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Unexplained Pediatric Recurrent Acute Pancreatitis Associated With a Likely Pathogenic *CFTR* Splice-Site Variant Without Classical Cystic Fibrosis Features: A Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Female, 7-year-old
Final Diagnosis: Recurrent acute pancreatitis of undetermined etiology
Symptoms: Recurrent abdominal pain • epigastric pain • vomiting
Clinical Procedure: —
Specialty: Pediatrics and Neonatology
Objective: Unknown etiology
Background: Recurrent acute pancreatitis in children requires systematic evaluation for structural, metabolic, autoimmune, and genetic etiologies. When standard etiologic evaluation is unrevealing, phenotype-driven pancreatitis-panel testing may identify clinically relevant *CFTR*-associated findings, even in children without classical cystic fibrosis features.
Case Report: We report a case of a 7-year-old Vietnamese girl with 4 episodes of acute pancreatitis over 3 years, beginning at 4 years of age. Each episode required hospitalization and resolved completely with conservative treatment. She had no recurrent respiratory infections, chronic cough, chronic diarrhea, steatorrhea, or failure to thrive. During the fourth episode, magnetic resonance imaging showed acute pancreatitis with pancreatic enlargement and a 10-mm peripancreatic fluid collection, without pancreatic duct dilation, biliary dilation, or pancreaticobiliary malformation. Serum calcium and triglycerides were normal, autoimmune investigations were unremarkable, and fecal elastase indicated preserved exocrine pancreatic function. Targeted next-generation sequencing using a pancreatitis-associated gene panel identified a heterozygous *CFTR* splice-site region variant, NM_000492.4: c.1210-11T>G, classified by the diagnostic laboratory as likely pathogenic and confirmed by Sanger sequencing. A heterozygous *SPINK1* p.Asn34Ser variant, classified as a variant of uncertain significance, was also detected. No further pancreatitis requiring hospitalization was documented during 12 months of follow-up.
Conclusions: This case illustrates that phenotype-driven pancreatitis-panel testing can identify clinically relevant *CFTR*-associated findings in children with recurrent acute pancreatitis after standard evaluation is unrevealing. The identified *CFTR* variant supports a possible *CFTR*-related contribution to a pancreas-predominant phenotype but should be interpreted as hypothesis-supporting rather than establishing causality in the absence of sweat chloride testing, functional studies, and parental segregation analysis.
Keywords: Case Reports • Child • Cystic Fibrosis Transmembrane Conductance Regulator • Genetic Testing • Nucleotide Sequencing • Pancreatitis
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Introduction

Acute recurrent pancreatitis (ARP) in children is an uncommon but clinically important condition that requires a systematic search for underlying causes. According to the INSPPIRE definitions, pediatric ARP is characterized by at least 2 distinct episodes of acute pancreatitis, with complete resolution of symptoms or normalization of pancreatic enzymes between attacks and without evidence of irreversible structural pancreatic damage [1]. Unlike adult pancreatitis, in which alcohol and smoking are major contributors, pediatric ARP is more often associated with pancreaticobiliary anatomical abnormalities, metabolic disturbances, autoimmune disease, and genetic susceptibility [2,3].

Identifying the etiology of pediatric ARP is clinically relevant because recurrent inflammatory episodes can progress to chronic pancreatitis or lead to long-term pancreatic sequelae, including chronic abdominal pain, exocrine pancreatic insufficiency, nutritional impairment, and endocrine dysfunction [2-4]. Consensus recommendations therefore support a structured evaluation that includes assessment for structural pancreaticobiliary abnormalities, metabolic causes, autoimmune disease, and pancreatitis-associated genetic risk factors when first-line investigations do not reveal a clear cause [2,3].

Among pancreatitis-associated genes, *CFTR* is of particular interest. Biallelic pathogenic *CFTR* variants are classically associated with cystic fibrosis; however, *CFTR* dysfunction can also present as *CFTR*-related disorders, defined as clinical entities associated with *CFTR* dysfunction that do not fulfill diagnostic criteria for cystic fibrosis [5,6]. Pancreatic manifestations can occur without classical respiratory or malabsorptive features, particularly in individuals with residual exocrine pancreatic function [7-9]. This creates a diagnostic challenge because recurrent pancreatitis can be the predominant clinical manifestation associated with *CFTR* dysfunction in individuals who lack classical cystic fibrosis features.

