HHS Public Access

Author manuscript

J Clin Gastroenterol. Author manuscript; available in PMC 2020 July 01.

Published in final edited form as:

J Clin Gastroenterol. 2019 July ; 53(6): e232–e238. doi:10.1097/MCG.0000000000001063.

Pancreas Divisum in Pediatric Acute Recurrent and Chronic Pancreatitis: Report from INSPPIRE

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Conflicts of Interest: The other authors declare no conflicts of interest.

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Abstract

Introduction—The significance of pancreas divisum (PD) as a risk factor for pancreatitis is controversial. We analyzed the characteristics of children with PD associated with acute recurrent (ARP) or chronic pancreatitis (CP) to better understand its impact.

Patients and methods—We compared children with or without PD in the well-phenotyped INSPPIRE (**IN**ternational **S**tudy group of **P**ediatric **P**ancreatitis: **I**n search for a cu**RE**) cohort. Differences were analyzed using two-sample t-test or Wilcoxon rank sum test for continuous variables, Pearson Chi-square or Fisher's exact test for categorical variables.

Results—PD was found in 52 of 359 (14.5%) subjects, a higher prevalence than the general population (~ 7%). Females more commonly had PD (71% vs 55%; p=0.02). Children with PD did not have a higher incidence of mutations in *SPINK1, CFTR, CTRC* compared to children with no PD. Children with PD were less likely to have *PRSS1* mutations (10% vs 34%; p<0.01) or a family history of pancreatitis (p<0.05), and more likely to have hypertriglyceridemia (11% vs 3%; p=0.03). Children with PD underwent significantly more endoscopic procedures and pancreatic sphincterotomy. Patients with PD had fewer attacks of acute pancreatitis (p=0.03) and were less likely to develop exocrine pancreatic insufficiency (p=0.01). Therapeutic ERCP was considered most helpful if pancreatic duct was impacted with stones (83% helpful).

Conclusions—PD is likely a risk factor for ARP and CP in children that appears to act independently of genetic risk factors. Patients with PD and stones obstructing the pancreatic duct benefit most from therapeutic ERCP.

Keywords

Children; ERCP; MRCP; Endoscopy; Pancreatitis

INTRODUCTION

Pancreas divisum (PD), caused by the failure of ventral and dorsal pancreatic buds to fuse, is a common congenital anomaly of the pancreas [1, 2]. Pooled analysis of 23 autopsy studies demonstrates a PD incidence of 7.8% (95% CI 6.8–8.8)[3]. Studies showing a higher frequency of PD in adult patients with idiopathic pancreatitis [4] suggest that PD is a risk factor for pancreatitis. The postulated pathogenesis for pancreatitis in patients with PD is functional obstruction at the minor papilla that prevents effective drainage of the dorsal pancreatic duct, thereby increasing intraductal pressure. This theory is supported by studies describing a clinical benefit from therapeutic drainage interventions.[5–7]

In contrast, some studies have questioned the role of PD in the development of pancreatitis and its contribution to the pathogenesis of pancreatitis as controversial. The majority of individuals with PD (>95%) are asymptomatic, with PD detected during autopsy or by imaging done for reasons other than pancreatic disease. [1–3] Other studies did not find an increased frequency of PD in patients with idiopathic pancreatitis [8] or a change in the natural history of alcoholic chronic pancreatitis (CP) if PD was present.[9, 10] In addition, not all studies show a benefit from therapeutic interventions. Thus, it is not clear whether there is a causal relationship between PD and risk for acute recurrent pancreatitis (ARP) and CP and whether endoscopic or surgical interventions benefit patients with PD, or if a subset of patients may benefit from endoscopic therapy. Most studies are retrospective or small case series without proper controls.[6, 7, 11, 12] Finally, several studies have reported an association of PD with genetic variants that in themselves increase risk for pancreatitis (i.e. cystic fibrosis transmembrane conductance regulator (*CFTR*), serine protease inhibitor Kazal-type 1 (*SPINK1*)).[8, 13, 14] These authors proposed that PD alone does not cause pancreatitis, but may be a co-factor or “the second hit” that contributes to the development of pancreatitis.

