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Misfolding cationic trypsinogen variant p.L104P causes hereditary pancreatitis

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We read the recent publication of Schnúr et al. [1] with great interest, in which the authors proposed that a subset of human cationic trypsinogen (*PRSS1*) variants cause chronic pancreatitis by inducing misfolding and endoplasmic reticulum (ER) stress rather than increased intra-pancreatic trypsin activity. *PRSS1* variants that promote premature trypsinogen activation are the strongest known risk factors for chronic pancreatitis; often associated with autosomal dominant hereditary pancreatitis. ER-stress causing *PRSS1* variants, on the other hand, have been mostly found in sporadic disease with no family history suggesting these variants might confer lower risk.

To refute this notion, here we report a hereditary pancreatitis family of Hungarian origin carrying the heterozygous c.311T>C (p.L104P) *PRSS1* variant which was recently demonstrated to induce misfolding and ER stress.[2] The index patient, his mother and first cousin developed recurrent acute or chronic pancreatitis in this family (Figure 1). Sanger sequencing was carried out on genomic DNA of all 12 live family members after informed consent was obtained. All exons of the *PRSS1, SPINK1, CTRC* and *CPA1* genes and exons 4, 10 and 11 of the *CFTR* gene were sequenced in all affected subjects. In all unaffected family members *PRSS1* exon 3 was sequenced. In the unaffected children of the index patient's cousin *CTRC* exons 2 and 3 were also analyzed. All three affected members were heterozygous for the p.L104P *PRSS1* variant. Interestingly, both children of the index

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patient and two children of the first cousin were unaffected despite carrying the pathogenic variant. While this observation may indicate lower penetrance of the mutation, we note that age of onset was delayed in the index patient (36 y) and his mother (32 y) suggesting that some of the children are likely to develop pancreatitis at a later age. All affected individuals were smokers and all quit at the time of diagnosis. Alcohol consumption was clinically not significant. Pancreatolithiasis was documented in all three affected subjects and removal of the intraductal stones prevented further acute attacks. All relevant clinical findings in the three affected family members are summarized in Table 1.

In addition to the *PRSS1* p.L104P variant, the index patient's affected cousin also carried a heterozygous c.180C>T (p.G60=) variant in the *CTRC* gene. This variant increases risk for chronic pancreatitis about 2-fold and may have been responsible for the earlier onset of pancreatitis (18 y) and more severe exocrine insufficiency in this subject relative to the other two affected family members (Table 1). No other pathogenic variants were identified in the tested susceptibility genes in the affected family members.

Our observations indicate that misfolding PRSS1 variants may act as strong risk factors for chronic pancreatitis and may be associated with autosomal dominant hereditary pancreatitis. Furthermore, the findings argue that ER stress is a highly relevant pathological mechanism in chronic pancreatitis and alleviating pancreatic ER stress should be a therapeutic target.

