Genetic risk factors for pancreatitis: A retrospective analysis of 400 patients

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Introduction

Pancreatitis is a heterogeneous condition caused by both genetic and non-genetic factors. While some associated genetic variants have high penetrance, other “disease-modifying” variants have low penetrance and follow a complex inheritance pattern. The yield of genetic testing in well-defined cohorts of patients with pancreatitis has been published, but these studies do not consistently describe the classification and inheritance of reported variants. This study reports the classification and inheritance patterns of variants identified in patients with pancreatitis.

Methods

Genetic test results of 403 consecutive patients with suspected pancreatitis were retrospectively reviewed. Patients had been tested by a next-generation sequencing (NGS)-based pancreatitis panel comprising either 5 (*CFTR*, *CPA1*, *CTRC*, *PRSS1*, *SPINK1*) or 9 genes (5 gene panel plus *APOA5*, *APOC2*, *GPIHBP1*, *UBR1*), including sequencing and copy number variant (CNV) analysis. Patients with variants classified as risk factor (RF), or, pathogenic (P) or likely pathogenic (LP) based on a modified ACMG/AMP classification scheme, were considered to have a result associated with increased risk of pancreatitis. Complex inheritance was defined as a result with both autosomal dominant (AD) and autosomal recessive (AR) variants, variants in >1 gene, or a single AR variant. Chi-square analysis was used to determine statistical significance; a *P*-value <0.05 was considered significant.

Results

Of the 403 patients, 36% (145/403) were pediatric (<18 years old) at the time of testing. Most had testing for 9 genes (92%, 369/403). A total of 21% (85/403) of patients had ≥1 gene variant reported: higher in children (27%, 39/145) than adults (18%, 46/258) (*P*<0.05). Four patients (5% 4/85) with ≥1 variant reported had LP/P CNVs.

If *CFTR* carriers (one LP/P variant, n=17) are excluded, 17% of patients (68/403) have ≥1 variant in a gene associated with pancreatitis. In this case, there remains a significant difference between the yield in children (22%, 32/145) compared to adults (14%, 36/258) (*P*<0.05).

The most frequent variants reported were a heterozygous RF variant in *SPINK1* (34%, 29/85), a single LP/P/RF variant in *CFTR* (20%, 17/85) and an LP/P variant in *PRSS1* (12%, 10/85). Further, 9% (8/85) of patients had variants in >1 gene and 4% (3/85) had >1 LP/P variant in the *CFTR* gene. Among patients with ≥1 variant in a gene associated with pancreatitis, complex inheritance was seen in 71% (60/85), 18% (15/85) with AD and 12% (10/85) with AR (Figure).

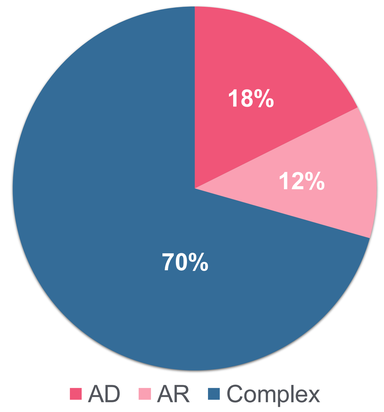
One in 5 patients with suspected hereditary pancreatitis who underwent next-generation sequencing (NGS) panel testing had ≥1 variant in a gene associated with pancreatitis.

Table. Genetic findings in a cohort of patients with suspected hereditary pancreatitis.

Genetic Findings	Pediatric	Adults	Total	Inheritance
PRSS1 LP/P	5	5	10	AD
CPA1 LP/P	0	1	1	AD
SPINK1 LP/P	1	2	3	AD
SPINK1 LP/P + *SPINK1* RF hz	1	0	1	Complex
SPINK1 RF hz	5	0	5	AR
SPINK1 RF het	11	18	29	Complex
SPINK1 RF hz + *CFTR* RF	0	1	1	Complex
SPINK1 RF hz + *CTRC* RF	1	1	2	Complex
CTRC LP/P	0	1	1	AD
CTRC RF + *CTRC* RF	1	0	1	Complex
CTRC RF	0	4	4	Complex
CTRC LP/P + *SPINK1* RF het	0	1	1	Complex
CFTR LP/P + *CFTR* LP/P	2	0	2	AR
CFTR LP/P + *CFTR* 5T	3	0	3	AR
CFTR LP/P	7	10	17	Complex
CFTR LP/P + *CFTR* LP/P + *CTRC* RF het	0	1	1	Complex
CFTR LP/P + *SPINK1* RF het	1	0	1	Complex
CFTR 5T + *SPINK1* RF het	1	0	1	Complex
CFTR LP/P + *CTRC* RF het	0	1	1	Complex
Total patients with informative variants	39	46	85	

Het=heterozygous; hz=homozygous; *SPINK1* RF: NM_003122.3(*SPINK1*) c.101A>G (p.Asn34Ser), *CTRC* RF=NM_007272.3 (*CTRC*) c.760C>T (p.Arg254Trp), NM_007272.3 (*CTRC*) c.738_761del p.(Lys247_Arg254del); *CFTR* RF= NM_000492.4 (*CFTR*) c.220C>T p.(Arg74Trp), NM_000492.4 (*CFTR*) c.2900T>C p.(Leu967Ser), NM_000492.4 (*CFTR*) c.3808G>A p.(Asp1270Asn)

Figure. Genetic test results: Inheritance patterns



Conclusion

- Over 1 in 5 patients in this cohort had ≥1 gene variant associated with an increased risk for pancreatitis.
- If *CFTR* carriers are excluded, 1 in 6 patients in this cohort had ≥1 gene variant associated with an increased risk for pancreatitis. While single heterozygous *CFTR* variants have been associated with an increased risk for pancreatitis[1], the *CFTR* carrier rate in this cohort is close to that which is reported in the white population[2]. Further research on the clinical significance of single heterozygous variants in *CFTR* in patients with pancreatitis is needed.
- Most patient results follow a complex inheritance pattern with common variants often reported, highlighting the importance of genetic counseling and the evaluation of the clinical history for accurate genetic test result interpretation.

References:

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Conflict of interest statement: All authors are employed by Blueprint Genetics.