Here, we report the case of a 7-year-old Vietnamese girl with recurrent acute pancreatitis in whom standard etiologic evaluation was unrevealing. Subsequent phenotype-driven testing using a targeted pancreatitis-associated gene panel identified a heterozygous *CFTR* splice-site region variant (NM_000492.4: c.1210-11T>G), classified by the diagnostic laboratory as likely pathogenic and confirmed by Sanger sequencing. This case report shows that phenotype-driven pancreatitis-panel testing can identify clinically relevant *CFTR*-associated findings in children with recurrent acute pancreatitis after standard etiologic evaluation is unrevealing. The observed genotype–phenotype association supports biological plausibility for a possible *CFTR*-related contribution to recurrent acute pancreatitis but should be interpreted as hypothesis-supporting rather than establishing causality.

Case Report

A previously healthy 7-year-old Vietnamese girl was admitted to a tertiary pediatric hospital with severe epigastric abdominal pain. This admission was her fourth episode of acute pancreatitis within 3 years, with the first episode occurring at 4 years of age. The first 2 episodes occurred at 4 years of age, approximately 6 months apart, and were diagnosed and treated as acute pancreatitis at local hospitals. Detailed admission laboratory and imaging data from these 2 admissions were not available from retrospective records. The third episode occurred at 6 years of age and was associated with abdominal pain and vomiting; serum amylase was 842.51 U/L, serum lipase was 1258.46 U/L, and abdominal ultrasonography showed pancreatic enlargement. All previous episodes required hospitalization, were managed supportively, and resolved clinically. Between episodes, she had no abdominal pain or other persistent symptoms and maintained normal oral intake and daily activities. The clinical timeline is summarized in **Figure 1**, and comparative episode-level documentation is provided in **Table 1**.

The patient had no history of abdominal trauma, pancreatitis-associated medication exposure, gallstone disease, recurrent respiratory infections, chronic cough, chronic diarrhea, steatorrhea, or failure to thrive. No family history of recurrent pancreatitis, cystic fibrosis, chronic pulmonary disease, or other known hereditary disorders was reported.

On admission, physical examination revealed epigastric tenderness without signs of peritoneal irritation. Laboratory investigations were consistent with acute pancreatitis, with a serum amylase level of 988 IU/L and a serum lipase level greater than 3000 IU/L. Serum calcium was within the reference range, and the serum triglyceride concentration was 0.76 mmol/L (reference range, 0.51-2.38 mmol/L), making hypercalcemia- and hypertriglyceridemia-associated pancreatitis unlikely. Autoimmune investigations, including serum IgG4 and autoantibody testing, were unremarkable. Fecal elastase was 294.43 µg/g stool, indicating preserved exocrine pancreatic function. Available liver function tests during the acute pancreatitis episodes were within the applicable reference ranges; however, liver function testing was not performed between episodes.

Magnetic resonance imaging of the hepatobiliary system demonstrated pancreatic enlargement with a 10-mm peripancreatic fluid collection, consistent with acute pancreatitis. No pancreatic necrosis was identified. The main pancreatic duct was not dilated, and no pancreaticobiliary malformation or biliary dilation was detected. The systematic etiologic evaluation is summarized in **Table 2**.

