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Case Report

The SPINK1 c.101A>G variant in a 6-year-old with recurrent pancreatitis: causal mutation or phenotypic modifier?

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ABSTRACT

The serine peptidase inhibitor Kazal-type 1 (*SPINK1*) p.Asn34Ser variant is a pancreatitis risk factor often linked to a c.-4141G>T upstream enhancer mutation that reduces protective enzyme expression. Symptoms usually begin in late adolescence or early adulthood and typically require environmental triggers. Early pediatric presentation is exceptionally rare. A six-year-old male presented with recurrent periumbilical and epigastric abdominal pain. Investigations revealed elevated serum amylase and lipase levels and a mildly enlarged pancreas. Fecal elastase-1 testing indicated severe exocrine pancreatic insufficiency. There was a positive paternal history of early-adulthood pancreatitis. Confirmatory whole-exome sequencing identified a heterozygous c.101A>G (p.Asn34Ser) *SPINK1* mutation. Initial management included bowel rest, analgesics, and intravenous hydration, followed by pancreatic enzyme replacement therapy. Parents were counseled to strictly avoid environmental triggers, such as high-fat meals. At the six-month follow-up, the patient remained asymptomatic and pain-free, with successful weight gain. Identifying *SPINK1* variants in early-childhood recurrent pancreatitis is critical. Understanding its pathogenic mechanism, potentially driven by linked upstream regulatory mutations, guides targeted interventions. Early enzyme replacement and strict trigger avoidance are essential to prevent future attacks and to optimize pediatric growth.

Keywords: SPINK1, Recurrent pancreatitis, Hereditary pancreatitis, Trypsin

INTRODUCTION

Hereditary pancreatitis is primarily characterized by genetic mutations-including those in the *PRSS1*, *SPINK1*, *CFTR*, and *CTRC* genes-that facilitate the premature activation of trypsin within the pancreatic ducts.[1] The *SPINK1* (Serine peptidase inhibitor Kazal-type 1) gene encodes the pancreatic secretory trypsin inhibitor (PSTI), which acts as a primary cellular defense by physically and competitively blocking the active site of prematurely activated trypsin.[2] The *SPINK1* c.101A>G (p.Asn34Ser) variant is present in approximately 1% to 2% of the general population. While the mean age of symptom onset among carriers usually occurs in the late teens or twenties, early pediatric-onset cases are exceptionally rare.

CASE REPORT

A 6-year-old male, born of a non-consanguineous marriage, presented with a 3-day history of periumbilical and epigastric abdominal pain. Abdominal examination revealed a soft abdomen with no tenderness or organomegaly. One month prior, he had been diagnosed with acute pancreatitis at an external facility, characterized by markedly elevated serum amylase (2,482 U/l) and lipase (17,963 U/l). Computed tomography at that time revealed acute interstitial pancreatitis with a severity score of 2/10. On current admission, serum amylase (415 U/l) and lipase (206 U/l) levels were elevated but showed a downward trend compared with the previous admission. Secondary aetiologies, including

hypercalcemia, hyperparathyroidism, and hyperlipidemia, were excluded.

Magnetic resonance cholangiopancreatography revealed a mildly bulky pancreas (Figure 1) and a prominent main pancreatic duct. Functional evaluation demonstrated severe exocrine pancreatic insufficiency, evidenced by a low fecal elastase-1 level of 71.59 µg/g (reference >200 µg/g). The patient had a significant family history; his father was diagnosed with pancreatitis in early adulthood and subsequently died by suicide following alcohol intoxication. Given the early age of onset and positive family history, we performed whole-exome sequencing (WES). Genetic analysis identified a heterozygous c.101A>G (p.Asn34Ser) mutation in Exon 3 of the *SPINK1* gene.

Management and outcome

The patient was initially managed with bowel rest, analgesics, and intravenous hydration. Following clinical improvement, oral feeds were gradually reintroduced. To manage the documented EPI, pancreatic enzyme replacement therapy was initiated with Pancreatin 10,000 units thrice daily with meals.

Parents were counselled on the genetic nature of the disease and the role of SPINK1 as a disease modifier that lowers the threshold for inflammation in the presence of environmental triggers. They were advised to avoid environmental stressors and dietary stimulants, such as high-fat meals. At the 6-month follow-up, the patient remained asymptomatic and pain-free and had achieved successful weight gain.

DISCUSSION

The *SPINK1* (Serine peptidase inhibitor Kazal-type 1) gene encodes the PSTI. PSTI is synthesized by acinar cells and co-packaged into zymogen granules with trypsinogen.[2] It provides a first-line defense by physically and competitively blocking the active site of prematurely activated trypsin. PSTI can neutralize approximately 20% of the total potential trypsin activity within the organ.[3]

The common *SPINK1* c.101A>G (p.Asn34Ser) variant is present in approximately 1% to 2% of the general population. Carrying this variant does not automatically cause the disease, as it has low penetrance and many carriers remain healthy throughout their lives. Although N34S was originally thought to reduce trypsin inhibitory capacity, in vitro testing has shown that the mutation is functionally neutral.[4] Recent evidence has identified a functional enhancer variant, c.-4141G >T (rs142703147:C >A), located approximately 4 kb upstream of the *SPINK1* promoter. This variant resides within an evolutionarily conserved HNF1A-PTF1L cis-regulatory module (Figure 1). The mutation disrupts a PTF1L-binding site, which leads to significantly reduced *SPINK1* gene expression and lower PSTI production.[5] This imbalance results in inadequate trypsin inactivation and a higher risk of autodigestion.

