Pancreatitis Due to *De Novo PRSS1* Pathogenic Mutations

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

BACKGROUND

- *PRSS1*-related hereditary pancreatitis (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 patient's parents.
- *De novo* pathogenic mutations in *PRSS1*-related HP have been previously reported; however, the proportion of cases is unknown.

METHODS

- We performed a retrospective review of approximately 9,000 cases received for analysis of the *PRSS1* gene between 2005 and June 2017.
- Data from 2 multigene panels (*CFTR, PRSS1, SPINK1 +/- CTRC*) as well as sequencing of the *PRSS1* gene was included in the analysis.
- *De novo* alterations were confirmed by our laboratory by re-isolation of the specimens with repeat PCR and analysis.
- Familial relationships in Family 1 were verified by analysis of 7-9 different short tandem repeat (STR) loci.

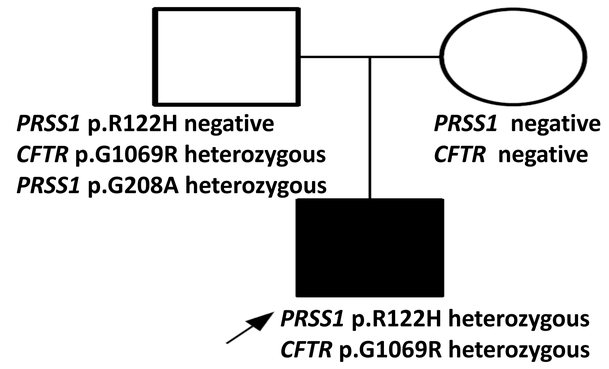
FAMILY 1

- The proband is a 20-year-old male with acute pancreatitis; clinical history included stent placement in the pancreatic duct.
- Analysis of this individual's sample included sequence analysis of the *CFTR, CTRC, PRSS1,* and *SPINK1* genes.
- Parental testing was performed via a multigene panel including sequence analysis of the *CFTR, CTRC, PRSS1,* and *SPINK1* genes.

RESULTS:

- The proband was found to have a heterozygous missense mutation in *PRSS1*, p.R122H, and a heterozygous missense likely pathogenic variant in *CFTR*, p.G1069R.
- Parental analysis for *PRSS1* p.R122H was negative; the proband's unaffected father carried the *CFTR* variant.
- Unexpectedly, the proband's father was also heterozygous for a different likely pathogenic variant in *PRSS1,* p.G208A.
- Analysis of STR loci confirmed familial relationships.

FAMILY 1: Pedigree with co-segregation data



FAMILY 2

- The proband is a 15-year-old female with acute pancreatitis.
- Analysis of this individual's sample included sequence analysis of the *CFTR, CTRC, PRSS1,* and *SPINK1* genes, as well as deletion/duplication analysis of *CFTR.*
- Parental testing was performed via targeted Sanger sequencing of *PRSS1.*

RESULTS:

- The proband was found to have a heterozygous missense mutation in *PRSS1,* p.R122H.
- Parental analysis for this alteration was negative.

TAKE-HOME POINTS

- *PRSS1*-related HP due to *de novo* alterations is rare; we identified this in less than 0.05% of cases (2/9,000 samples).
- Parental testing and genetic counseling should be considered for accurate risk assessment and appropriate clinical follow-up.

REFERENCES

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15 Argonaut, Aliso Viejo, CA 92656 Toll Free 866 262 7943 Fax 949 900 5501 ambrygen.com