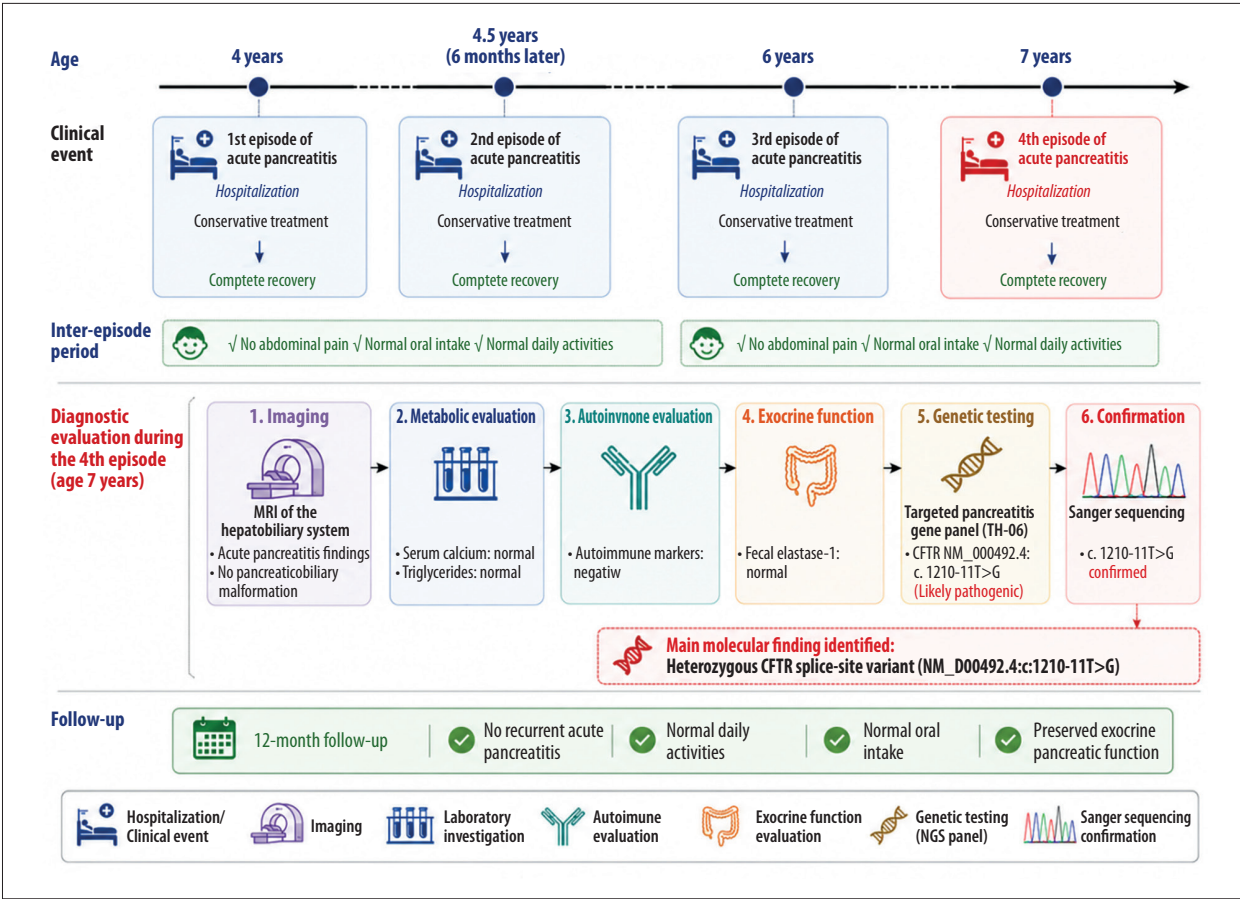


Figure 1. Clinical timeline of recurrent acute pancreatitis, diagnostic evaluation, and CFTR-associated molecular finding. The patient experienced 4 episodes of acute pancreatitis requiring hospitalization between 4 and 7 years of age. Complete clinical recovery occurred after each episode, with no abdominal pain or functional impairment between attacks. During the fourth episode, magnetic resonance imaging showed acute pancreatitis without pancreaticobiliary structural abnormalities, while metabolic and autoimmune investigations were unremarkable. Targeted next-generation sequencing using a pancreatitis-associated gene panel identified a heterozygous *CFTR* splice-site region variant, NM_000492.4: c.1210-11T>G, which was confirmed by Sanger sequencing. No further episode of acute pancreatitis was documented during 12 months of follow-up. AP, acute pancreatitis; MRI, magnetic resonance imaging; NGS, next-generation sequencing.

Given the recurrent episodes of acute pancreatitis and unrevealing standard etiologic evaluation, phenotype-driven genetic testing was performed using a targeted next-generation sequencing pancreatitis panel (TH-06), comprising *APOA5*, *CFTR*, *CTRC*, *GPIHBP1*, *PRSS1*, *SPINK1*, and *UBR1*. This stepwise diagnostic approach is illustrated in **Figure 2**. The targeted pancreatitis panel identified a heterozygous splice-site region variant in *CFTR* (NM_000492.4: c.1210-11T>G), classified by the diagnostic laboratory as likely pathogenic and subsequently confirmed by Sanger sequencing. The panel also detected a heterozygous *SPINK1* variant (NM_001379610.1: c.101A>G; p.Asn34Ser), which was classified as a variant of uncertain significance. The molecular findings are summarized in **Table 3**, and the Sanger-confirmed *CFTR* variant is shown in **Figure 3**.

The patient was managed conservatively with bowel rest, intravenous fluid therapy, analgesia, and gradual reintroduction of enteral feeding. Her abdominal pain resolved completely, and pancreatic enzyme levels normalized, with serum amylase decreasing to 83 IU/L and serum lipase to 53 IU/L. She was discharged in stable clinical condition.

During 12 months of follow-up, no further episode of acute pancreatitis requiring hospitalization was documented. The patient remained clinically well, with no abdominal pain between follow-up visits and she had preserved exocrine pancreatic function. No respiratory symptoms or other clinical features suggestive of classical cystic fibrosis were observed during follow-up.

Table 1. Comparative clinical documentation of the 4 acute pancreatitis episodes.

