Pancreatitis Due to *De Novo PRSS1* Pathogenic Mutations: The Ambry Genetics Experience

Melissa Samons, MS, CGC; Brissa Martin, MS, CGC; Jing Wang, MD, FACMG, CGMBS
Ambry Genetics

A combination of factors, including genetic and environmental, contribute to the development and recurrence of pancreatitis. The protease, serine 1 (*PRSS1*) gene encodes the cationic trypsinogen protein and is associated with hereditary pancreatitis (HP). Two common *PRSS1* pathogenic mutations, p.R122H and p.N29I, account for approximately 90% of pathogenic alterations observed in *PRSS1*-related HP. *PRSS1*-related HP is typically inherited in an autosomal dominant fashion with reduced penetrance; in cases without a family history of pancreatitis, the mutation is likely to be identified in one of the individual's parents. *De novo* pathogenic mutations in *PRSS1*-related HP have been previously reported; however, the proportion of cases is unknown. Here we report two unrelated individuals with acute pancreatitis and a *de novo PRSS1* mutation. Both individuals underwent gene sequencing analysis of the *CFTR*, *PRSS1*, *SPINK1*, and *CTRC* genes. The first individual was heterozygous for the *PRSS1* p.R122H pathogenic mutation. Targeted sequencing analysis of this individual's parents was negative for the familial alteration. The second individual was heterozygous for a *PRSS1* p.R122H pathogenic mutation and a *CFTR* p.G1069R likely pathogenic variant. This individual's parents underwent gene sequencing analysis of the same four genes as the proband; no pathogenic mutations or variants of unknown significance were detected in the mother. The unaffected father was positive for the familial *CFTR* alteration, but was negative for the familial *PRSS1* p.R122H mutation. Ambry Genetics has been offering pancreatitis genetic testing since 2003 and has tested approximately 9,000 individuals. The finding of two cases of *de novo PRSS1* mutations in over a decade's worth of genetic analysis of this gene suggests that *PRSS1*-related HP due to *de novo* alterations is rare, less than 0.05% of cases. Therefore, parental testing and genetic counseling should be considered for accurate risk assessment and appropriate clinical follow-up.