

## Gross Duplication and Uncertain Significance: First Case Report of Hereditary Pancreatitis in a Female Ecuadorian Child

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### Abstract

Hereditary pancreatitis is a type of chronic pancreatitis which is a rare autosomal dominant genetic disease. In Latin America just Venezuela, Brazil, and Chile reported cases of hereditary pancreatitis. The lack of data probably makes wrong the diagnosis in some patients. The aim of these study is to shown the presentation of the disease, family history related with chronic pancreatitis and diagnosis test. We reported a 9-year-old female patient with recurrent severe abdominal pain that begins at 8 years 8 month of age. She went through several hospitalizations [13], different laboratories test and many interventions such abdominal ultrasound, abdominal tomography, cholangioresonance and others. We made a correlation between the levels of amylase and lipase in every hospitalization. The genetic test performed shown a gross duplication of the genomic region encompassing the full coding sequence of the PRSS1 and two variants of uncertain significance PRSS1, Exon 3, c.389C.>T, (p. Thr130Ile), heterozygous; and PRSS1, Exon 3, c.398C>G (p. Pro133Arg), heterozygous are on the same chromosome (Ch37).

**Conclusion:** This rare case of variant PRSS-1 mutation seen in this patient may explain the expressivity varied on the severity of the disease, the huge number of hospitalization and all the procedure that this patient had experimented. This case report is important to compare similar cases around the world, and should be the bases to understand the behavior, the beginning and the expression of the disease.

**Keywords:** Hereditary Pancreatitis; Chronic Pancreatitis; Genetic Mutations

### Introduction

Hereditary pancreatitis is a type of chronic pancreatitis (CP). It is a rare autosomal dominant genetic disease, first described by Comfort in 1952 [1,2]. Their incidence and prevalence in children have increased over the last decade, from 2 to 6 cases per 100,00 persons per year, respectively [3]. Over the decades the development of technology allows as to know more about hereditary pancreatitis.

There are few genes involved in the pathology, the most prevalent genetic mutation is PRSS 1 or cationic trypsinogen producing a switch in the amino acid arginine to histidine at position 122 in the enzyme (Arg122His or R122H), this pathogenic change cause the activation of the trypsinogen in the pancreas producing autodigestion of the gland before it is release to the jejunum [2,4,5,13].

Also, other gene are enrolled in this disease like SPINK1, CFTR and CTSC for acute recurrent and chronic pancreatitis [7]. Assessing a child to pancreatitis may be confuse sometime, this is where INSPPIRE 2 study become an excellent tool nowadays to understand the pathogenesis and the progression of chronic or acute recurrent pancreatitis [6].

In Latin America just Venezuela [8], Brazil [9] and Chile [10] reported cases of hereditary pancreatitis. The lack of data probably makes wrong the diagnosis in some patients. Just the 6% of patients diagnosed with intestinal bowel disease diarrhoea-like present chronic pancreatitis with exocrine insufficiency, but their relationship remains unknown [11,12].

The most clinical presentation of CP is abdominal pain, that goes mild to severe, and sometime can delay the diagnosis [1,3] the diagnosis approach should be based making a good clinical history, laboratory testing, genetic testing, imaging and another test if necessary [14]. Magnetic resonance imaging or magnetic resonance cholangiopancreatography remains the tool of choice, either diagnosis and therapeutic. Have two main advantage, does not involve radiation and detect chronic patterns such as irregular shape like atrophy, small filling defect, ductal dilatation, strictures and irregularity of side branches [1,15].

### Materials and Methods

We researched data from Pubmed, Chochrane and related articles from the web such as eminent congress and articles in press. In result as a multiple hospitalization we made a correlation (Pearson *R*) between amylase and lipase serum levels. For stactical analysis and graphic we used Excel program. The sample for genetic test was sent to E.E.U.U. (Invitae) and the genomic DNA submitted from the sample was enriched for targeted regions using a hybridization-based protocol and sequenced using illumine technology.