Episode	Age/time of occurrence	Presenting symptoms	Hospitalization	Laboratory findings
1	4 years	Abdominal pain and vomiting	5 days at a local hospital	Detailed admission enzyme values were not available from retrospective records
2	Approximately 6 months after episode 1	Abdominal pain	7 days at a local hospital	Detailed admission enzyme values were not available from retrospective records
3	6 years	Abdominal pain and vomiting	10 days at a local hospital	Amylase 842.51 U/L; lipase 1258.46 U/L
4	7 years	Severe epigastric abdominal pain with epigastric tenderness	8 days	Amylase 988 U/L; lipase > 3000 U/L; calcium and triglycerides normal; autoimmune investigations unremarkable; fecal elastase 294.43 µg/g stool
Episode	Age/time of occurrence	Imaging findings	Treatment	Recovery and inter-episode status
1	4 years	Detailed admission imaging findings were not available from retrospective records	Supportive treatment	Symptoms resolved by discharge. The patient was asymptomatic between episodes
2	Approximately 6 months after episode 1	Detailed admission imaging findings were not available from retrospective records	Supportive treatment	Symptoms resolved by discharge, with normalization of pancreatic enzymes. The patient was asymptomatic between episodes
3	6 years	Abdominal ultrasonography showed pancreatic enlargement	Supportive treatment	Symptoms resolved by discharge. At follow-up, amylase, lipase, and abdominal ultrasonography were normal. The patient was asymptomatic after recovery
4	7 years	MRI showed pancreatic enlargement with a 10-mm peripancreatic fluid collection; no pancreatic necrosis, pancreatic duct dilation, biliary dilation, or pancreaticobiliary malformation	Bowel rest, intravenous fluid therapy, analgesia, and gradual reintroduction of enteral feeding	Symptoms resolved completely; amylase decreased to 83 U/L and lipase to 53 U/L. No further pancreatitis requiring hospitalization was documented during 12 months of follow-up

MRI, magnetic resonance imaging. The first 2 episodes were diagnosed and treated as acute pancreatitis at local hospitals; however, detailed admission laboratory and imaging data from these admissions were not available from retrospective records.

Discussion

This case shows how phenotype-driven pancreatitis-panel testing can identify clinically relevant *CFTR*-associated findings in a child with recurrent acute pancreatitis after standard etiologic evaluation was unrevealing. Rather than demonstrating a definitive genetic etiology, this case supports the clinical value

of a structured diagnostic approach in selecting appropriate molecular testing and illustrates a pancreas-predominant phenotype compatible with a possible *CFTR*-related contribution in the absence of classical cystic fibrosis features. According to the INSPPIRE definitions, pediatric acute recurrent pancreatitis is diagnosed when a child has at least 2 distinct episodes of acute pancreatitis, with complete resolution of pain

Table 2. Systematic etiologic evaluation and diagnostic implications.

Etiological domain	Investigation	Findings	Diagnostic implication
Structural/anatomical	Hepatobiliary magnetic resonance imaging	Acute pancreatitis with pancreatic enlargement and a 10-mm peripancreatic fluid collection; no pancreatic duct dilation, biliary dilation, or pancreaticobiliary malformation	No evidence of a structural pancreaticobiliary cause
Metabolic	Serum calcium and triglycerides	Calcium within reference range; triglycerides 0.76 mmol/L (reference range, 0.51-2.38 mmol/L)	Hypercalcemia- or hypertriglyceridemia-associated pancreatitis not supported
Autoimmune	Serum IgG4 and autoantibody testing	Unremarkable	Autoimmune pancreatitis not supported
Exocrine pancreatic function	Fecal elastase	294.43 µg/g stool, within the normal range	Preserved exocrine pancreatic function
Genetic	Targeted next-generation sequencing pancreatitis panel (TH-06), followed by Sanger confirmation	Heterozygous <i>CFTR</i> NM_000492.4: c.1210-11T>G, classified as likely pathogenic; heterozygous <i>SPINK1</i> NM_001379610.1: c.101A>G (p.Asn34Ser), classified as a variant of uncertain significance	Molecular findings support a possible <i>CFTR</i> -related contribution to recurrent acute pancreatitis; the clinical significance of the <i>SPINK1</i> variant remains uncertain.

This table summarizes the structured etiologic evaluation performed during the fourth episode of acute pancreatitis. *CFTR*, cystic fibrosis transmembrane conductance regulator; IgG4, immunoglobulin G4; *SPINK1*, serine protease inhibitor Kazal type 1.

or normalization of pancreatic enzymes between episodes and without evidence of irreversible structural pancreatic damage [1,2]. Our patient fulfilled these criteria, with 4 discrete episodes requiring hospitalization between 4 and 7 years of age, complete clinical recovery between attacks, and no persistent inter-episode symptoms, as summarized in **Table 1**. The absence of persistent abdominal pain, impaired oral intake, or functional limitation between episodes supported an acute recurrent rather than established chronic pancreatitis phenotype.