The literature on PD has primarily focused on adults. It is not known whether PD alone or in combination with genetic or other risk factors leads to the development of ARP and CP in childhood. Because the majority of children with ARP or CP have genetic risk factors [15, 16] whereas most adult disease is associated with alcohol, tobacco and gallstones [17], we hypothesized that PD is an additional risk factor for childhood ARP and CP, likely in combination with the presence of genetic variants.

To address our hypothesis, we took advantage of the well-characterized **IN**ternational **S**tudy Group of **P**ediatric **P**ancreatitis: **I**n search for a cu**RE** (INSPPIRE) cohort of children with ARP or CP. [18, 19] Herein, we compare children in our database with and without PD to determine if PD is more common than expected in the general population and whether PD associates with genetic risk factors or other clinical characteristics of children with ARP or CP. Our objective is to improve our limited understanding of this anatomical anomaly.

MATERIALS AND METHODS

Demographic and clinical information of children with ARP or CP ≤19 years of age at the time of enrollment were entered into the Research Electronic Data Capture (REDCap™, Vanderbilt University, Nashville, TN)™ at nineteen INSPPIRE centers. The complete data entered to the database between September 2012 and August 2017 were included and represented baseline information of the INSPPIRE cohort. The INSPPIRE database structure, patient inclusion and exclusion criteria and the specific information collected from the physician-completed questionnaires have been previously described.[19] All subjects met the criteria for ARP or CP as previously defined by INSPPIRE.[18] Diagnosis of PD was made by magnetic retrograde cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP) or both performed at each participating center. Information related to all other radiological studies including computerized tomography (CT), and endoscopic ultrasound (EUS) was collected from the physician questionnaires. All sites obtained Institutional Review Board approval or the equivalent for their country for this

study. Written consent was obtained from the parent or guardian and assent was obtained from children 11 years or older.

Data presented from some of the patients in this study were published in references 15 and 16.

Statistical Analysis

Summary statistics used were mean with standard deviation (SD) or median with interquartile range (IQR) according to the normality of distribution. Differences between children with or without PD were analyzed using two-sample t-test or Wilcoxon-rank sum test for the continuous variables, and Pearson Chi-square or Fisher's exact test for categorical variables.

RESULTS

Demographics

Among 359 children with ARP or CP, a total of 52 (14.5%) were identified as having PD. This prevalence is higher than the reported prevalence for the general population (~7%) [3]. Females were more likely to have PD than were males (PD-71% vs no PD-55%, p=0.02) (Table 1). Otherwise, patients with PD did not differ in race, ethnicity, age at first diagnosis of acute pancreatitis (AP), CP or time interval from AP to CP. Patients with PD did not have an increased frequency of CP (54% vs 53%, p=0.92). The majority of children with or without PD were white (>80%).

Associated Risk Factors

Children with PD were significantly less likely to have a family history of AP (PD-16% vs *no* PD-31%, p=0.04) or CP (PD-9% vs no PD-25%, p=0.02) when compared with subjects without PD (Table 2).

Genetic testing for at least one mutation was performed in 303 subjects (PD: 43/52, no PD: 260/307). Among the evaluated pancreatitis-associated mutations, the protease serine 1 (*PRSS1*) gene mutation was tested most frequently (n=277), followed by *CFTR* (n=264), *SPINK1* (n=257) and trypsinogen-degrading enzyme chymotrypsin C (*CTRC*; n=175). *CFTR* (15/41, 37%) and *SPINK1* (12/40, 30%) were the most common mutations identified in the PD subjects; *PRSS1* was the most common mutation identified in the subjects without PD (79/235, 34%). The prevalence of *CFTR, SPINK1* or *CTRC* mutations did not differ between subjects with or without PD (*CFTR* p=0.28, *SPINK1* p=0.17, *CTRC* p=0.40). *PRSS1* mutations were found at a lower frequency in subjects with PD (PD-10% vs no PD-34%, p<0.01) (Table 2).

