

Abstract

Two Novel Severe Mutations in the Pancreatic Secretory Trypsin Inhibitor Gene (*SPINK1*) Cause Familial or/and Hereditary Pancreatitis

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Mutations in the serine protease inhibitor Kazal type 1 gene (*SPINK1*; OMIM 167790) encoding pancreatic secretory trypsin inhibitor (PSTI) have recently been found to be associated with chronic pancreatitis. The aim of this study was to identify novel severe *SPINK1* mutations with a view to expanding the gene's mutational spectrum and providing further insights into PSTI's role in pancreatitis. 46 unrelated families, each including at least two pancreatitis patients and carrying neither cationic trypsinogen mutations or the frequent *SPINK1* N34S mutation, participated in this study. The four exons and their flanking sequences of the *SPINK1* gene were screened by denaturing high performance liquid chromatography analysis; and mutations were identified by direct sequencing. A heterozygous microdeletion mutation (c.27delC), which occurs within a symmetric element, was identified in two families. In one family, c.27delC showed segregation with the disease across two generations, with a penetrance of up to 75%. But in the other family, however, the same mutation manifested as a low-penetrance susceptibility factor. In addition, a novel heterozygous splicing mutation, IVS2+1G>A, was found in one family with familial pancreatitis. Our results demonstrated that whenever possible, mutational screening rather than genotyping should be performed, given the "loss-of-function" nature of *SPINK1* mutations. Moreover, genetic testing for *SPINK1* mutations in pancreatitis families wherein no cationic trypsinogen mutations were found is warranted. Furthermore, our results suggested that it might be more appropriate to assign *SPINK1* as a pancreatitis susceptibility locus; and the differing views about *SPINK1*'s role (ie, disease-causing vs. disease modifier) in pancreatitis should be discussed in the context of specific mutations.