

# R116C mutation in PRSS1 gene causes hereditary pancreatitis and elevated creatine kinase in one child—a case report

**Yong Wei Cheng**

Shenzhen Children's Hospital

**Shao Ming Zhou**

Shenzhen Children's Hospital

**Dong Ling Dai** (✉ [daidongling932@163.com](mailto:daidongling932@163.com))

Shenzhen Children's Hospital <https://orcid.org/0000-0001-8386-5170>

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## Research Article

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# Abstract

## Background

Functionally acquired mutations in the PRSS1 gene can lead to autosomal dominant hereditary pancreatitis (Hereditary Pancreatitis, HP). The most frequently reported mutation sites are R122H, N29I, A16V, and R122C. R116C mutation was less frequently reported to be associated with HP. Moreover, there are few reports about association of hereditary pancreatitis with elevated creatine kinase in children.

## Case presentation:

We reported a patient presented with repeated abdominal pain and recurrent acute pancreatitis accompanied by elevated creatine kinase. The genomic DNA of lymphocytes from peripheral blood was extracted for whole exon gene analysis. The patient had a heterozygous mutation in exon 3 c.346C > T, resulting in substitution of cysteine at position 116 with arginine (p.R116C). Her father had the same mutation in exon 3 c.346C > T. The diagnosis of hereditary pancreatitis due to R116C mutation in PRSS1 gene was confirmed.

## Conclusions

The patient's hereditary pancreatitis is caused by the mutation of PRSS1 gene R116C, characterized by elevated creatine kinase in patient.

## Background

Mutations in the PRSS1 gene can cause autosomal dominant hereditary pancreatitis (HP), clinically characterized by acute pancreatitis (AP) and recurrent acute pancreatitis (RAP:>1 AP), often developing chronic pancreatitis (CP) [1,2]. PRSS1 encodes cationic trypsinogen, and mutations in this gene often lead to increased trypsinogen function or reduced inactivation, causing pancreatitis [3]. In 1996, Whitcomb et al [4] reported for the first time that mutations in the PRSS1 gene can cause hereditary pancreatitis. The most frequently reported mutations leading to autosomal dominant hereditary pancreatitis are R122H, N29I, A16V and R122C in the literature [5-6], while R116C mutation was rarely reported. Furthermore, there was no report about hereditary pancreatitis accompanied by elevated creatine kinase in childhood. Here we report a case of hereditary pancreatitis caused by R116C mutation in the PRSS1 gene characterized as recurrent pancreatitis, who presented with repeated abdominal pain and elevated creatine kinase. We also review the literature on hereditary pancreatitis in childhood due to mutations in the PRSS1 gene.

## Case Presentation

This girl was delivered at term after an uneventful pregnancy with a birth weight of 3400 grams. She is the second child of her family and the fourth pregnancy of her mother. Two of her mother's pregnancies were

terminated by abortion due to social reasons. Her parents were non-consanguineous. Her father, grandmother and two uncles had diabetes. Her mother, grandfather and brother were healthy. None of her family members had pancreatitis. When she was 4 years old, this girl presented to our hospital with persistent upper abdominal pain for more than 20 days. Laboratory tests showed elevated levels of serum lipase, amylase and creatine kinase. Serum lipid profile, electrolyte, autoimmune antibodies, liver and kidney function were normal. Abdominal ultrasound showed normality. A CT scan of the abdomen revealed acute edematous pancreatitis. MRCP of abdomen indicates pancreatitis edema with normal shape of bile duct. She was diagnosed with acute pancreatitis and treated with intravenous octreotide following rehydration and fasting. Her abdominal pain relieved. But 15 days later, the child still suffered intermittent abdominal pain.

We performed genetic analysis with exome sequencing to confirm the causative diagnosis of her pancreatitis the diagnosis. With informed consent, gene analysis was performed using genomic DNA from peripheral lymphocytes from the patient, her grandparents, her parents, her uncles and her brother. The result of genetic analysis showed the patient was compound heterozygous for loss of heterozygosity and c.346C> T in exon 3 of PRSS1 gene, which leads to an amino acid substitution of arginine by cysteine at amino acid position 116 (p.R116C), as well as her grandma, father and uncles. This mutation was not found in her mother, brother and grandfather. The diagnosis of hereditary pancreatitis was confirmed based on the result genetic analysis. Low-fat diet (partially hydrolyzed formula) was given through nasojejunal feeding tube. She was discharged for that the abdominal pain disappeared two weeks later, and the serum lipase, amylase, and creatine kinase decreased to normal. However, this girl had another episode of abdominal pain 2 week after discharge, and hip and knee pain. Laboratory result showed an increase in serum lipase, amylase and creatine kinase again. The second abdominal MRCP examination revealed pancreatic inflammatory edema and normal bile duct. MRI of hip and knee joint demonstrated low-density shadow of surrounding soft tissue. The patient was administrated with the previous treatment strategy for 2 weeks, the serum lipase, amylase, and creatine kinase were normal. He was discharged on October 23, 2019. After discharge, she insisted on nasojejunal feeding of partially hydrolyzed formula and is currently followed up every 2 weeks. the patient is normal. The following is the curve 2 of serum lipase, amylase, and creatine kinase during this treatment. (see Figure 2).