PD was found less commonly in children with *PRSS1* mutations (4/83, 5%) than in children with *CFTR* (15/81, 19%), *SPINK1* (12/56, 21%) or *CTRC* mutations (3/12, 25%). If PD was present along with at least one genetic mutation, the likelihood of CP was high (PD with any mutation 17/22 CP (77%) vs PD with no mutation 7/21 CP (33%), p<0.01). This finding seemed to be independent of PD as patients with genetic mutations who did not have PD

also had a high chance of having CP (no PD with any mutation 110/161 CP (68%) vs no PD with no mutation 36/99 CP (36%), p<0.001).

Other obstructive factors were uncommon in both groups, with 5 in PD group and 43 subjects without PD having at least one obstructive factor (Table 2). At least one toxic-metabolic risk factor was identified in 11 subjects with PD, and in 74 subjects without PD. Interestingly, hypertriglyceridemia was more common in subjects with PD (11% vs 3%, p=0.03).

Imaging Studies

All of the patients in this study had an MRCP (174 patients) or ERCP (46 patients) or both (139 patients). Patients with CP were more likely to have both MRCP and ERCP compared to patients with ARP (CP-52% vs ARP-23%, p=0.001) whereas patients with ARP were more likely to have had only an MRCP (CP-29% vs ARP-71%, p=0.001). When both tests were done, PD was found more frequently with ERCP than with MRCP although the difference was not significant (ERCP-90% vs MRCP-68%, p=0.06). Patients with PD were more likely to have an ERCP than patients without PD (PD-71% vs no PD-51%, p<0.01) (Table 3). The other imaging methods were performed at similar rates for those with and without PD including MRI (PD-67% vs no PD-74%, p=0.34), CT (PD-52% vs no PD-49%, p=0.68) and EUS (PD-17% vs no PD-13%, p=0.36). It was not known whether secretin was used with MRCP in 66 of the total 313 subjects who had MRCP only or MRCP and ERCP; it was utilized in a subset of subjects in both groups (PD: 10/52, 19%; no PD: 45/307, 15%). The frequency of abnormal imaging findings was similar between subjects with and no PD although a non-significant trend was present for a greater frequency of main pancreatic duct irregularities in PD (PD-56% vs. no PD-40%, p=0.07) and pancreatic duct dilatation (PD-58% vs. no PD-41%, p=051).

Treatments

We tracked treatment options including medical (analgesics, anti-oxidants and pancreatic enzyme replacement therapy), endoscopic and surgical therapies in children with ARP or CP. We found no difference in utilization of medical or surgical therapies between the groups (Table 4).

Pancreatic sphincterotomy was performed more frequently in patients with PD (54% vs 28%, p<0.001); biliary sphincterotomy was more common in non-PD group (4% vs 22%, p<0.01) (Table 4). Twenty children had minor papillotomy only; two major papilla sphincterotomy (minor papillotomy was unsuccessful in 1) and four a combination of major and minor papilla sphincterotomy. Of 27 children who underwent minor papillotomy for PD, pancreatic duct dilatation (dorsal, ventral or both) was found in 17 (63%), 9 had no dilatation, unknown in 1. In patients with PD, pancreatic sphincterotomy or minor papillotomy was found most helpful by the treating physician if done for pancreatic ductal stones (5/6 patients or 83%). Therapeutic ERCP in patients with PD was less helpful for abdominal pain (11/20 patients or 55%), acute recurrent pancreatitis (9/24 patients or 38%) and overall for at least one reason (13 of 27 patients or 48%). In patients without PD, pancreatic sphincterotomy was also most helpful if done for pancreatic ductal stone (24 of

39 patients or 62%). Patients with abdominal pain (19 of 58 patients or 33%), ARP (17/69 patients or 10%) and overall for at least one reason (37 of 81 patients or 46%) had poorer responses to treatment.

