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Geno-phenotypic Analysis of Pediatric Patients With Acute Recurrent and Chronic Pancreatitis

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Abstract

Objectives—The aim of this study was to determine if comprehensive genetic testing was useful to identify genetic variants that discriminate chronic pancreatitis (CP) from acute recurrent pancreatitis (ARP) in a pediatric population.

Methods—We conducted a retrospective review of 50 patients enrolled in our institutional pancreatitis registry between April 2013 and January 2015. Genetic analysis of *PRSS1*, *CFTR*, *SPINK1* and *CTRC* classified variants as mutations or variants of unknown clinical significance and the minor allele frequency of variants in our cohort was obtained.

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Results—Genetic testing was obtained in 16/16 of CP (100%) and 29/34 of ARP (85%) patients. A total of 39 genetic variants were found in 27 of 45 subjects tested (60%) with 5 subjects (11%) having two different genes affected. Variant frequency was greatest in patients for *CFTR* (17/45, 38%) followed by *SPINK1* (11/44, 25%), *CTRC* (2/27, 7%) and *PRSS1* (2/44, 4%). *CFTR* variants were more likely in those with CP compared to ARP (63% and 24%, $p=0.01$).

Conclusion—This study is the first to find a higher rate of *CFTR* mutations in CP versus ARP groups utilizing comprehensive genetic testing in a pediatric population.

Keywords

pediatric pancreatitis; chronic pancreatitis; recurrent pancreatitis; hereditary pancreatitis

Introduction

The incidence of acute pancreatitis (AP) in pediatrics has been steadily increasing with etiologies that significantly differ from those causes found in adults.^{1,2} A subset of children and adolescents with AP will progress to acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP). While ARP and CP in adults are most often secondary to gallstones or excessive alcohol usage,^{3–5} the risk factors involved in the disease progression in children are poorly delineated and less likely to be environmental factors.^{6,7} Recently published proposed definitions for pediatric pancreatitis have been refined from adult criteria.⁶ As it relates to CP, diagnostic criteria is reflective of the injury sustained by the pancreas and can include changes in duct morphology, gland atrophy, calcifications or pancreatic insufficiency. An evidence-based algorithm to confirm the diagnosis of CP proposed by the American Pancreatic Association utilizes criteria that can be sequentially assessed starting with the less invasive testing that include imaging findings from multiple modalities as well as pancreatic functional studies.⁸ However, this approach fails to identify early CP or patients at increased risk for developing CP. In children ultimately diagnosed with CP, it is plausible that a number of pathogenic pathways exist resulting in fibrotic replacement of pancreatic tissue with the associated sequelae of pancreatic endocrine and exocrine insufficiency. Understanding whether specific factors are more often associated with CP than ARP may provide insight into the pathophysiology of disease progression and help identify those patients that would most benefit from therapeutic interventions when they become available.

Since the identification of *PRSS1* as a cause of hereditary pancreatitis, genetic associations with idiopathic recurrent or chronic pancreatitis have been reported for a number of other genes including *SPINK1*, *CFTR* and *CTRC*.^{9–14} In pediatric CP, the International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPIRE) has recently identified genetic variants in 67% of patients reporting the most common variants as *PRSS1* (54%), *SPINK1* (26%), *CFTR* (18%) and *CTRC* (5%).¹⁵ While additional pediatric studies have reported varying proportions of genetic associations in CP and ARP, the extent that genetic mutations segregate with CP or ARP remains obscure.^{7,16–18} The objective of our study was to determine the ability for comprehensive genetic testing to identify genetic variants capable of differentiating children with ARP versus CP.