### Case Report

This is a 9-year-old female patient with recurrent severe abdominal pain that begins at 8 years 8 month of age. Within the clinical and family history, the older brother and her, born at 32 and 34 gestational weeks respectively (both premature); the mother in both pregnancies developed preeclampsia; and paternal grandmother is diabetic. The older brother at 11 year of age began with obesity, then developed secondary metabolic syndrome and subsequent development of pancreatitis as a complication; he presented a pancreatic pseudocyst treated surgically and has remained stable to date. She began with the first crisis of pancreatitis in July 2018, in her first hospitalization were performed complementary test, showing increasing levels of amylase and lipase; for which an abdominal ultrasound was requested, demonstrating edema of the pancreas. In December of the same year, and abdominal tomography was performed, exhibit an enlarged pancreas with a homogeneous density; also, special test such as sweat test was requested, which came out negative; but fecal elastase was positive for severe pancreatic insufficiency. In April 2019, in one of her hospitalizations, it was decided to perform a cholangioresonance demonstrating an increase in size of the pancreas with fluid around it, as well as fluid in the hepatorenal and splenorenal spaces. In August of the same year, a sample was sent to the United States for the genetic test, where 6 genes (CFTR, CPA1, CTSC, PRSS1, SPINK1) were tested, also ruling out cystic fibrosis, resulting negative. It was used in the hybridization target regions using illumina technology where a probable pathogenic variant, Gain (complete coding sequence) was identified. A gross duplication of the genomic region encompassing the full coding sequence of the PRSS1 gene has been identified and two variants of uncertain significance PRSS1, Exon 3, c.389C>T, (p. Thr130Ile), heterozygous; and PRSS1, Exon 3, c.398C>G (p. Pro133Arg), heterozygous are on the same chromosome (Ch37). Parents were explained about the disease, its complications and limitations. In June 2020 she presented another episode of abdominal pain that did not warrant hospital admission; however, test for celiac disease (serology) were performed, the same one that was negative; therefore, it was decided to perform esophagogastroduodenoscopy (Figure 1) with biopsy, demonstrating finding compatible with chronic moderate nonspecific duodenitis and esophagitis by reflux. In July another episode of abdominal pain appeared, which was admitted for study, performing a linear endoscopic ultrasound (EUS) (Figure 2) manifesting a non-dilated Wirsung at the level of

pancreatic body, with hyperechogenic walls, without lithiasis inside, heterogeneous gland with hyperechogenic tracts and a strain ratio to elastosonography ranging from 3.6 to 6 with strain histogram from 56 to 67; the common bile duct size was 3.5 mm with biliary sludge inside; the head of the pancreas presented heterogeneous alterations similar to the body. In addition, biliary sludge was found inside the gallbladder. Subsequently, an endoscopic retrograde cholangiopancreatography (ERCP) was performed (Figure 3) plus biliary cannulation using the double guide technique; sphincterotomy with disposable sphincterotome was performed and biliary sludge was removed with disposable extractor balloon catheter; a pancreatic plastic prosthesis was placed to decrease the risk of pancreatitis. The following day she underwent cholecystectomy plus biopsy showing chronic cholecystitis in the histopathology; after 15 days post-cholecystectomy, the pancreatic plastic prosthesis was removed. As of August 10, she had her thirteenth hospitalization for abdominal pain with amylase (755) and lipase (999) values; doppler abdominal ultrasound was performed, reporting a normal pancreas. It should be noted that, during the pandemic of COVID-19, the period between March and May presented 4 episodes of abdominal pain, treated at home. The management of her was treat the pain with non-opiates drugs, she did not require a nasogastric tube, the decrease in pancreatic enzymes were after 48 hours of fasting and subsequent introduction of a soft diet, improving satisfactorily.



Figure 1: Esophagogastroduodenoscopy.

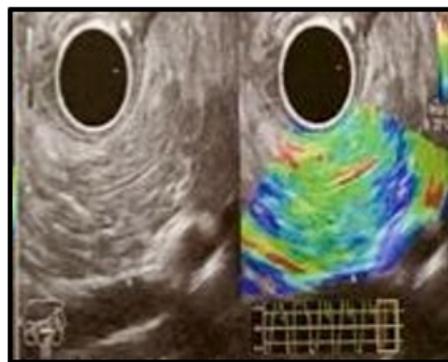


Figure 2: Endoscopic ultrasound (EUS) elastography and strain ratio.



**Figure 3:** Sphincterotomy and implantation of the plastic pancreatic catheter.

**Discussion**

This is the first case report of hereditary pancreatitis in Ecuador, and one of the few cases described in South America [8-10]. The presence of PRSS1 gene mutation like in this patient is the most prevalent compared with the reported worldwide and in the huge cohort of Konzen K., *et al.* and Oracz G., *et al.* of hereditary pancreatitis. Also, these two cationic trypsinogen mutations p. R122H and p.N29I have been the most prevalent in the literature, around 90% of the cases PRSS-1 positive [1,8-10,16,25].