Disease Burden

Children with PD had fewer attacks of pancreatitis per year (p=0.02) (Table 5). Compared to children without PD, children with PD were less likely to develop exocrine pancreatic insufficiency in the time-frame of the study (9% *vs* 25%, p=0.01). No significant differences were found in the frequency or nature of pancreatitis-related pain, emergency room visits or number of hospitalizations between the groups. The frequency of diabetes was no different between the groups (8% *vs* 7%, p=0.76).

DISCUSSION

We previously reported that genetic and obstructive lesions are the primary risk factors for ARP and CP in children.[16] In this study, we focused on the role of PD as an obstructive risk factor for pediatric ARP and CP. PD was found in 14.6% of children with ARP or CP, which is significantly greater than the incidence reported in the general population [3]. Fogel et al. reviewed the literature for reports of the PD prevalence determined by autopsy, ERCP or MRCP in the general population [3]. The prevalence of PD was 7.8% by autopsy, 3.5% by ERCP, and 7.1% by MRCP. The PD prevalence in children was significantly higher than the reported PD prevalence by autopsy studies (226 PD in 2895 subjects or 7.8%, p=<0.001), by ERCP (1413 PD in 39,632 subjects or 3.5%, p=<0.001) and by MRCP (188 PD in 2231 subjects, 8.4%, p=<0.001) [3]. A recent MRCP study of healthy individuals found a prevalence of 9.6% [20]. Of course, we have compared the PD prevalence in children to studies of adults and there is a possibility of technical bias for ERCP and MRCP because of the smaller size of many pediatric patients. Even so, the technical bias associated with smaller spatial resolution and difficulty in accessing and injecting the dorsal pancreatic duct would underestimate the prevalence of PD in children. Thus, our findings support the conclusion that PD is a risk factor for ARP and CP in children.

Interestingly, we found the majority of children with PD to be female (72%) whereas children without PD were equally distributed in gender. Lucidi et al observed a similar trend in their ARP pediatric cohort where 60% of subjects with structural abnormalities including PD were noted to be female.[21] Despite this intriguing observation, the clinical relevance of female sex and how it may influence susceptibility to pancreatitis or interact with PD to increase risk remains unclear.

The association between PD and pancreatitis-related genetic mutations has been reported in adult patients with idiopathic pancreatitis.[8, 22, 23] In all cases, PD was reported as a “co-factor” or as participating in a “two-hit” phenomenon to increase the susceptibility to pancreatitis. A potential association between PD and *CFTR* mutations has received the greater attention.[8, 22, 23] Bertin et al found the frequency of PD to be no different in patients with idiopathic pancreatitis (5%) and controls (7%), yet, the combined presence of *CFTR* and PD was significantly higher (47%) suggesting perhaps they interact as cofactors in the development of pancreatitis. We did not find an increased incidence of genetic

mutations in patients with PD. We have to note that only 84% of our cohort underwent at least one gene testing for known pancreatitis-associated mutations (*PRSS1, SPINK1, CFTR, CTRC*) and many did not have all 4 genes tested. Thus, we cannot reliably conclude that PD interacted with genetic risk factors to cause CP in our cohort.

When comparing subjects with and without PD, we identified significantly lower number of children with PD as having a family history of pancreatitis and the *PRSS1* genetic variant. Given the autosomal dominant mode of inheritance for *PRSS1* with a disease penetrance of >80% [24, 25], it may not be surprising that non-PD group has a more frequent family history of AP and CP. In addition, only 5% of children with *PRSS1* mutations had PD, much lower than the remainder of the cohort. The negative association of PD with *PRSS1* mutations in this study is most curious. In a pediatric ARP and CP cohort from Korea, 4 of 6 children had *SPINK1* or *PRSS1* mutations and children with PD plus a mutation were more likely to have CP [26]. We have found a high likelihood of CP in children with PD and genetic mutations, but this seemed to be driven by genetic variants, not PD. The negative association of *PRSS1* mutations with PD needs further investigation.