## Discussion

We summarized the analysis of the PRSS1 gene and hereditary pancreatitis gene variants reported by the NCBI search Clinvar database as of the end of February 2020. Variations in the PRSS1 gene lead to hereditary pancreatitis due to mutations in mononuclear acid. The mutation of PRSS1 gene causes the trypsinogen function to be dominated by missense mutations. There are six types of PRSS1 gene missense mutations, which are as follows: R122H, R122C, V39A, C139S, D22G, R116C. Judging from reports in adult literature [7,8,9], the most common mutation sites are R122H, N29I, A16V, R122C. These four PRSS1 mutations often cause autosomal dominant hereditary pancreatitis. However, judging from the reports of children with hereditary pancreatitis caused by mutations in the PRSS1 gene, R122H and R122C mutations are predominant [10,11,12], and reports of children with hereditary pancreatitis caused by R116C mutations

are rare [13,14,15]. We found hereditary pancreatitis caused by R116C mutation in children with recurrent pancreatitis.

The patient we reported had upper abdominal pain at the age of 4 years. The serum lipase and amylase were elevated. The Pancreatic magnetic resonance showed pancreatic edema. After giving symptomatic support, the patient's symptoms improved and he was discharged. After an interval of one month, the child had abdominal pain again. After excluding pancreatic and bile duct obstruction, poisoning-metabolic disorders, drugs and autoimmune diseases, the father had diabetes, and we strongly suspect hereditary pancreatitis. In order to confirm the etiology of hereditary pancreatitis, we extracted peripheral blood DNA from patients and their family members for full exon gene analysis. Genetic analysis showed (see Figure 3).

The patient's father had a heterozygous mutation c.346C> T in the PRSS1 gene, her grandma had a heterozygous mutation c.346C> T in the PRSS1 gene, and there was also a heterozygous mutation c.346C>T in her uncles PRSS1 genes; no mutation in her mother's PRSS1 gene, and no mutation in her brother's PRSS1 gene. Her father has diabetes, so we infer that the patient has hereditary pancreatitis. As reported by Le Maréchal C, et al. [16], heterozygous mutations in the c.346C> T (R116C) PRSS1 gene in children can lead to inherited pancreatitis. Tautermann G, et al [17] reported that a family of recurrent pancreatitis in adult patients in Turkey found that the patient had a heterozygous mutation in the PRSS1 gene c.346C> T (R116C). Family screening showed that the father of the patient had a heterozygous mutation in R116C. The patient's daughter has a R116C heterozygous mutation, and she has been diagnosed with pancreatitis since the age of 3, which is not completely consistent with our report of the child. However, we took a child with recurrent pancreatitis as a proband, her father had diabetes, and genetic testing of the family revealed that the child had a heterozygous mutation in the PRSS1 gene c.346C> T (R116C). To clarify the pathogenesis of hereditary pancreatitis caused by the R116C mutation of the PRSS1 gene. Kereszturi E et al. [18] found that the R116C mutation of the PRSS1 gene was found in the German family of hereditary pancreatitis. The cell transfection technique showed that the R116C mutation of the PRSS1 gene induces the misfolding of cationic trypsinogen, triggering endoplasmic reticulum stress and intracellular retention, leading to hereditary pancreatitis. From these literature reports[19,20], the R116C mutation of the PRSS1 gene induces the misfolding of cationic trypsinogen, triggering endoplasmic reticulum stress and intracellular retention, leading to hereditary pancreatitis. It can start in children, repeated pancreatitis, or diabetes. [21]

We found that in addition to elevated pancreatitis-related enzymes, children have elevated creatine kinase. It is consistent with the increase in creatine kinase caused by previous pancreatitis in adults [22], but there has been no report of hereditary pancreatitis. Whether elevated creatine kinase is a clinical feature of hereditary pancreatitis caused by the R116C mutation of the PRSS1 gene. It remains to be confirmed by more clinical cases.

