serum laboratory tests were all within the normal range, with the exception of C-reactive protein (CRP) 12.5 mg/L (reference range: 0-5 mg/L), amylase 17.29 μ kat/L (reference range: 0-1.7 μ kat/L), pancreatic amylase 14.9 μ kat/L (reference range: 0-0.58 μ kat/L), lipase 61.63 μ kat/L (reference range: 0.67-2.34 μ kat/L) and uric acid 442 μ mol/L (reference range: 100-360 μ mol/L). Urinalysis showed high levels of amylase 149.29 μ kat/L (reference range: 0-7.7 μ kat/L) and pancreatic amylase 149.2 μ kat/L (0-5.43 μ kat/L). Transabdominal ultrasound revealed slightly inhomogeneous parenchyma and coarse texture. Under conservative therapy, which included i.v. fluids administration, gastroprotective therapy and enzyme supplementation, amylase, lipase and CRP values returned to normal levels. After 1 week of hospitalization the child was released in good condition and hypolipidemic diet, proton pump inhibitor and pancreatic enzyme supplementation therapy were recommended. The next month a re-hospitalization was planned to perform ERCP and consider transpapillary

pancreatic stent utilization. During the examination the diagnosis of pancreas divisum was ruled out and because of Wirsung duct stenosis pancreatic stent was implanted. Since that time stent replacement was three times provided and the stent was extracted half a year ago due to acute exacerbation of the disease with obturation of the pancreatic stent. At follow-up visits no further episodes of abdominal pain were reported, the laboratory tests showed repeatedly elevated cholesterol 5.41 mmol/L (reference range: 3.21-4.80 mmol/L) and triglyceride 3.87 mmol/L (reference range: 0-1.3 mmol/L) levels, but HDL, LDL, ApoA and ApoB values were within normal range.

Given the unexplained attacks of pancreatitis since early childhood and despite the negative family history, genetic counseling and molecular-genetic analysis of four pancreatitis susceptibility genes (*PRSS1*, *SPINK1*, *CTRC* and *CFTR*) were provided. Direct sequencing of all exons of *PRSS1*, *SPINK1* and of 2nd, 3rd and 7th exon of *CTRC* was performed. Most common mutations of *CFTR* (51 total) were analyzed. To exclude large genomic rearrangements, multiplex ligation-dependent probe amplification assay (MLPA) of *PRSS1* and *SPINK1* was also applied. The proband was found to carry the c.623G>C (p.G208A) mutation of the *PRSS1* gene and the c.180C>T (p.G60G) mutation of the *CTRC* gene, both in the heterozygous state (Figure 2). Except the mentioned mutations and the common polymorphisms c.486C>T (p.D162D) and c.738C>T (p.N246N) of the *PRSS1* gene no other variants in *PRSS1*, *SPINK1*, *CTRC* and *CFTR* were detected. The index patient's parents were subsequently tested

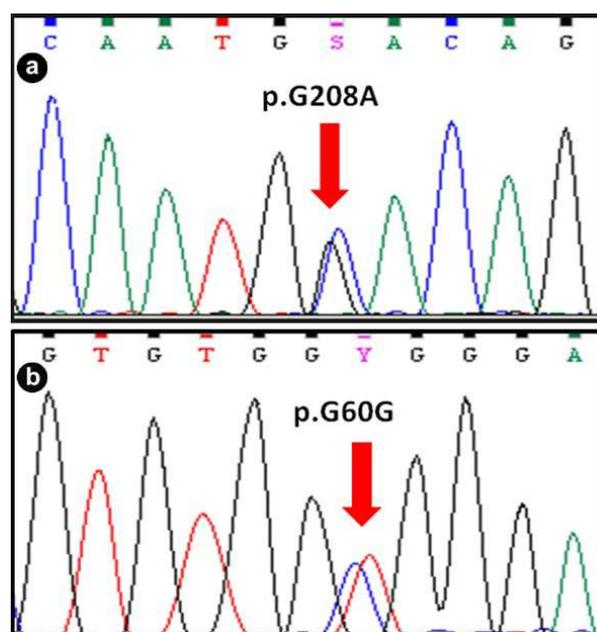


Figure 2. Sequence chromatograms of p.G208A mutation of cationic trypsinogen gene (*PRSS1*) (a.) and p.G60G mutation of chymotrypsin C gene (*CTRC*) (b.), both in heterozygous state.