Methods

Patient population

We conducted a single institution retrospective review of patients with ARP and CP enrolled in our institutional pediatric pancreatitis registry between April 2013 and January 2015 (IRB # 2012–4050). Patients were defined as ARP if they had greater than one episode of pancreatitis defined by the revised Atlanta classification and INSPPIRE criteria.^{6,19} The diagnosis of CP was based on the INSPPIRE criteria and required at least one of the following: (1) abdominal pain consistent with pancreatic origin and imaging findings suggestive of chronic pancreatic damage; (2) evidence of exocrine pancreatic insufficiency and imaging findings suggestive of pancreatic damage; (3) evidence of endocrine pancreatic insufficiency and imaging findings suggestive of pancreatic damage; or (4) a surgical or pancreatic biopsy demonstrating histopathology features compatible with chronic pancreatitis. Genetic pancreatitis testing was obtained at the discretion of the provider. In the majority of cases either single gene Sanger sequencing or next generation panel testing for *PRSS1*, *CFTR*, *SPINK1* and *CTRC* was performed by a commercial clinical laboratory. Demographic and clinical data were extracted from a physician survey completed at enrollment and from retrospective chart review. Results of the physician survey were recorded in REDCap (Research Electronic Data Capture, Vanderbilt University, Nashville, Tennessee) System database to allow secure electronic capture of the data. This study was approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board.

Genetic analysis

Minor allele frequency—The minor allele frequency (MAF) of variants in our pancreatitis cohort was obtained by examining the Exome Aggregation Consortium (ExAC) database established by the Broad Institute (<http://exac.broadinstitute.org/>). The data set provided on this website spans 60,706 unrelated individuals sequenced as part of various disease-specific and population genetic studies. The ExAC is a coalition of investigators seeking to aggregate and harmonize exome sequencing data from a wide variety of large-scale sequencing projects, and to make summary data available for the wider scientific community.

Variant pathogenicity classification—Variants found in our patient cohort were classified into five categories based on the American College of Medical Genetics guidelines:^{20,21} pathogenic, likely pathogenic, variant of unknown clinical significance (VUCS), likely benign and benign. Classification was based on population frequency, mutation type, in-silico predictions, amino acid conservation, functional data and literature searches. Pathogenic and likely pathogenic variants have been binned into a mutation category. VUCS remained its own category and likely benign and benign variants were not included in the analysis.

Statistical analysis

Data were analyzed using SAS®, version 9.3 (SAS Institute, Cary, NC). Due to sample sizes and the distribution of variables, continuous data were summarized as medians with 25th and 75th percentiles while categorical data were summarized as frequency counts with

percentages. Chi-square and Fisher's exact tests were used as appropriate for group comparisons of categorical variables. For continuous data, nonparametric Wilcoxon Rank Sum test and Exact Wilcoxon tests were used to compare characteristics between groups. Odds ratios with 95% confidence limits were calculated to assess proportional differences of variants present in our registry sample versus controls. Statistical significance was set *a priori* at $\alpha=0.05$.

Results

A total of 50 pediatric ARP and CP patients were enrolled in our registry during the designated study period of which 16 (32%) met criteria for CP. When comparing the ARP and CP patient groups, there were no differences in sex, race, ethnicity, body mass index (BMI) or the frequency of genetic testing (Table 1). Patients with CP had their first AP episode at an earlier age (median of 9.0 years vs 13.5 years, $p=0.002$) and experienced a greater number of recurrent AP episodes (9.0 vs 3.0, $p=0.01$) than those in the ARP group. Exocrine pancreatic insufficiency was also found to occur at a higher rate in CP patients when compared to ARP patients ($p<0.0001$) without findings of a difference in endocrine pancreatic insufficiency between the two groups (Table 2). Genetic testing was obtained in 16/16 of CP (100%) and 29/34 of ARP (85%) patients. A total of 39 genetic variants were found in 27 of 45 subjects tested (60%) with 5 subjects (11%) having two different genes affected. Only the p.N34S mutation of *SPINK1* ($n=10$) and the p.F508del of *CFTR* ($n=6$) were identified in more than one patient (Table 3). Allele frequencies for 13/21 unique variants were significantly different from the ExAC controls with reported values ($p < 0.05$). Thirty-six variants were categorized as pathogenic and likely pathogenic, and only three variants were considered to be of an unknown clinical significance. The number of patients with variants was greatest for the *CFTR* gene (17/45, 38%) followed by *SPINK1* (11/44, 25%), *CTRC* (2/27, 7%) and *PRSSI* (2/44, 4%). With genetic testing of 90% of enrolled subjects, *CFTR* variants were more likely in those with CP compared to ARP (63% and 24%, $p=0.01$) (Table 4). The distribution of pathogenic mutations and VUCS was similar between the CP and ARP groups. The distribution of the genetic variants in the general population was also assessed by ethnic background as shown in supplementary table 1. In patients with genetic testing completed, 13/45 (29%) had obstructive risk factors including pancreas divisum ($n=7$), but there was no difference in obstructive risk factors between CP and ARP groups or between those with or without genetic variants (Tables 5 and 6). For the 6 patients with both obstructive factors and a genetic variant, all four CP patients had at least one *CFTR* variant while the two ARP patients had the *SPINK1* p.N34S variant.