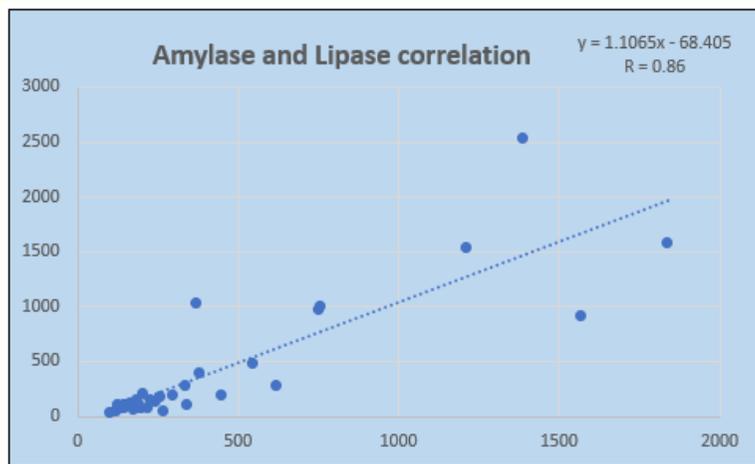
However, in this case probably the cause of the disease is the gross duplication of the cationic trypsinogen, comparing to Masson., *et al.* this duplication might not be associated with less severe phenotype [26]. Also, those missense variant p. Thr130Ile and p. Pro133Arg, have not been reported in the literature in individuals with PRSS-1 related conditions, for this reason are cataloged as uncertain significance [23,24] and this patient is the first case around the world reported with these two rare variant mutations.

The age of symptomatic onset of pancreatitis is similar to other cohort well described, she started her symptoms at age of 8 years which is predominant in female patients according to our case [1,3]. The most frequent symptom at the onset and in the recurrence was severe abdominal pain, comparing to other studies it goes from mild, intermittent or severe [1,14,17]. The diagnosis criteria assessed in this patient had based on INSPPIRE criteria; clinical history, laboratory test, imaging test and genetic test [6,14].

In every recurrence, amylase and lipase testing had been elevated, according to Benini., *et al.* trypsin and lipase are increased in patients with chronic pancreatitis with elevated serum levels of elastase-1 [18] but in our region serum levels of trypsin has not been test, the correlation has to be probe in the future, up to date remains unknow. in the literature no data about correlation between amylase and lipase has made, instead of that, we made Pearson’s correlation (R:0.86) demonstrating a strong positive relation between them (Figure 4) with a mean and standard deviation of 384.15 416.11 for amylase (n = 40); and 356.65 532.78 for lipase (n = 40) (Table 1).

	<b>Amylase</b>	<b>Lipase</b>
Number (n)	40	40
Mean	384.15	356.65
Median	199	128.50
SD	416.11	532.78

**Table 1:** Measure of quantitative variables.



**Figure 4:** Graphic between amylase and lipase serum levels. Pearson correlation ( $R$ ) 0.86, there is a strong positive correlation.

It is important to detect serum levels of fecal elastase to diagnose and follow up patients with chronic pancreatitis [21] and complication such as diabetes mellitus which is very important.

Endoscopic ultrasound (EUS) is the most sensitive test to diagnose chronic pancreatitis and early stages of the disease by Rosemont criteria, also detect complications that may accompany disease progression [20] EUS elastography correlated EUS criteria and tissue strain (stiffness) ratio measuring pancreatic fibrosis to diagnosed chronic pancreatitis, also further studies should be demonstrated [20] in this case the values of the EUS elastography varies from 3.6 - 6, corresponding to an early stage of chronic pancreatitis. Magnetic resonance cholangiopancreatography still the non-invasive exam of choice to show what happens in the pancreatobiliary tract (chronic patterns such as irregular shape like atrophy, small filling defect, ductal dilatation, strictures and irregularity of side branches) and has no radiation. Endoscopic retrograde cholangiopancreatography (ERCP) may be indicated for acute recurrent pancreatitis; such as obstructions, missed stone or sludge, ductal anomalies and the performance of minor papilla cannulation [1,15,19,20] necessary in this case to eliminate the sludge and perform the cannulation previous cholecystectomy.

Furthermore, patients with hereditary pancreatitis have a very increase risk of pancreatic cancer [22] is important to have a strict control for life and the specialist has to check and assess the correct tool to evaluate the state and reduce the progression of the disease choosing a right management.

## Conclusion

This rare case of variant PRSS-1 mutation seen in this patient may explain the expressivity varied on the severity of the disease, the huge number of hospitalization and all the procedure that this patient had experimented. The expression of those missense may be related with the presence of the sludge and the requirement of cholecystectomy. Also, the normal structure of the pancreas should be related with these abnormal variations. This case report is important to compare similar cases around the world, and should be the bases to understand the behavior, the beginning and the expression of the disease. Following her disease about the time, is the main goal for us and her evolution would be posted in further papers.

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