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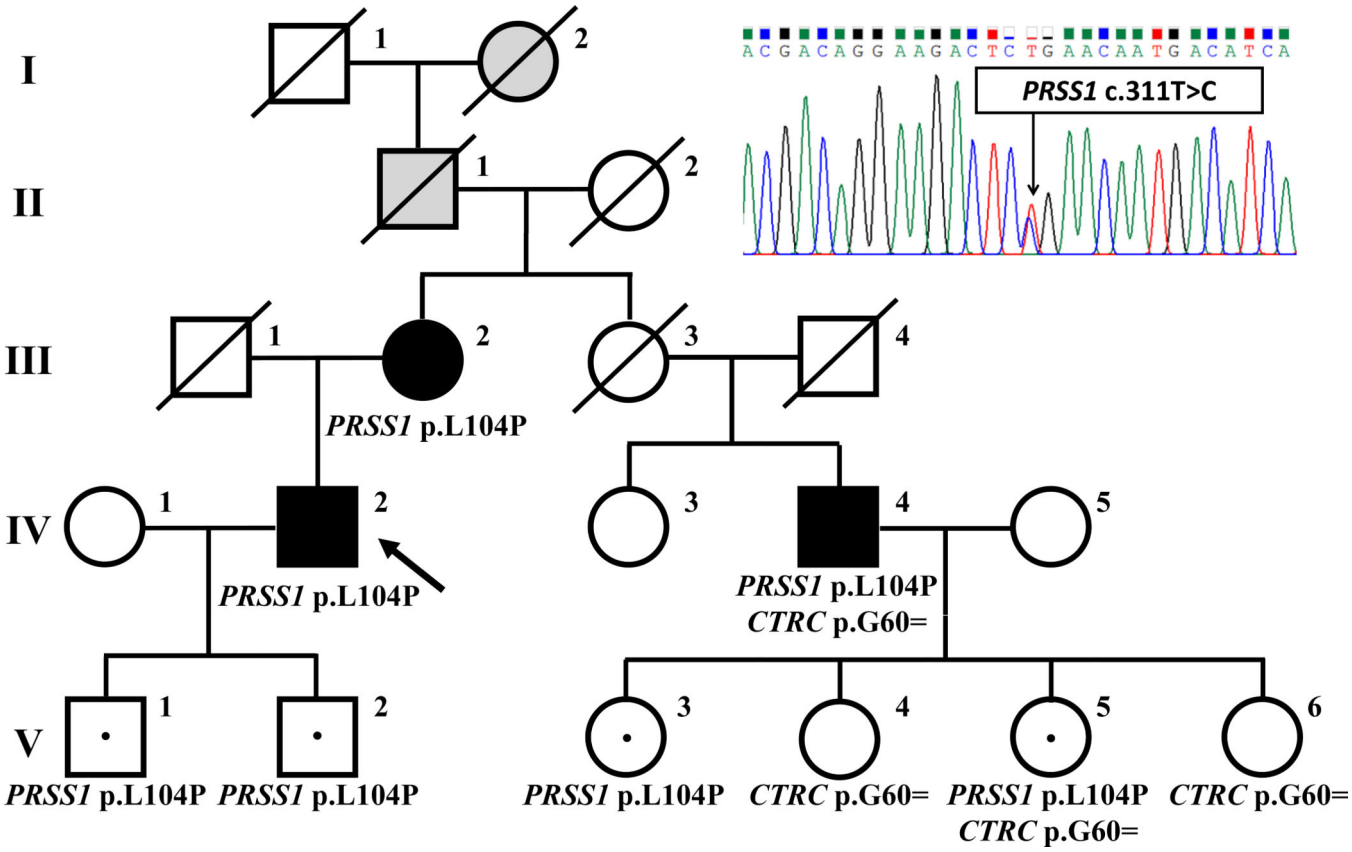

Figure 1.

Pedigree of a Hungarian family with hereditary pancreatitis associated with the p.L104P *PRSS1* variant. The arrow points to the index patient. Solid black symbols indicate affected family members; solid grey symbols indicate subjects with suspected pancreatitis. Open symbols with a dot designate unaffected carriers. Crossed symbols indicate deceased family members. All living family members were tested for *PRSS1* p.L104P. Known carriers of the p.G60= *CTRC* variant are also indicated. The inset shows an electropherogram of a heterozygous carrier of the c.311T>C (p.L104P) *PRSS1* variant.

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Table 1

Clinical characteristics of family members with chronic pancreatitis. Patients were designated according to the pedigree in Figure 1.

	IV/2	III/2	IV/4
age	50	72	46
age of onset	36	32	18
number of acute episodes	5	3	0
chronic pancreatitis	yes	yes	yes
pancreatolithiasis	yes	yes	yes
chronic diarrhoea	yes	yes	yes
exocrine insufficiency	moderate (Lundh)	no data	severe (Lundh)
diabetes mellitus	yes	no	yes
pancreatic cancer	no	no	no
Ca-oxalate crystals in urine	yes	yes	yes
smoking	yes	yes	yes
alcohol consumption	not significant	not significant	not significant
cholelithiasis	no	yes	no
other diseases	appendicitis	duodenal ulcer	no
	multiple myeloma	gastric ulcer	
	acute hepatitis A	acute hepatitis C	