The only toxic or metabolic risk factors we observed to have an increased association with PD in our patients was hypertriglyceridemia. To our knowledge, an association between PD and hypertriglyceridemia has not been previously reported. Hypertriglyceridemia is a well-known risk for AP in children and adults.[27, 28] In a recent review of adults with hypertriglyceridemia and pancreatitis, a large number had ARP and a smaller subset had CP suggesting elevated triglycerides may be a risk factor for ARP and CP.[29] Most patients with hypertriglyceridemia had other risk factors such as obesity, poorly controlled diabetes mellitus, use of medications associated with AP, heavy alcohol consumption or smoking. The authors did not report the incidence of PD in the population. The explanation for why we found an association between PD and hypertriglyceridemia and not with other risk factors is not clear.

We did not observe a higher disease burden (increased pain, ER visits, hospitalizations, medical or surgical therapies) in children with PD, compared with children without PD. Children with PD underwent significantly more ERCPs and pancreatic sphincterotomies (specifically minor papillotomy) and were less likely to have acute attacks and exocrine pancreatic insufficiency (EPI) compared with the non-PD group over the study period. Biliary sphincterotomy was performed only in 3 children with PD for unclear reasons. It has to be noted that the data were obtained from the treating physician in the form of a questionnaire. To adequately interpret the utility of endoscopic procedures in PD, future studies require adequate power, detailed histories and endoscopic findings, type of endoscopic intervention performed (e.g. papillotomy +/− stent placement, stone extraction, stricture dilation), in addition to short- and long-term outcomes.

Despite defining the PD diagnosis based on standard criteria (radiographic imaging or direct ductal opacification during ERCP), it is possible that PD diagnosis was under-reported due to diagnostic limitations of MRCP and ERCP including the omission of secretin in some cases which has been shown to increase the MRCP sensitivity and specificity for the detection of PD.[30] Due to the variable MRCP imaging protocols at each INSPPIRE site,

secretin-MRCP was not standardized in all cases and its usage was left to the discretion and routine practice of the participating institution. In the future, secretin-MRCP should be considered for the diagnosis of pancreatic ductal disease or anomalies.

Although ERCP is the gold standard for PD confirmation, our physician-completed questionnaires did not collect information on ERCP success rates of obtaining an adequate or complete pancreatogram via the major and minor papilla, therefore it is possible true PD failed to be appropriately diagnosed in some cases. However, the pervasiveness of this potential limitation is unlikely given that an active effort would be made by the therapeutic endoscopist to prove or disprove the presence of abnormal or atypical pancreatic ductal anatomy at the time of ERCP.

EUS is an alternative method for diagnosing PD.[31, 32] The INSPPIRE physician-completed questionnaire for EUS findings was designed to mainly collect information related to findings that would be supportive of CP and the development of complications including pancreatic cysts. Therefore, EUS data cannot be used for the diagnosis of PD in this study.

The prevalence of PD in the INSPPIRE cohort of children with ARP or CP is greater than the prevalence reported in the healthy adult population. The prevalence of PD was significantly lower in patients with *PRSS1* mutations. The prevalence of *CFTR, SPINK1, CTRC* did not differ statistically with the presence or absence of PD. Still, more than half of patients with PD tested for genetic risk variants carried at least one genetic risk variant. The presence of PD should not preclude genetic testing for other genetic risk factors in children. Patients with PD and ductal obstruction benefit most from therapeutic ERCP. Additional research is needed to better define the role of PD in the onset and progression of pediatric pancreatitis and the role of interventional ERCP in therapy.

Acknowledgments

Funding: Dr. Aliye Uc is supported by the National Institute of Health grants (R21 DK096327, U01 DK108334, R01 DK097820) and National Pancreas Foundation; INSPPIRE registry was developed by CTSA (2UL1 TR000442) and REDCap.