Discussion

This pediatric-based study is the first to show *CFTR* variants are present at a higher rate in CP patients when compared to patients with ARP. Our patient population was similar to other published pediatric ARP/CP studies in gender, ethnicity and chronology of pancreatitis presentation.^{7,15–17} The identification of CP patients with genetic variants (68.8%) was similar to the largest pediatric cohort studied to date by the INSPPIRE consortium (67%) but differed in the genes most frequently altered (*CFTR* and *PRSSI*, respectively).¹⁵ This difference may be due in part to the high percentage of patients in our study with complete

genetic testing for the four most common genetic variants.¹⁵ Notably, in our patient cohort, the number of children with *PRSS1* mutations was much lower than the INSPPIRE cohort (4% vs 54%) which may reflect several factors including our smaller sample size, a possible founder effect in the referral base of other centers and a large referral population for total pancreatectomy and islet autotransplantation at one center in the INSPPIRE consortium. Our rates of *CFTR* and *PRSS1* variants are similar to the Italian ARP cohort of 39% and 4%, respectively,⁷ but with a higher rate of *SPINK1* variants (25% vs 7%). There was a higher rate of gene involvement in our ARP/CP patients in those patients tested for the four most common genes (27/45, 60%), compared to other published studies.^{22,23} This difference may reflect that our cohort was comprised of all pediatric patients compared to other cohorts that included pediatric and adult patients and emphasizes the importance of gene involvement in children with ARP and CP.

CFTR mutations in pancreatitis

The association of *CFTR* variants with pancreatitis has been reported as 5–39% of pediatric patients with ARP/CP.^{7,15–17} Some studies have questioned the importance of the *CFTR* variants and its relation to pancreatic disease, since the prevalence of these variants is similar to the general population,²⁴ which makes the correlation of *CFTR* involvement to pancreatic disease intriguing but incomplete. In our combined ARP/CP population, the rate of *CFTR* variants was 38%. However, the wide range reported in the literature may represent an underestimation of the role of *CFTR* abnormalities in ARP and CP since some studies assessed only known mutations associated with pulmonary disease or failed to test for *CFTR* variants in patients with other known mutations. Newer genetic testing methodology, namely next generation sequencing, allows for more detailed genotyping of *CFTR* and may uncover novel variants that alter pancreatic *CFTR* function without corresponding pulmonary disease. LaRusch and colleagues elucidated the importance of such variants showing that eight previously characterized benign *CFTR* variants found in patients with CP had a deleterious effect on bicarbonate secretion *in vitro*.²⁵

CFTR is a chloride transporter located in the plasma membrane of numerous epithelia including the lung, pancreas and intestines. Regulation of chloride transport is critical to fluid secretion across the epithelium and abnormal CFTR function results in increased luminal viscosity leading to the clinical findings seen in these organs of patients with cystic fibrosis. While CFTR functions primarily as a chloride channel, its role in HCO₃⁻ secretion has become more apparent in both pulmonary and extrapulmonary disease.^{26,27} Gray et al showed the importance of CFTR in pancreatic ductal HCO₃⁻ secretion and began the exploration of the complex regulation of pancreatic CFTR HCO₃⁻ secretion.²⁸ CFTR plays an important role in the pancreatic acinar- ductal cell harmony and the disruption of this function could result in a cascade of events from pancreatitis to pancreatic insufficiency.²⁹ Factors including luminal Cl⁻,³⁰ bile salts³¹ and ethanol³² have all been shown to influence CFTR HCO₃⁻ secretion, often independent of Cl⁻ modulation. Studies have shown that HCO₃⁻ transport by CFTR can be regulated by IRBIT via intracellular calcium and cAMP signaling pathways.³³ CFTR mutations may also alter the interactions with other apical proteins such as the SLC26 anion exchanger to further decrease HCO₃⁻ secretion.³⁴ In addition, CFTR function is altered by its internalization in acute and autoimmune