A major strength of this case report is that genetic testing was undertaken after a systematic evaluation of common etiologic domains had not identified an alternative explanation for recurrent pancreatitis. Pediatric recurrent pancreatitis differs from adult disease because alcohol- and smoking-related causes are uncommon, whereas structural pancreaticobiliary abnormalities, metabolic disorders, autoimmune disease, and genetic susceptibility account for a greater proportion of cases [2-4]. In our patient, magnetic resonance imaging documented acute pancreatitis but did not show pancreatic duct dilation, biliary dilation, pancreaticobiliary malformation, or necrosis [10]. Metabolic causes were not supported because serum calcium was within the reference range and triglyceride concentration was normal. Autoimmune evaluation was unremarkable, and fecal elastase was within the normal range, indicating preserved exocrine pancreatic function. This diagnostic sequence is consistent with consensus recommendations that children with recurrent or chronic pancreatitis should be

evaluated for structural, metabolic, autoimmune, and genetic risk factors when the etiology remains unclear [2,3].

The decision to use a targeted pancreatitis gene panel was guided by the patient's phenotype of early-onset recurrent acute pancreatitis after systematic evaluation had not identified a structural, metabolic, or autoimmune cause. In the INSPPIRE cohort, pancreatitis-associated genetic variants were frequently identified in children with acute recurrent and chronic pancreatitis, supporting the contribution of genetic susceptibility to pediatric disease [3,4]. A phenotype-driven panel is useful in this setting because it focuses on genes with established relevance to pancreatitis, reduces the likelihood of unrelated incidental findings, and facilitates clinically oriented interpretation. In the present case, the TH-06 panel included *APOA5*, *CFTR*, *CTRC*, *GPIHBP1*, *PRSS1*, *SPINK1*, and *UBR1*, providing an appropriate molecular investigation for the observed clinical phenotype rather than a comprehensive genomic evaluation.

The principal molecular finding was a heterozygous *CFTR* splice-site region variant, NM_000492.4: c.1210-11T>G, which was classified by the diagnostic laboratory as likely pathogenic according to an ACMG/AMP-based interpretation and subsequently confirmed by Sanger sequencing [11,12]. The diagnostic report noted that this variant had been recorded as pathogenic/likely pathogenic in ClinVar, and current ClinVar records classify NM_000492.4(CFTR): c.1210-11T>G as pathogenic/likely pathogenic, with criteria provided by multiple submitters and