Dr. Mark Lowe is on the Board of Directors of the National Pancreas Association; receives royalties from Millipore Inc and UpToDate. Dr. Tanja Gonska received a research grant from Vertex Pharmaceuticals. Dr. John Pohl is on the speaker's bureau for Medical Education Resources, Inc.; Dr. Melena Bellin is a consultant for AbbVie Inc and ARIEL Precision Medicine. Dr. Aliye Uc is a member of American Board of Pediatrics, Subboard of Pediatric Gastroenterology.

References

1. MacCarty RL, Stephens DH, Brown AL Jr, et al. Retrograde pancreatography in autopsy specimens. Am J Roentgenol Radium Ther Nucl Med. 1975; 123:359–366.
2. Stimec B, Bulajic M, Tatic S, et al. Unusual variants of the tributaries of the main pancreatic duct revealed by postmortem and endoscopic pancreatography. Ann Anat. 1996; 178:169–171. [PubMed: 8638771]
3. Fogel EL, Toth TG, Lehman GA, et al. Does endoscopic therapy favorably affect the outcome of patients who have recurrent acute pancreatitis and pancreas divisum? Pancreas. 2007; 34:21–45. [PubMed: 17198181]

4. Dhar A, Goenka MK, Kochhar R, et al. Pancrease divisum: five years' experience in a teaching hospital. Indian J Gastroenterol. 1996; 15:7–9. [PubMed: 8840617]
5. Lans JI, Geenen JE, Johanson JF, et al. Endoscopic therapy in patients with pancreas divisum and acute pancreatitis: a prospective, randomized, controlled clinical trial. Gastrointest Endosc. 1992; 38:430–434. [PubMed: 1511816]
6. Chacko LN, Chen YK, Shah RJ. Clinical outcomes and nonendoscopic interventions after minor papilla endotherapy in patients with symptomatic pancreas divisum. Gastrointest Endosc. 2008; 68:667–673. [PubMed: 18436218]
7. Borak GD, Romagnuolo J, Alsolaiman M, et al. Long-term clinical outcomes after endoscopic minor papilla therapy in symptomatic patients with pancreas divisum. Pancreas. 2009; 38:903–906. [PubMed: 19672208]
8. Bertin C, Pelletier AL, Vullierme MP, et al. Pancreas divisum is not a cause of pancreatitis by itself but acts as a partner of genetic mutations. Am J Gastroenterol. 2012; 107:311–317. [PubMed: 22158025]
9. Barthet M, Valantin V, Spinosa S, et al. Clinical course and morphological features of chronic calcifying pancreatitis associated with pancreas divisum. Eur J Gastroenterol Hepatol. 1995; 7:993–998. [PubMed: 8590148]
10. Spicak J, Poulova P, Plucnarova J, et al. Pancreas divisum does not modify the natural course of chronic pancreatitis. J Gastroenterol. 2007; 42:135–139.
11. Liao Z, Gao R, Wang W, et al. A systematic review on endoscopic detection rate, endotherapy, and surgery for pancreas divisum. Endoscopy. 2009; 41:439–444. [PubMed: 19337962]
12. Kanth R, Samji NS, Inaganti A, et al. Endotherapy in symptomatic pancreas divisum: a systematic review. Pancreatology. 2014; 14:244–250. [PubMed: 25062871]
13. Choudari CP, Imperiale TF, Sherman S, et al. Risk of pancreatitis with mutation of the cystic fibrosis gene. Am.J.Gastroenterol. 2004; 99:1358–1363. [PubMed: 15233679]
14. Garg PK, Khajuria R, Kabra M, et al. Association of SPINK1 gene mutation and CFTR gene polymorphisms in patients with pancreas divisum presenting with idiopathic pancreatitis. J Clin. Gastroenterol. 2009; 43:848–852. [PubMed: 19593166]
15. Kumar S, Ooi CY, Werlin S, et al. Risk Factors Associated With Pediatric Acute Recurrent and Chronic Pancreatitis: Lessons From INSPPIRE. JAMA Pediatr. 2016; 170:562–569. [PubMed: 27064572]
16. Schwarzenberg SJ, Bellin M, Husain SZ, et al. Pediatric chronic pancreatitis is associated with genetic risk factors and substantial disease burden. J Pediatr. 2015; 166:890–896. e891. [PubMed: 25556020]
17. Yadav D, Hawes RH, Brand RE, et al. Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. Arch Intern Med. 2009; 169:1035–1045. [PubMed: 19506173]
18. Morinville VD, Husain SZ, Bai H, et al. Definitions of pediatric pancreatitis and survey of present clinical practices. J Pediatr Gastroenterol Nutr. 2012; 55:261–265. [PubMed: 22357117]
19. Morinville VD, Lowe ME, Ahuja M, et al. Design and implementation of INSPPIRE. J Pediatr Gastroenterol Nutr. 2014; 59:360–364. [PubMed: 24824361]
20. Bulow R, Simon P, Thiel R, et al. Anatomic variants of the pancreatic duct and their clinical relevance: an MR-guided study in the general population. Eur Radiol. 2014; 24:3142–3149. [PubMed: 25120204]
21. Lucidi V, Alghisi F, Dall'Oglio L, et al. The etiology of acute recurrent pancreatitis in children: a challenge for pediatricians. Pancreas. 2011; 40:517–521. [PubMed: 21499205]
22. Dray X, Fajac I, Bienvenu T, et al. Association of pancreas divisum and recurrent acute pancreatitis with the IVS8-5T-12TG allele of the CFTR gene and CFTR dysfunction. Pancreas. 2007; 35:90–93. [PubMed: 17575549]
23. Gelrud A, Sheth S, Banerjee S, et al. Analysis of cystic fibrosis gener product (CFTR) function in patients with pancreas divisum and recurrent acute pancreatitis. Am J Gastroenterol. 2004; 99:1557–1562. [PubMed: 15307877]