pancreatitis,³⁵ an effect that is reversed by steroids in autoimmune pancreatitis.³⁶ These findings highlight the critical role of *CFTR* in the normal physiology of pancreatic ductal epithelium and the multiple paths through which aberrant *CFTR* function may contribute to acute and chronic pancreatitis.

Understanding the possible contribution of *CFTR* dysfunction as a risk factor for CP will require larger prospective studies but may provide the impetus for therapeutic trials of *CFTR* modulators in ARP patients with *CFTR* variants.

Gene mutations and pancreas divisum

Our study did not find a significant association between pancreas divisum and genetic variants. However, it is interesting that for subjects with obstructive factors and genetic variants, those with CP (n=4) had *CFTR* variants while those with ARP (n=2) had *SPINK1* variants, supporting the hypothesis that abnormal viscosity of pancreatic secretions may compound the adverse effects of anatomic abnormalities.

Our single center study is limited by sample size and its retrospective nature. In addition, 10% of patients did not have any genetic testing (all in the ARP group) and only 54% had *CTRC* testing. We felt it was important to include VUCS in our analysis so that the data is comprehensive and future studies may prove relevance of these variants in pancreatic pathophysiology.

The complex pathophysiology of CP likely involves the interplay of genetic and environmental factors leading to the fibrotic pancreatic destruction that differentiates CP from AP/ARP. Our pediatric-based study is the first to find a higher rate of *CFTR* mutations in CP versus ARP patients and spotlights *CFTR* dysfunction as a possible focus for the first therapeutic target in pediatric ARP to halt or reverse disease progression. Larger prospective studies are warranted to better delineate the role of *CFTR* variants in the development of pediatric and adult CP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographics

	All (n=50)	CP (n=16)	ARP (n=34)	P-value
Sex, female	28 (56.0%)	8 (50.0%)	20 (58.8%)	0.56
Race				
White	40 (80.0%)	12 (75.0%)	28 (82.4%)	0.64
African American	5 (10.0%)	2 (12.5%)	3 (8.8%)	
Other	5 (10.0%)	2 (12.5%)	3 (8.8%)	
Ethnicity				
Non-Hispanic	48 (96.0%)	15 (92.3%)	33 (97.1%)	0.54
Hispanic	2 (4.0%)	1 (7.7%)	1 (2.9%)	
BMI Percentile	83.5 (54.4, 96.7)	71.6 (28.8, 94.4)	87.5 (63.1, 97.9)	0.12
BMI Percentile 85th	24 (48.0%)	6 (37.5%)	18 (52.9%)	0.54
Age enrollment, yrs	14.6 (10.9, 17.4)	12.2(9.3, 14.5)	15.9 (12.9, 18.5)	0.01
Genetic Testing done, yes	45/50 (90.0%)	16/16 (100%)	29/34 (85.3%)	0.16
Genetic variants, yes	27/45 (60.0%)	11/16 (68.8%)	16/29 (55.2%)	0.37

* Data presented as n (%) or median (25th, 75th percentile)

CP, chronic pancreatitis; ARP, acute recurrent pancreatitis; BMI, body mass index