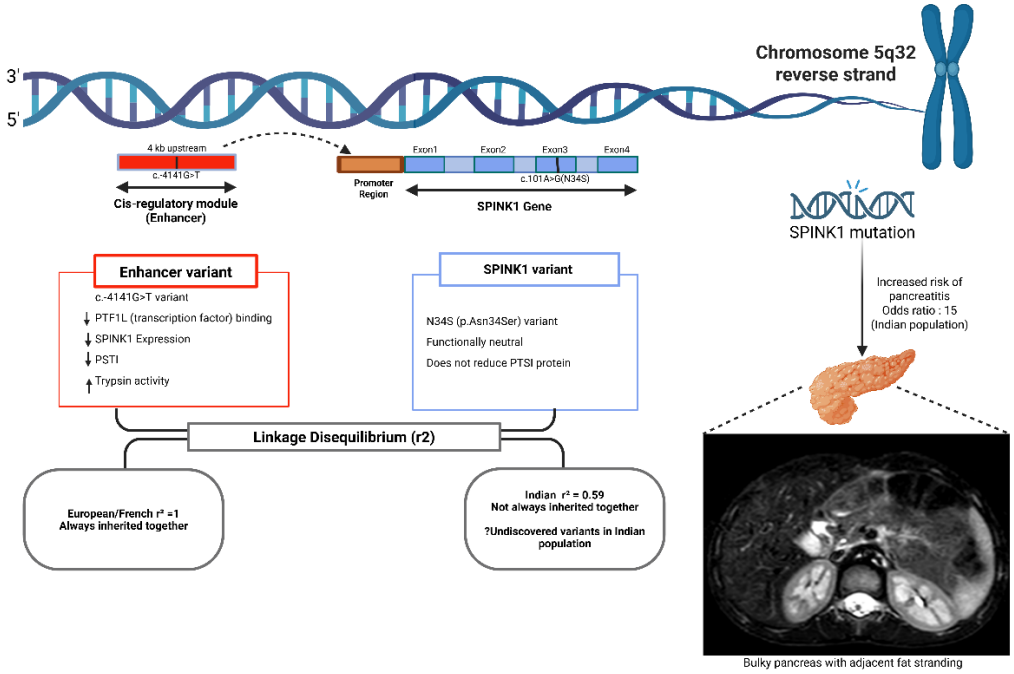


Figure 1: Genomic architecture and linkage disequilibrium of SPINK1 N34S haplotype.

*SPINK1 N34S(c.101A>G) is in strong linkage disequilibrium in the European population with the enhancer variant but not in the Indian population. SPINK1: serine protease inhibitor Kazal type 1; PSTI: Pancreatic Secretory Trypsin Inhibitor; PTF1L: Pancreas-specific Transcription Factor 1-L.

In European and French populations, the c.-4141G >T enhancer variant is in perfect linkage disequilibrium (r^2=1) with the c.101A>G (p.Asn34Ser) variant. However, in the Indian population, the correlation is significantly lower (r^2=0.59).[6] A study of Indian patients with chronic pancreatitis found that the c.101A>G (p.Asn34Ser) variant had a slightly higher odds ratio (15.12) than the enhancer variant (14.82). This finding is considered counterintuitive and may be due to sampling error, complex population stratification, or the presence of a third, unidentified variant that is more strongly linked to c.101A>G (p.Asn34Ser) variant in our population.

The *SPINK1* c.101A>G (p.Asn34Ser) variant is typically viewed as a disease modifier or risk factor rather than a direct cause.[7] The development of the disease often requires a "second hit," such as co-existing mutations in genes like *CFTR* or *CTRC* (trans-heterozygosity) or environmental triggers. While the mean age of symptom onset among carriers is often in the late teens or twenties, early pediatric-onset cases, as in our case, are rare. Environmental triggers of pancreatitis include obesity, alcohol consumption, smoking, high-fat meals, viral infections (EBV, influenza), abdominal trauma, oxidative stress (petrochemical fume exposure, micronutrient deficiency), and associated concurrent illness. Knowledge of these triggers is important for patients, as avoiding the first event can prevent or delay the onset of pancreatitis.

Therapeutic research is currently focused on gene-based interventions. Experimental models have used adeno-associated virus type 8 (AAV8) vectors to overexpress the human *SPINK1* protein, which significantly reduced the severity of pancreatitis and fibrosis in mice.[8] Other strategies under investigation include "intron-mediated enhancement" to boost mRNA expression and CRISPR/Cas9 gene editing to directly correct pathogenic variants, such as the c.-4141G >T enhancer variant. These gene therapy options offer exciting opportunities for treating these patients in the future.

CONCLUSION

This case highlights an exceptionally rare early childhood presentation of recurrent pancreatitis associated with the *SPINK1* c.101A>G (p.Asn34Ser) variant, a condition that typically does not manifest until late adolescence or early adulthood. It underscores the critical value of early whole-exome sequencing in pediatric patients presenting with unexplained recurrent abdominal pain and severe exocrine pancreatic insufficiency. Crucially, the case emphasizes the importance of understanding the variant's underlying pathogenic mechanism, linked to a functional enhancer mutation (c.-4141G >T) upstream of the *SPINK1* promoter. This upstream variant disrupts gene expression and reduces the production of protective PSTI, acting as a key disease modifier that lowers the threshold for inflammation. Recognizing this complex genetic interplay allows clinicians to implement early, targeted interventions-such as enzyme replacement therapy and strict avoidance of environmental triggers-that are essential for preventing future attacks and optimizing pediatric growth and development.

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