24. Sossenheimer MJ, Aston CE, Preston RA, et al. Clinical characteristics of hereditary pancreatitis in a large family, based on high-risk haplotype. The Midwest Multicenter Pancreatic Study Group (MMPSG). Am J Gastroenterol. 1997; 92:1113–1116. [PubMed: 9219780]
25. Rebours V, Boutron-Ruault MC, Schnee M, et al. The natural history of hereditary pancreatitis: a national series. Gut. 2009; 58:97–103. [PubMed: 18755888]
26. Lee YJ, Kim KM, Choi JH, et al. High incidence of PRSS1 and SPINK1 mutations in Korean children with acute recurrent and chronic pancreatitis. J Pediatr Gastroenterol Nutr. 2011; 52:478–481. [PubMed: 21415673]
27. Abu-El-Haija M, El-Dika S, Hinton A, et al. Acute Pancreatitis Admission Trends: A National Estimate through the Kids' Inpatient Database. J Pediatr. 2017
28. Pedersen SB, Langsted A, Nordestgaard BG. Nonfasting Mild-to-Moderate Hypertriglyceridemia and Risk of Acute Pancreatitis. JAMA Intern Med. 2016; 176:1834–1842. [PubMed: 27820614]
29. Vipperla K, Somerville C, Furlan A, et al. Clinical Profile and Natural Course in a Large Cohort of Patients With Hypertriglyceridemia and Pancreatitis. J Clin Gastroenterol. 2017; 51:77–85. [PubMed: 27322530]
30. Rustagi T, Njei B. Magnetic resonance cholangiopancreatography in the diagnosis of pancreas divisum: a systematic review and meta-analysis. Pancreas. 2014; 43:823–828. [PubMed: 24743381]
31. Rana SS, Bhasin DK, Sharma V, et al. Role of endoscopic ultrasound in the diagnosis of pancreas divisum. Endosc Ultrasound. 2013; 2:7–10. [PubMed: 24949360]
32. Kushnir VM, Wani SB, Fowler K, et al. Sensitivity of endoscopic ultrasound, multidetector computed tomography, and magnetic resonance cholangiopancreatography in the diagnosis of pancreas divisum: a tertiary center experience. Pancreas. 2013; 42:436–441. [PubMed: 23211370]