and both mutations were present in his clinically healthy mother and absent in his father. In maternal grandmother without any history of pancreatitis the p.G208A mutation of *PRSS1* was confirmed (Figure 3).

DISCUSSION

To the best of our knowledge, this is the first description of a European patient with chronic pancreatitis associated with the p.G208A mutation of *PRSS1* gene. Our index patient and all members of his family were originally from Slovakia. In addition to this mutation, the child carries also the p.G60G variant of the *CTRC* gene in a heterozygous state.

Concerning the functional effect of this rare *PRSS1* variant, a recent study reported that the p.G208A mutation resulted in reduced trypsinogen secretion likely caused by mutation-induced misfolding [7]. This mechanism is different from those of the more frequent p.N29I and p.R122H mutations, which increase trypsinogen autoactivation and result in elevated intra-pancreatic trypsin activity [8]. Misfolding may result in endoplasmic reticulum stress which may explain the increased risk for pancreatitis, as described previously for the p.R116C and p.C139S mutations ([9], www.pancreasgenetics.org). To date, only 21 cases of pancreatitis associated with the p.G208A mutation have been reported, among them 18 patients were Japanese, 2 Korean and 1 had Asian origin not further specified [6, 10, 11]. Four patients carrying this variant had additional mutations in *CTRC* (p.R29Q), *SPINK1* (p.N34S) or *CFTR* (p.F508del, p.Q1352H) genes, suggesting that p.G208A is less penetrant than the p.N29I and p.R122H mutations and it may act as a strong risk factor in the context of other risk factors. This notion is supported by our finding of the p.G208A (*PRSS1*)/p.G60G (*CTRC*) trans-heterozygous status in the presented patient. The common synonymous

p.G60G variant of *CTRC* gene is associated with a 1.5-2-fold higher risk of chronic pancreatitis in the heterozygous state, compared with those carrying the wild-type allele. The risk is magnified to approximately 10-fold for homozygous individuals ([12], www.pancreasgenetics.org).

The p.G208A (*PRSS1*)/p.G60G (*CTRC*) trans-heterozygous status was also confirmed in the index patient's clinically healthy mother and grandmother. As chronic pancreatitis is a complex genetic disorder that develops through the interaction of environmental and genetic factors, this finding may be due to the effect of other unknown risk factors in the boy which are missing or act milder in his mother and grandmother.

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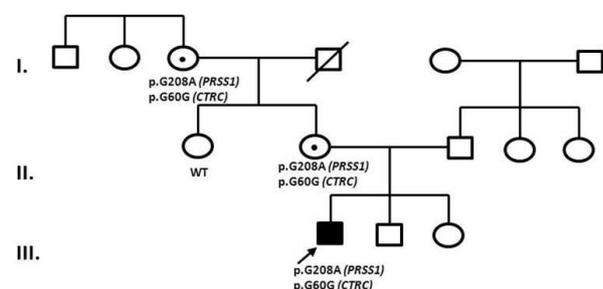


Figure 3. Pedigree of the family. Heterozygous carriers of the p.G208A mutation of cationic trypsinogen gene (*PRSS1*) and p.G60G mutation of chymotrypsin C gene (*CTRC*) are indicated. Subjects affected with chronic pancreatitis are shown by solid black symbols. The arrow points to the index patient. The central black dot signifies clinically healthy carriers of the p.G208A mutation of *PRSS1* and p.G60G mutation of *CTRC*. Crossed symbols designate deceased family members. WT: wild type

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