Table 2

Phenotype

	All (n=50)	CP (n=16)	ARP (n=34)	P-value
Age 1 st AP attack, yrs	12.8 (9.0, 15.5)	9.0 (4.1, 11.0)	13.5 (10.9, 16.9)	0.002
Age CP diagnosis, yrs	10.6 (5.5, 13.1)	10.6 (5.5, 13.1)	-	-
Duration 1 st AP to CP dx, yrs	1.0 (0.8, 2.4)	1.0 (0.8, 2.4)	-	-
Additional AP attacks	3.0 (2.0, 7.0)	9.0 (3.0, 11.0)	3.0 (2.0, 4.0)	0.01
Exocrine Insufficiency	14/39 (35.9%)	11/14 (78.6%)	3/25 (12.0%)	<0.0001
Endocrine Insufficiency	0/44 (0%)	0/16 (0%)	0/28 (0%)	-

* Data presented as n (%) or median (25th, 75th percentile)

AP, acute pancreatitis; CP, chronic pancreatitis; ARP, acute recurrent pancreatitis

Table 3

Comparison of Variants in Chronic Pancreatitis/Acute Recurrent Pancreatitis and Controls

Gene	# Mutations	# with CP	Mutations	Patients	Controls (ExAC database)	ExAC P value	ExAC OR (95% CI)
CFTR	1	1/1	p.R170H (het)	1/45	29/59247	0.02	46.41 (6.19 – 348.19)
	1	1/1	p.D1152H (het)	1/45	16/60518	0.01	85.94 (11.15 – 662.12)
	6	3/6	p.Phe508del (het)	6/45	412/60648	<0.0001	22.49 (9.47 – 53.42)
	1	0/1	p.I1139V (het)	1/45	4/60623	0.004	344.43 (37.74 – 3143.31)
	1	1/1	p.Y1032C (het)	1/45	2/60441	0.002	686.81 (61.16 – 7712.82)
	1	1/1	p.R1070W (het)	1/45	3/60030	0.003	454.75 (46.40 – 4456.59)
	1	1/1	p.F508C (het)	1/45	58/59827	0.04	23.42 (3.17 – 172.84)
	1	0/1	p.G576A (het)	1/45	312/60282	0.21	4.37 (0.60 – 31.81)
	1	1/1	p.R1070Q (het)	1/45	49/60049	0.04	27.83 (3.76 – 206.00)
	1	0/1	p.S895N (het)	1/45	20/60586	0.02	68.83 (9.04 – 524.04)
	1	0/1	p.R117H (het)	1/45	93/60180	0.07	14.68 (2.00 – 107.69)
	1	0/1	p.L275F (het)	1/45	2/55949	0.002	635.76 (56.61 – 7139.59)
PRSS1	1	0/1	p.S1235R (het)	1/44	300/60091	0.20	4.64 (0.64 – 33.77)
	1	1/1	p.L997F (het)	1/44	127/60348	0.09	11.03 (1.51 – 80.69)
	1	1/1	p.L967S (het)	1/44	127/60348	0.09	11.03 (1.51 – 80.69)
	1	0/1	p.A16V (het)	1/44	968/60321	0.51	1.43 (0.20 – 10.37)
	1	0/1	P.R122H (het)	1/44	2/60672	0.002	705.47 (62.79 – 7925.68)
	10	4/10	p.N34S (het)	10/44	552/55901	<0.0001	29.49 (14.50 – 59.99)
SPINK1	1	1/1	c.-53C>T (het)	1/44	NR	--	--

Gene	# Mutations	# with CP	Mutations	Patients	Controls (ExAC database)	ExAC P value	ExAC OR (95% CI)
<i>CTRC</i>	1	0/1	c.55+1G>A (het)	1/44	NR	--	--
	1	0/1	p.R254W (het)	1/27	243/60581	0.10	10.35 (1.39 – 76.78)
	1	0/1	p.K247_R254del (het)	1/27	NR	--	--
Gene	# VUCS	# with CP	VUCS	Patients	Controls (ExAC database)	ExAC P value	ExAC OR (95% CI)
<i>CFTR</i>	1	1/1	p.V111 (het)	1/44	10/60437	0.008	140.53 (17.60 – 1121.77)
	1	0/1	p.R668C (het)	1/44	370/60076	0.24	3.75 (0.52 – 27.32)
<i>PRSSI</i>			None				
<i>SPINK1</i>	1	1/1	c.194+184T>A (het)	1/44	NR	--	--
<i>CTRC</i>			None				