In summary, the patient's hereditary pancreatitis is caused by the mutation of PRSS1 gene R116C, characterized by elevated creatine kinase in patient.

## Declarations

## Author Declarations

\*Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration. The study was approved by the Bioethics Committee of Shenzhen Children's Hospital.

\*Consent for publication:

Informed consent was obtained from all individual participants included in the study.

\*Availability of data and materials: Not applicable

\*Competing interests: None

\*Funding: Not applicable

\*Authors' contributions: Yong Wei Cheng and Dong Ling Dai were in charge of curing the patients and wrote the manuscript; Shao Ming Zhou tested the sequence of PRSS1 gene and tested the creatine kinase.

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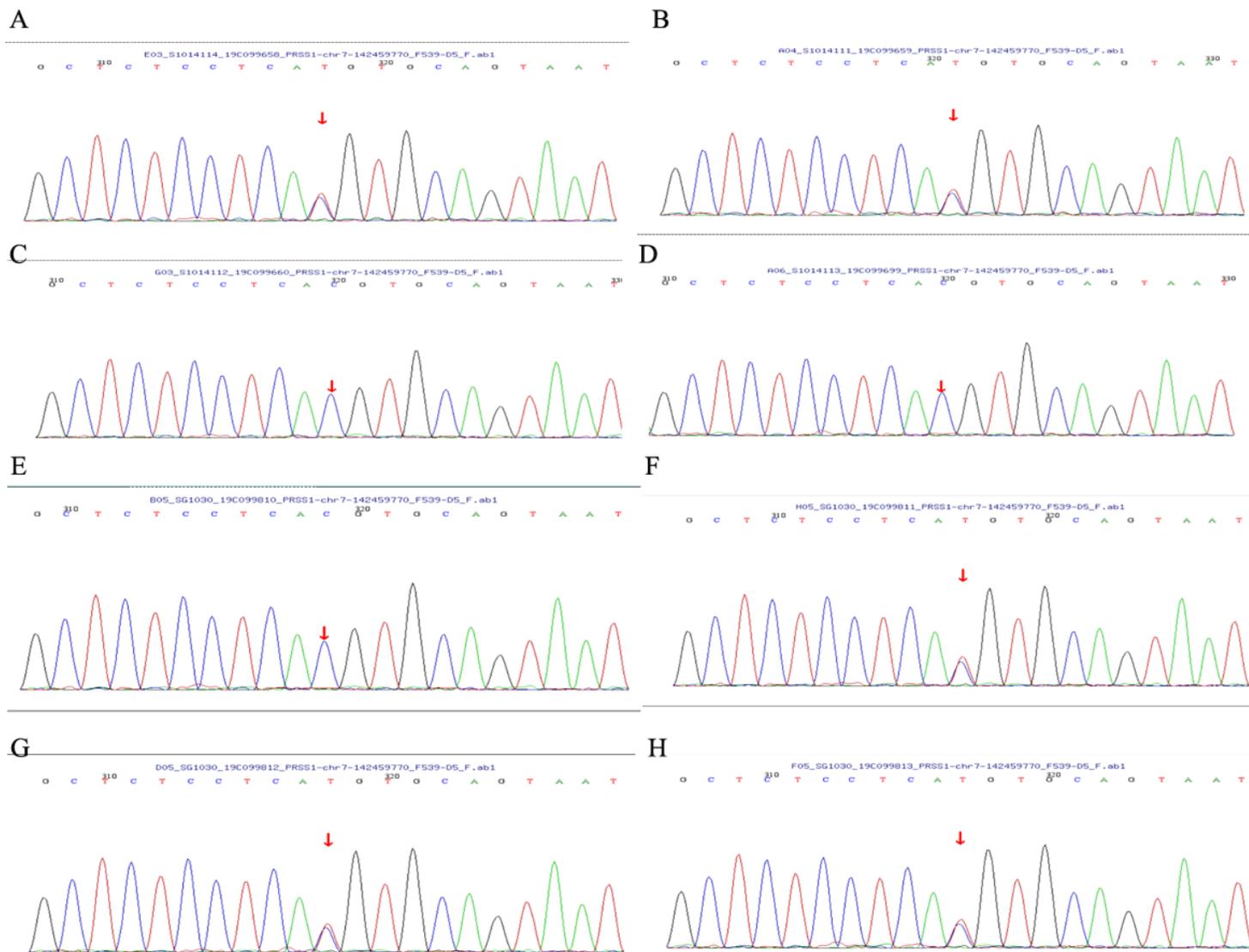
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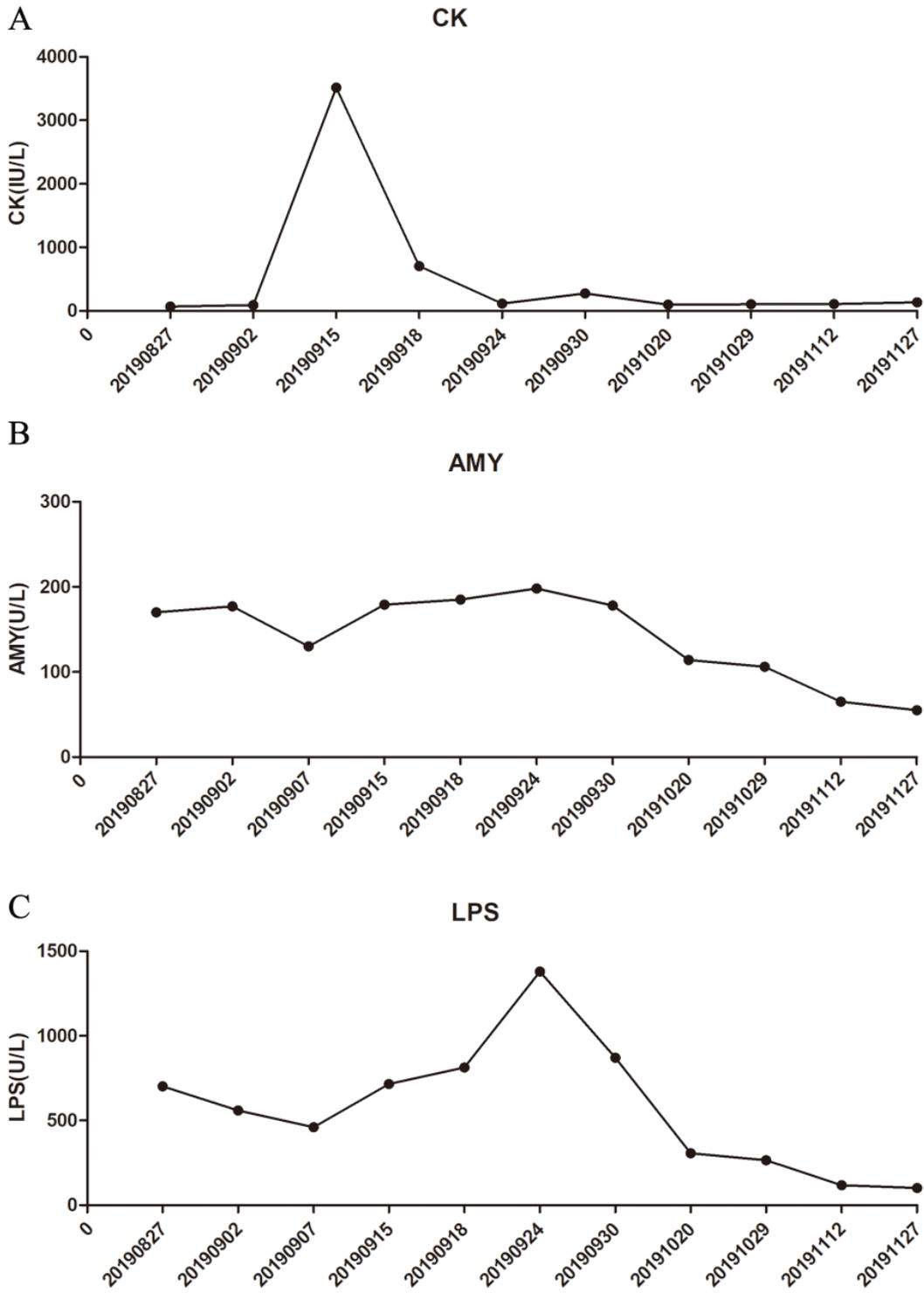
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## Figures