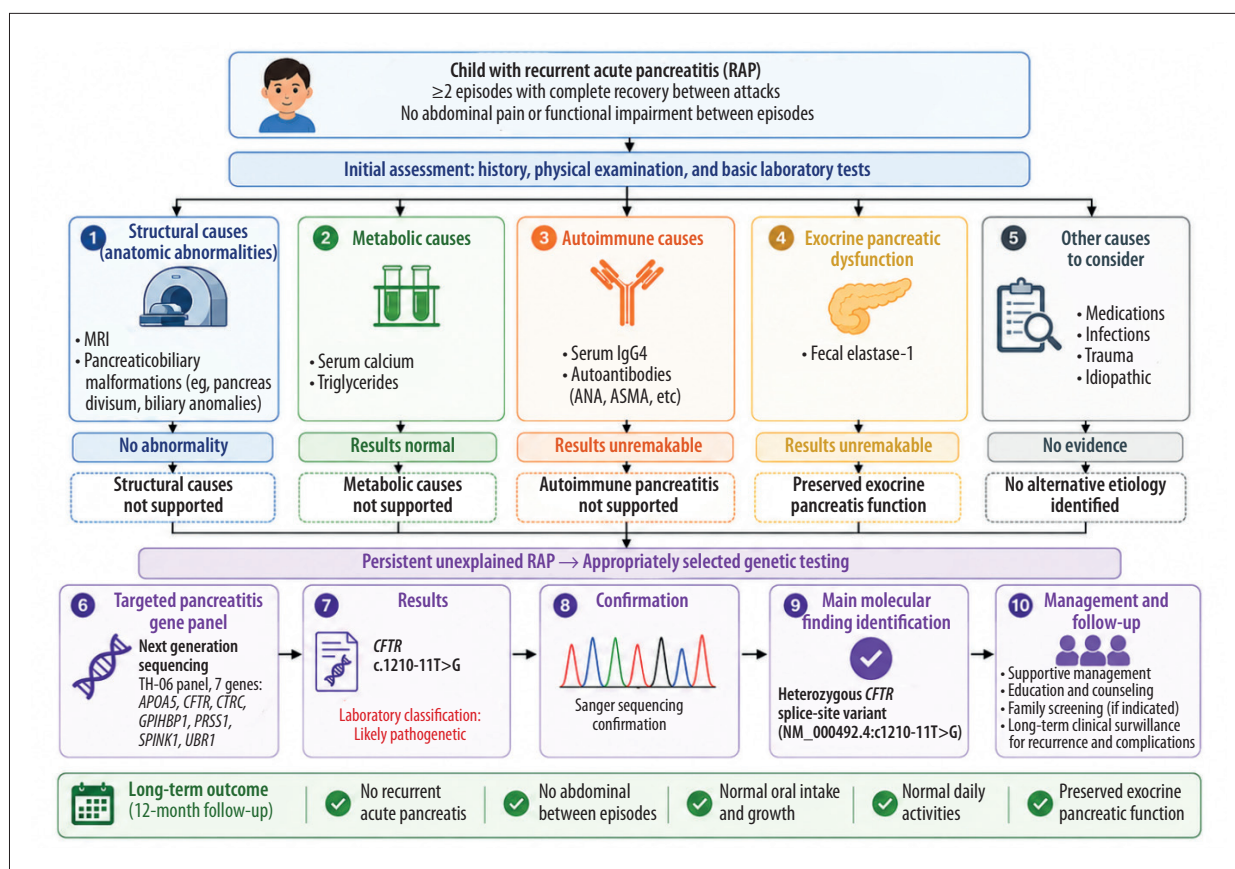


Figure 2. Stepwise diagnostic approach to recurrent acute pancreatitis in children, illustrated by the present case. The diagnostic pathway summarizes a structured etiologic evaluation for children with recurrent acute pancreatitis. After confirmation of recurrent attacks with complete clinical recovery between episodes, common etiologic domains were assessed, including structural pancreaticobiliary abnormalities, metabolic disorders, autoimmune pancreatitis, and exocrine pancreatic function. In the absence of an identifiable cause, targeted next-generation sequencing using the TH-06 pancreatitis panel was performed. The panel included *APOA5*, *CFTR*, *CTRC*, *GPIHBP1*, *PRSS1*, *SPINK1*, and *UBR1* and identified a heterozygous *CFTR* splice-site region variant, NM_000492.4: c.1210-11T>G, which was confirmed by Sanger sequencing. This figure summarizes the diagnostic reasoning applied in the present case and is intended as an educational illustration rather than a clinical practice guideline. ANA, antinuclear antibody; ASMA, anti-smooth muscle antibody; *CFTR*, cystic fibrosis transmembrane conductance regulator; IgG4, immunoglobulin G4; MRI, magnetic resonance imaging; NGS, next-generation sequencing; RAP, recurrent acute pancreatitis; *SPINK1*, serine protease inhibitor Kazal type 1.

no conflicts [13]. Because the initial next-generation sequencing report indicated suboptimal signal quality at this locus, Sanger confirmation was performed. However, the diagnostic report did not provide the specific ACMG/AMP evidence codes used for classification. Therefore, the laboratory-assigned classification should be interpreted in conjunction with the clinical phenotype rather than as definitive evidence of causality. *CFTR* variant interpretation remains clinically complex because *CFTR* is associated with classical cystic fibrosis, *CFTR*-related disorders, carrier states, and pancreatitis susceptibility with variable penetrance [5-7,12].

The biological plausibility of a *CFTR*-related contribution is supported by the role of *CFTR* in pancreatic ductal chloride, bicarbonate, and fluid secretion. Impaired *CFTR*-mediated

bicarbonate transport can alter ductal fluid alkalization and viscosity, potentially contributing to protein plugging, ductal obstruction, and susceptibility to pancreatitis [14,15]. These mechanisms support a possible *CFTR*-related contribution in the present case but do not prove that the specific variant identified in this patient was the sole cause of disease. Without sweat chloride testing, *CFTR* functional assays, RNA studies, or parental segregation analysis, the available evidence cannot distinguish between carrier-associated susceptibility, a *CFTR*-related disorder, and a broader multifactorial genetic predisposition. Accordingly, the Sanger-confirmed, likely pathogenic *CFTR* splice-site region variant is best interpreted as supportive of a possible *CFTR*-related contribution to the recurrent pancreatitis phenotype rather than as evidence of definitive single-variant causality.

Table 3. Molecular findings from the targeted pancreatitis gene panel.

Gene	Transcript/HGVS nomenclature	Zygosity	Predicted consequence	Laboratory classification	Clinical interpretation
<i>CFTR</i>	NM_000492.4: c.1210-11T>G	Heterozygous	Intronic splice-site region variant	Likely pathogenic	Main molecular finding supporting a possible <i>CFTR</i> -related contribution to recurrent acute pancreatitis; confirmed by Sanger sequencing
<i>SPINK1</i>	NM_001379610.1: c.101A>G; p.Asn34Ser	Heterozygous	Missense variant	Variant of uncertain significance	Clinical significance uncertain; not used as a standalone diagnostic basis

HGVS nomenclature is reported according to the transcript specified in the diagnostic laboratory report. Variant classification was provided by the diagnostic laboratory using the ACMG/AMP framework. The *CFTR* NM_000492.4: c.1210-11T>G variant was confirmed by Sanger sequencing. ACMG/AMP, American College of Medical Genetics and Genomics/Association for Molecular Pathology; HGVS, Human Genome Variation Society.

