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CASE REPORT

Low Penetrance Pancreatitis Phenotype in a Venezuelan Kindred with a *PRSS1* R122H Mutation

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ABSTRACT

Context Hereditary pancreatitis is typically caused by the *PRSS1* R122H or N29I mutations resulting in high penetrance (about 80%) autosomal dominant disorder that is usually reported in North America, Northern Europe and Northeast Asia, but not South America, Africa or India. **Case report** Here we report a kindred from Venezuela, South America with the *PRSS1* R122H variant. Only the proband, an 11-year old boy with severe chronic pancreatitis, and a maternal grandmother with pancreatitis at age 60 years (confirmed *PRSS1* R122H), are symptomatic. **Conclusions** Issues of mutation prevalence, non-penetrance, and disease recognition in various countries are discussed.

INTRODUCTION

Hereditary pancreatitis (Online Mendelian Inheritance in Man - OMIM 167800: http://omim.org/entry/167800) is an autosomal dominant disorder characterized by multiple episodes of acute pancreatitis, chronic pancreatitis and increased risk of up to 40% for development of pancreatic cancer. To date, the only gene found to be associated with hereditary pancreatitis is the cationic trypsinogen gene (*PRSS1*) [1]. Hereditary pancreatitis has approximately 80% penetrance and variable expressivity [2, 3]. Hereditary pancreatitis is most often seen in families of Northern European ancestry, although occasional families from Japan [4, 5], Korea [6], China [7, 8] and Malaysian Chinese [9] have been reported. Here, we report a *PRSS1* R122H mutation in a Venezuelan family with hereditary pancreatitis with variable age of onset and low penetrance.

CASE REPORT

The proband was an 11-year-old male with a history of recurrent pancreatitis and episodes of severe abdominal pain with periods of narcotic dependency. The patient initially presented with abdominal pain at age 5 lasting 3-4 days. At that time, the symptoms were thought to be associated with "emotional issues" relating to a death in the family and other social family issues. Pancreatitis was first diagnosed at age 10. The nutritional status was within normal limits for expected height and growth for age. Albumen and associated laboratory values were within normal limits.

The patient was referred to the University of Pittsburgh Medical Center from Venezuela for evaluation. A CT revealed tortuous and diffusely dilated pancreatic ducts and a diffusely atrophic pancreatic parenchyma consistent with chronic pancreatitis with focal narrowing of the distal pancreatic duct. There was no evidence of pancreatic divisum, annular pancreas or biliary ductal dilatation. An ERCP was performed and a main pancreatic duct stent was placed. Fecal elastase testing identified severe pancreatic exocrine insufficiency with a laboratory value of 61 µg/g stool (reference values: greater than 200 µg/g).

The patient's pain decreased and his diet intake improved over a three-day admission and he was tapered off of narcotics. A family history suggest possible genetic etiology (Figure 1).

Family ethnicity was Venezuelan, with Spanish heritage. The proband had one 14-year-old healthy sibling. Both parents were alive and well in their forties. Both the maternal grandmother and maternal grandfather's bother were reported to have pancreatitis. Pancreatitis in the grandmother who developed pancreatitis at age 60, which was reported to be linked to pancreas divisum, was treated with minor sphincterotomy without improvement. Diabetic status and exocrine insufficiency data for the grandmother were not available, though she had no gross evidence of exocrine or endocrine insufficiency.

A distant great-uncle on the opposite side of the family was suspected to have had an attack of pancreatitis but this was not confirmed through medical records.

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Genetic counseling and full gene sequence analysis of pancreatitis susceptibility genes (*PRSS1*, *SPINK1* and *CFTR*) were offered to the proband and his grandmother.

The proband was found to carry the common *PRSS1* R122H mutation, which identified the primary etiologic factor for hereditary pancreatitis. His grandmother, who was subsequently tested, was also found to carry the R122H *PRSS1* mutation as well. This finding confirms hereditary pancreatitis syndrome in the family and provides insight into the proband's mother as an asymptomatic, obligate carrier. Therefore, this family carries a high-penetrance *PRSS1* mutation, but appears to have unusually low penetrance within this family.