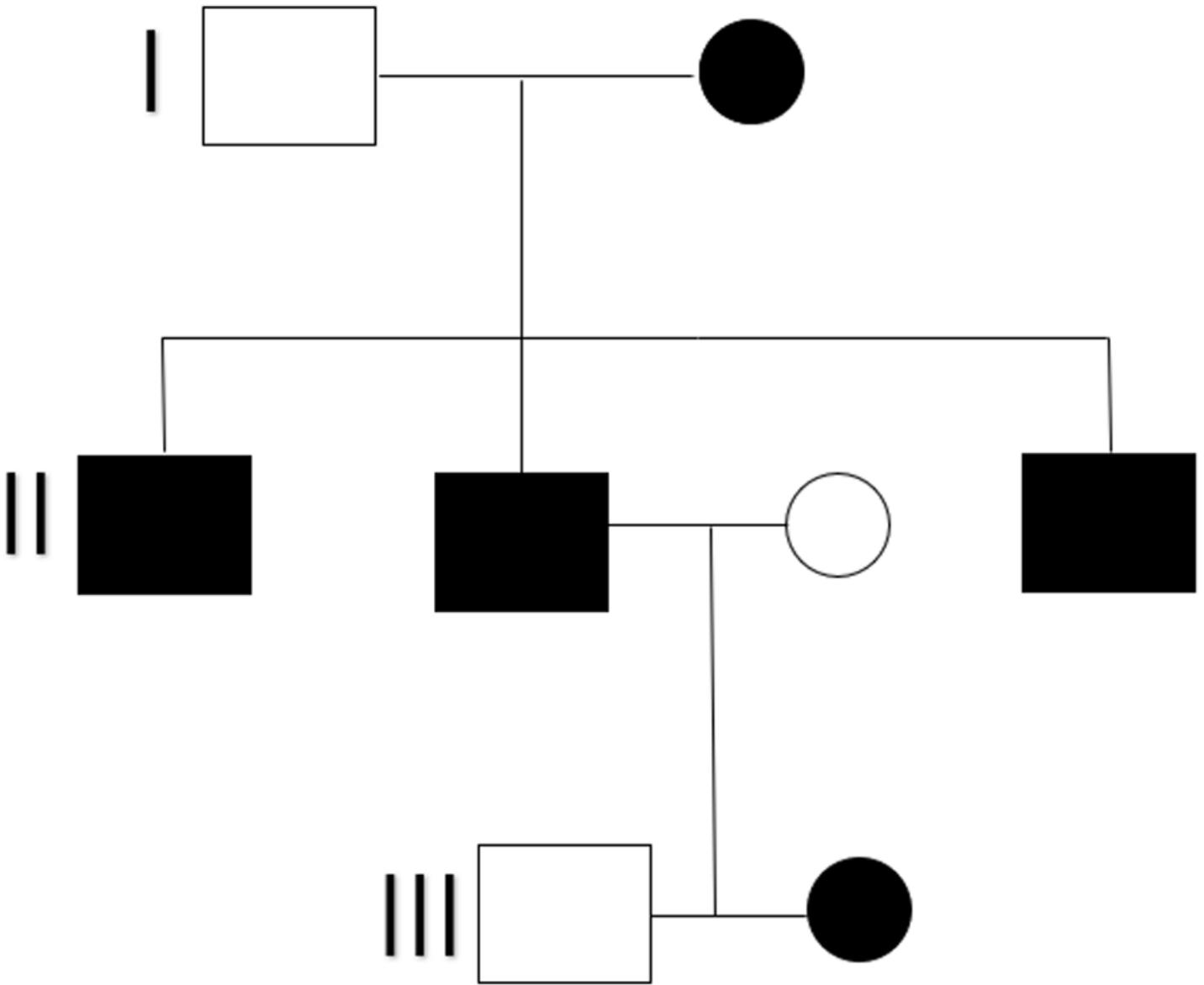
**Figure 1**

Genomic DNA sequences in exon 3 of the PRSS1 gene in the patient and her family. A: heterozygote in the patient (c.346C>T, R116C); B: Heterozygote in her father (c.346C>T, R116C); C: No variant in her mother; D: No variant in her brother; E: No variant in grandpa; F: Heterozygote in her grandma. (c.346C>T, R116C) ; G: Heterozygote in her uncles (c.346C>T, R116C) ; patient (Figure 1A), their parents (Figures 1B and 1C) and brother (Figure 1D), grandpa, grandma (Figures 1E and 1F), her uncles (Figure 1G and 1H)



**Figure 2**

Pancreatitis blood enzyme test index. The specific value of blood creatine kinase (A), blood amylase(B) and blood lipase(C) with different time.



**Figure 3**

Genetic analysis. The figure illustrates that the rectangle I represents males and the circles represent females. They are grandpa and grandma (grandma has diabetes); II from left to right are uncle, father, mother, and second uncle (uncle, father, and second uncle have diabetes); III from left to right (brother, patient)