CP, chronic pancreatitis; VUCS, variant of unknown clinical significance

ExAC, Exome Aggregation Consortium database established by the Broad Institute (<http://exac.broadinstitute.org/>)

TABLE 4

The Number of Patients with Genetic Variants

	CP (Total n=16) Genetic Testing N=16	ARP (Total n=34) Genetic Testing N=29	P-value
CFTR gene			
None detected	6 (37%)	22 (76%)	0.01
Not done	0	0	
Variant Detected	10 (63%)	7 (24%)	
Total # of Mutations	11	9	
Total # of VUCS	1	1	
Variant # in any patient:			
1	8 (80%)	4 (57%)	
2	2 (20%)	3 (43%)	
Cationic Trypsinogen gene PRSS1			
None detected	15 (94%)	27 (93%)	0.27
Not done	1 (6%)	0	
Variant Detected	0	2 (7%)	
Total # of Mutations	0	2	
Total # of VUCS	0	0	
SPINK1 gene			
None detected	10 (63%)	23 (79%)	0.28
Not done	1 (6%)	0	
Variant Detected	5 (31%)	6 (21%)	
Total # of Mutations	5	7	
Total # of VUCS	1	0	
Variant # in any patient:			
1	4 (80%)	5 (83%)	
2	1 (20%)	1 (17%)	
CTRC gene			
None detected	9 (56%)	16 (55%)	0.78
Not done	7 (44%)	11 (38%)	
Variant Detected	0	2 (7%)	
Total # of Mutations	0	2	
Total # of VUCS	0	0	
Genes affected:			
Only 1 gene	7 (64%)	15 (94%)	0.13
2 genes	4 (36%)	1 (6%)	
Obstructive Factors	6 (37.5%)	7 (24.1%)	0.49
Pancreas Divisum	3 (50.0%)	4 (57.1%)	

	CP (Total n=16) Genetic Testing N=16	ARP (Total n=34) Genetic Testing N=29	P-value
Sphincter of Oddi disorders	0	1 unknown	
Gallstones	0	1 (14.3%)	
Pancreaticobiliary malunion	1 (16.7%)	0	
Posttraumatic pancreatic stricture	1 (16.7%)	0	
Preampullary duodenal diverticulum	0	0	
Duct obstruction	0	0	
Annular pancreas	1 (16.7%)	0	
Choledochal Cyst	0	0	
Other	1 (16.7%)	4 (57.1%)	

Table 5

Obstructive Factors and Genetic variants between CP and ARP

N (%) yes	CP N=6	ARP N=9	P-value
Obstructive factors and:			
No variants detected	2 (33.3%)	5 (55.6%)	0.29
Unknown (no genetic testing)	0	2 (22.2%)	
Variant detected	4 (66.7%)	2 (22.2%)	
Mutations	4	2	
VUCS	1	0	
Total Variant #:			
1	1 (25%)	2 (100%)	
2	2 (50%)	0	
3	1 (25%)	0	
If genes affected, how many:			
Only 1 gene	2 (50%)	2 (100%)	0.47
2 genes	2 (50%)	0	

TABLE 6

Distribution of Variants

N (%) yes	Variants N=27	No Variants N=18	Unknown (no genetic testing) N=5	P-value
Obstructive Factors	6 (22.2%)	7 (38.9%)	2 (40.0%)	0.48
Pancreas Divisum	4 (66.7%)	3 (42.9%)	0	
Sphincter of Oddi disorders	0	1 unknown	0	
Gallstones	0	1 (14.3%)	1 (50%)	
Pancreaticobiliary malunion	0	1 (14.3%)	0	
Posttraumatic pancreatic stricture	0	1 (14.3%)	0	
Preampullary duodenal diverticulum	0	0	0	
Duct obstruction	0	0	0	
Annular pancreas	1 (16.7%)	0	0	
Choledochal Cyst	0	0	0	
Other	2 (33.3%)	3 (42.9%)	1 (50%)	