DISCUSSION

This is the first case of hereditary pancreatitis to be reported in a family from Venezuela, and only the second from South America. The present case was noted to have Southern European ancestor (Spain), with a mutation that is normally high penetrance. The only other cases from South America that we are aware of include a 17-year-old male with a family history of hereditary pancreatitis but unknown genetic mutation [10]. A rare *PRSS1* E79K mutation was also identified in a patient with chronic pancreatitis patient from Brazil [11]. The *PRSS1* E79K has been reported in 9 cases, and is thought to be possible pathologic with low penetrance (http://www.pancreasgenetics.org). Mutations in *PRSS1* and hereditary pancreatitis families are otherwise rare in Brazil [12]. In Central American there is one reported case of pancreatitis associated with a *PRSS1* N291 from Mexico [13]. In addition to hereditary pancreatitis being rare in South and Central America, neither hereditary pancreatitis families or *PRSS1* mutations are seen or reported on the Indian subcontinent [14, 15] or Africa.

The most common *PRSS1* mutations associated with hereditary pancreatitis are R122H, N29I and A16V, which are all conversion-like mutations, where the "mutation" is the transposition of the sequence from other trypsinogen genes or pseudogenes into *PRSS1* to create N29I (from *PRSS2*), A16V (from *PRSS3*) or R122H (from *TR6*) [16]. The other major factor associated with hereditary pancreatitis is the *PRSS1* copy number variant (CNV), which has been reported in France [17] and in one patient in the United States with a complex genotype [18].

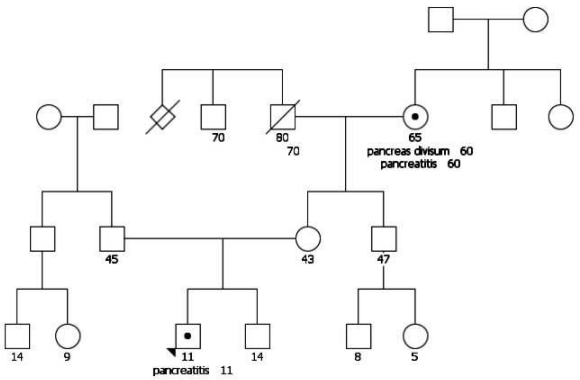

Figure 1. Pedigree of the Venezuelan kindred. Other than the proband, the only relative to have *PRSS1* mutation and pancreatitis is the maternal grandmother who had a mild case in the context of pancreas divisum.

The reason that hereditary pancreatitis and *PRSS1* mutations seems to occur more commonly in some populations than others is unknown. Possible explanations include random chance, genomic structural variants, environmental factors that reduce penetrance, lack of awareness, lack of testing or lack of reporting in the scientific or medical literature.

The current case may be instructive. The grandmother, who is the only other family member to develop pancreatitis also had pancreas divisum. Recent studies suggest that pancreas divisum is only a risk factor for pancreatitis in the context of genetic mutations [19, 20, 21, 22]. No other family member in this pedigree has been identified with pancreatitis or pancreatitis-like symptoms. This may indicate that a second strong risk factor for pancreatitis may be necessary to cause pancreatitis some families. The factor that triggered pancreatitis in the proband is unknown.

Incomplete penetrance of the *PRSS1* mutation are well documented in all large hereditary pancreatitis families, but the reason remains a mystery. In a study of monozygotic twins, fewer than 50% of the twin pairs showed concordance with age of onset for or phenotypic expression of pancreatitis [23]. Furthermore, it was shown that both the wild type (R122) and mutant (H122) alleles were equally expressed of a 93-year-old patient with a strong family history of hereditary pancreatitis but no symptoms [24]. This finding suggests that nuclear encoded DNA is not the only precipitating genetic factor in the risk for developing pancreatitis in hereditary pancreatitis families.

In conclusion, we report the case of an 11-year-old male from Venezuela with severe recurrent acute and chronic pancreatitis from a R122H mutation in a family with otherwise very low penetrance. Further evaluation of these types of families is important to increase awareness of the disease, and to begin to understand the factors that may be protecting other family members from this severe and distressing disorder.

Conflicts of interest Dr. Whitcomb owns stock in Ambry Genetics (Aliso Viejo, CA, USA) and also the U.S. patent 6406846 entitled "Method for determining whether a human patient is susceptible to hereditary pancreatitis, and primers therefore", which has been licensed and provides royalty income

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