

## Case and Review

# Two *SPINK1* Mutations Induce Early-Onset Severe Chronic Pancreatitis

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## Keywords

SPINK1 · Acute pancreatitis · Chronic pancreatitis

## Abstract

The SPINK1 protein is a potent antiprotease that can inactivate any intrapancreatic trypsin activity that would otherwise induce autodigestion of the pancreas. *SPINK1* mutations have been recognized to be associated with chronic pancreatitis in patients without a family history of pancreatitis. We here describe the case of a 24-year-old woman referred to our service for recurrent abdominal pain and search for the cause of chronic calcifying pancreatitis, who was found to carry 2 *SPINK1* mutations.

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## Introduction

Acute pancreatitis is an inflammatory condition that usually affects a previously unaltered pancreas [1, 2]. In Western countries, common bile duct stone migration and alcohol abuse account for most cases of acute pancreatitis. Once the attack has occurred and the cause is treated, the gland will usually completely recover. On the other hand, recurrent attacks of pancreatitis or chronic pancreatitis may progressively alter the pancreatic parenchyma [3, 4]. Chronic pancreatitis is characterized by progressive loss of exocrine and endocrine functions that will ultimately lead to pancreas insufficiency with steatorrhea, weight loss, and diabetes [5]. Alcohol abuse, smoking, and autoimmune pancreatitis are the leading

causes of chronic pancreatitis. In 1996, hereditary pancreatitis was found to be caused by a mutation in the cationic trypsinogen gene *PRSS1* [6, 7]. However, *PRSS1* mutations explain only part of genetically transmitted disease, suggesting that other genes were involved in the pathogenesis of chronic pancreatitis. In 2000, the serine protease inhibitor Kazal type 1 (*SPINK1*) was identified as a second pancreatitis gene. The *SPINK1* protein is a potent anti-protease localized in the cytoplasm of acinar cells. Its function is to inactivate any intrapancreatic trypsin activity that would otherwise induce autodigestion of the gland [8]. The *SPINK1* mutation c.101A>G (p.Asn34Ser, commonly called N34S) has been recognized to be associated with chronic pancreatitis in patients without a family history of pancreatitis. N34S is a rare polymorphism, with a worldwide carrier frequency of 1–3%, and is a known predisposing or risk factor for chronic pancreatitis, although only a minority of carriers develop disease. Reports claim that 15–40% of patients with so-called idiopathic pancreatitis indeed carry N34S on one allele or on both alleles, and that little or no phenotypic differences between heterozygous and homozygous N34S patients have been detected so far [9]. A number of rarer *SPINK1* mutations are known (public mutation database at <http://www.uni-leipzig.de/pancreasmutation/db.html>).

## Case Report

We here describe the case of a 24-year-old woman referred to our service for recurrent abdominal pain and search for the cause of chronic calcifying pancreatitis, who was found to carry 2 *SPINK1* mutations. The first episode of abdominal pain appeared when she was 5 years old. From then on, she experienced 3–4 attacks/year consisting of epigastric pain with back irradiation as well as nausea and vomiting that usually lasted 3–4 days. By age 18, chronic calcifying pancreatitis was diagnosed on abdominal X-ray. A complete personal and family medical history was negative for hereditary pancreatitis. She was a mild smoker (1 pack/day) and stopped when she was referred to us. She generally drank <20 g alcohol/week. Clinical examination was normal. Her BMI was 19.6. Serum calcium, triglyceride, glucose, HbA1c, IgG4, total IgG, and rheumatoid factors were within normal range. MRI identified an enlarged main pancreatic duct 10 mm in size, multiple stenoses of branched ducts, and caudal atrophy (Fig. 1). Genomic DNA was extracted from blood by standard techniques and samples were tested for (1) 33 common CFTR variants, including the IVS8 5T variant (CFTR Genotyping Assay; Abbott Diagnostics, Baar, Switzerland), (2) *SPINK1* mutations (*SPINK1* exon 3), and (3) *PRSS1* mutations (ii and iii by PCR and bidirectional Sanger sequencing). *PRSS1* and CFTR results were normal. Exceptionally, 2 *SPINK1* mutations were identified: N34S (c.101A>G, p.Asn34Ser) and Y54H (c.160T>C, p.Tyr54His).

Several papers showed that the mutation N34S in the pancreatic secretory trypsin inhibitor gene was associated with idiopathic chronic pancreatitis. It is however unclear whether the N34S mutation can cause pancreatitis per se or whether it modifies the disease course. Y54H is a rare variant, previously identified in a Bangladeshi patient with tropical calcifying pancreatitis [10], that has been shown to almost eliminate *SPINK1* protein expression [11]. As other family members were not available, the phase of the 2 variants could not be determined; the formal genotype is NM\_003122.4:c.[101A>G(; )160T>C].

## Discussion

Mutations in the serine protease inhibitor Kazal type 1 (*SPINK1*) gene have been reported to lower the threshold for pancreatitis in the presence of other genetic or environmental factors. While mutations in the *SPINK1* gene have been excluded as the disease-causing mutations by 1 group, other groups have concluded that these are indeed associated with chronic pancreatitis [12]. The association of 2 *SPINK1* mutations in a patient with an early-onset, severe form of disease in the absence of any other evident risk factor suggests that, at least in some cases, such mutations can be causative of chronic pancreatitis. Early age of onset and/or a family history of pancreatitis should alert the physician to a possible underlying genetic cause of either acute or chronic pancreatitis. Early use of genetic testing can be useful in the early diagnosis and prognosis of pancreatic diseases, particularly in identifying an increased risk of progression of acute episodes to chronic pancreatitis.

The current case emphasizes the need to perform genetic testing in patients younger than 35 years, as is now recommended in various guidelines [9]. Increased understanding of disease pathogenesis could guide new and effective preventative and therapeutic interventions.

## Statement of Ethics

The current research complies with the guidelines for human studies and human regulations. The authors declare that the subject gave informed consent.

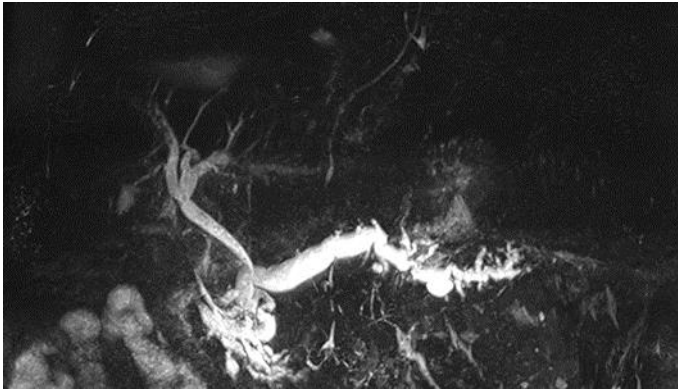
## Disclosure Statement

The authors have no conflict of interest to declare.

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**Fig. 1.** MRI: T2 sequence illustrating dilatation of the main pancreatic duct as well as branched ducts.