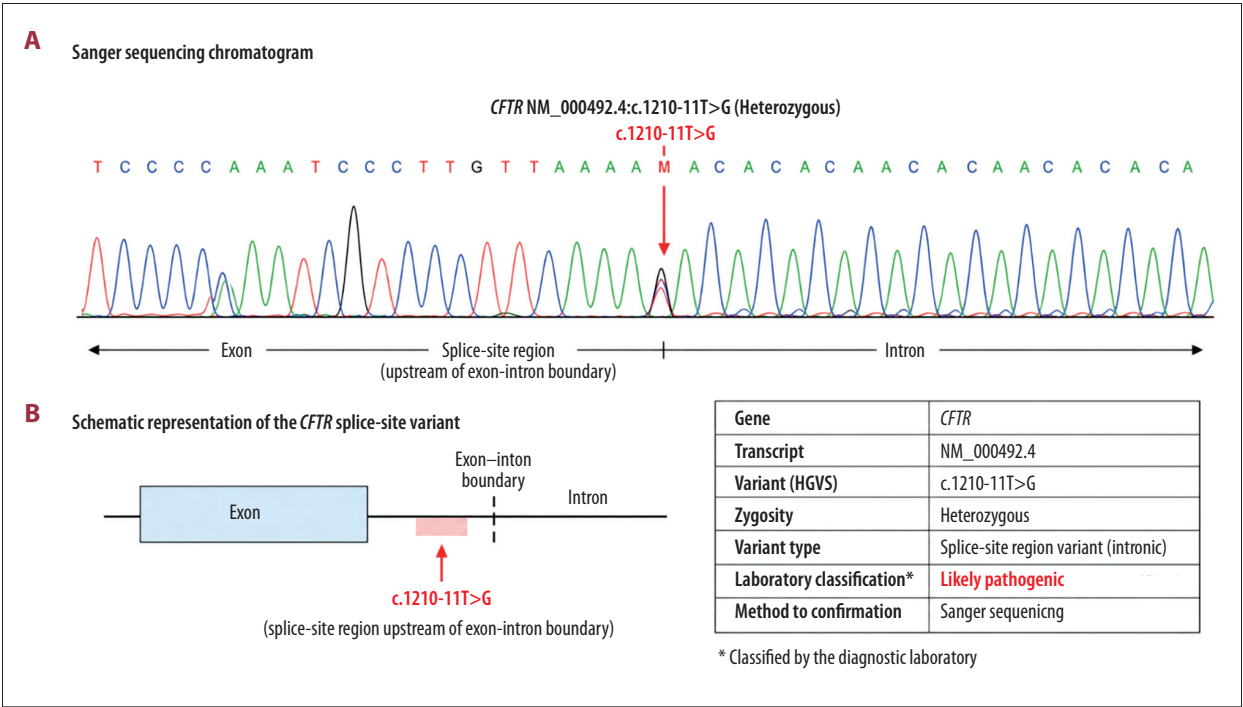


Figure 3. Molecular characterization of the *CFTR* variant identified in the present patient. (A) Sanger sequencing chromatogram confirming the heterozygous *CFTR* splice-site region variant NM_000492.4: c.1210-11T>G, which was initially detected by targeted next-generation sequencing using the TH-06 pancreatitis gene panel. The arrow indicates the position of the nucleotide substitution. (B) Schematic representation of the variant located within the splice-site region immediately upstream of the exon-intron boundary of the *CFTR* gene. The identified variant was classified by the diagnostic laboratory as likely pathogenic according to the ACMG/AMP variant interpretation framework and was confirmed by Sanger sequencing.

The clinical phenotype in this patient was pancreas-predominant and did not resemble classical cystic fibrosis. She had no recurrent respiratory infections, chronic cough, chronic diarrhea, steatorrhea, failure to thrive, or impaired exocrine pancreatic function. *CFTR*-related disorders are generally defined as clinical entities associated with *CFTR* dysfunction that do

not fulfill diagnostic criteria for cystic fibrosis [5]. Pancreatitis can be a presenting or predominant manifestation of *CFTR* dysfunction, particularly in individuals with residual exocrine pancreatic function [7-9]. Therefore, the normal fecal elastase result in this patient does not argue against a possible *CFTR*-associated pancreatic phenotype; rather, it indicates

that exocrine pancreatic function was preserved at the time of evaluation.

At the same time, the absence of respiratory or malabsorptive manifestations should not be interpreted as definitive exclusion of cystic fibrosis. Current diagnostic recommendations emphasize assessment of *CFTR* function, particularly sweat chloride testing, when evaluating clinical conditions associated with *CFTR* variants [6,7]. Sweat chloride testing was not performed because it was unavailable at the treating institution during the patient's diagnostic evaluation. Therefore, classical cystic fibrosis cannot be excluded on functional grounds. Consequently, the case is best described as recurrent acute pancreatitis with a pancreas-predominant phenotype compatible with a possible *CFTR*-related contribution, rather than as a confirmed *CFTR*-related disorder or a genetically established diagnosis.

The additional *SPINK1* finding also requires cautious interpretation. The targeted panel identified a heterozygous *SPINK1* variant, NM_001379610.1: c.101A>G, resulting in p.Asn34Ser, which was classified by the diagnostic laboratory as a variant of uncertain significance. Under the ACMG/AMP framework, a variant of uncertain significance should not be used as a standalone basis for clinical diagnosis or major clinical decision-making [11]. Previous studies have associated the *SPINK1* p.Asn34Ser variant with recurrent acute pancreatitis and chronic pancreatitis, but its role is generally considered that of a susceptibility factor or disease modifier rather than a fully penetrant monogenic cause [16,17]. In the present case, the coexistence of *CFTR* and *SPINK1* variants is compatible with a multifactorial genetic susceptibility model, but the available data do not allow determination of whether *SPINK1* contributed independently to the phenotype. Therefore, no causal inference should be made from the *SPINK1* variant alone.

This case has practical implications for pediatric care and illustrates the value of a structured diagnostic pathway in a Vietnamese child with recurrent acute pancreatitis. First, recurrent pancreatitis in childhood should not be managed only as repeated isolated attacks; it should prompt a structured etiologic evaluation when first-line investigations are unrevealing. Second, the normal growth, absence of respiratory symptoms, and preserved fecal elastase do not exclude a possible *CFTR*-associated pancreas-predominant phenotype. Third, genetic findings should be interpreted in clinical context, particularly when more than 1 pancreatitis-associated variant is detected and when 1 variant is classified as uncertain. Long-term follow-up remains important because children with acute recurrent pancreatitis can progress to chronic pancreatitis or develop pancreatic sequelae, including recurrent pain, exocrine pancreatic insufficiency, impaired nutrition, and endocrine dysfunction [4,18]. Follow-up should include monitoring for recurrent abdominal pain, growth and nutritional status,

exocrine pancreatic function when clinically indicated, glucose metabolism, and the emergence of respiratory or other *CFTR*-associated manifestations. Genetic counseling and parental testing should be considered when available.

This report has limitations. Sweat chloride testing was not performed, limiting assessment of *CFTR* function. Parental segregation analysis was not available, limiting interpretation of inheritance and variant contribution. No functional RNA study or *CFTR* activity assay was performed to directly assess the effect of the splice-site region variant. Therefore, this case report cannot distinguish among carrier-associated susceptibility, a *CFTR*-related disorder, or a broader multifactorial predisposition. The targeted gene panel was restricted to selected pancreatitis-associated genes and does not exclude variants outside the tested regions, copy-number changes, deep intronic variants, or other mechanisms not captured by the assay. Finally, the 12-month follow-up period is relatively short for evaluating long-term recurrence risk and progression to chronic pancreatitis.

Conclusions

This case illustrates how structured etiologic evaluation can guide phenotype-driven molecular testing in a child with recurrent acute pancreatitis. After standard etiologic evaluation was unrevealing, targeted pancreatitis-panel testing identified a Sanger-confirmed, likely pathogenic *CFTR* splice-site region variant. This finding supports a possible *CFTR*-related contribution to a pancreas-predominant recurrent pancreatitis phenotype but does not establish a *CFTR*-related diagnosis or causality in the absence of sweat chloride testing, parental segregation analysis, and functional validation. The case underscores the importance of systematic evaluation, careful variant interpretation, and long-term surveillance in children with recurrent acute pancreatitis after standard etiologic evaluation is unrevealing.

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Institution Where Work Was Done

Hanoi Children's Hospital, Hanoi, Vietnam.

Patient Consent

Written informed consent for publication of this case report and any accompanying images was obtained from the patient's legal guardian.

AI-Assisted Figure Preparation

AI-assisted tools were used only to support the visual layout of schematic figures. These tools were not used to generate, modify, analyze, or interpret any clinical, laboratory, imaging, or genetic data. The Sanger sequencing chromatogram was derived from the original diagnostic report and was not altered except for cropping, de-identification, and annotation.

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All figure content, labels, and scientific interpretations were reviewed and verified by the authors.

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