Table 1

Demographic Characteristics of the INSPPIRE Cohort by PD Status

	PD=Yes (n=52)	PD=No (n=307)	p-value
Sex (Female)	37 (71%)	168 (55%)	**0.02**
	(n=51)	(n=281)	
Ethnicity (Hispanic)	11 (22%)	74 (26%)	0.47
Race	(n=45)	(n=263)	
White	37 (82%)	221 (84%)	0.95
African American	2 (4%)	8 (3%)	
Asian	2 (4%)	15 (6%)	
Multi-racial	3 (7%)	14 (5%)	
Other	1 (2%)	5 (2%)	
Age at first diagnosis of AP	(n=47)	(n=289)	
Mean±SD	8.7±4.3	8.7±4.7	0.91
Range	2.2–18.2	0.4–18.4	
With CP	28 (54%)	163 (53%)	0.92
Age at diagnosis of CP	(n=22)	(n=150)	
Mean±SD	10.1±3.8	10.2±4.3	0.96
Range	3.4–17.4	1.5–18.0	
Time from AP to CP, years	(n=47)	(n=293)	
Median (25^{th}–75^{th} percentile)	3.1 (1.4–7.6)	2.9 (0.6–7.7)	0.57

PD, pancreas divisum; AP, acute pancreatitis; CP, chronic pancreatitis; SD: Standard deviation

Significant p values are highlighted

Table 2

Risk Factors of ARP or CP in INSPPIRE Cohort by PD Status

	PD=Yes (n=52)	PD=No (n=307)	p-value
Family history			
Acute pancreatitis	7/43 (16%)	79/252 (31%)	**0.04**
Chronic pancreatitis	4/43 (9%)	64/257 (25%)	**0.02**
Genetic Risk Factors:			
PRSS1	4/42 (10%)	79/235 (34%)	**<0.01**
SPINK1	12/40 (30%)	44/217 (20%)	0.17
CFTR	15/41 (37%)	66/223 (28%)	0.28
CTRC	3/27 (11%)	9/148 (6%)	0.40
Obstructive factors			
Sphincter of Oddi disorders	2/50 (4%)	8/295 (3%)	0.64
Gallstones	1 (2%)	14/299 (5%)	0.70
Pancreatic duct mal-union	1/51 (2%)	13/299 (4%)	0.70
Post-traumatic pancreatic stricture	0/50 (0%)	2/301 (1%)	1.0
Preampullary duodenal diverticulum	0/51 (0%)	1/301 (0.3%)	1.0
Duct obstruction	1 (2%)	8/301 (3%)	1.0
Annular pancreas	0 (0%)	3/301 (1%)	1.0
Biliary cyst	0 (0%)	8/302 (3%)	0.61
Toxic/Metabolic			
Alcoholic	0 (0%)	4/306 (1%)	1.0
Active/Passive smoking exposure	3/49 (6%)	23/296 (8%)	1.0
Hypertriglyceridemia	5/44 (11%)	9/266 (3%)	**0.03**
Medications	1/45 (2%)	27/282 (10%)	0.14
Autoimmune pancreatitis	0/43 (0%)	8/246 (3%)	0.61
Other autoimmune diseases	4/50 (8%)	21/294 (7%)	0.77
Crohn’s disease	0/49 (0%)	1/291 (0.3%)	1.0
Ulcerative colitis	1/50 (2%)	2/291 (1%)	0.38
Intedeterminate colitis	0/49 (0%)	2/291 (1%)	1.0
Azathioprine or 6-MP treatment	0/50 (0%)	3/292 (1%)	1.0

ARP: Acute Recurrent Pancreatitis; CP: Chronic Pancreatitis; PD, pancreas divisum; PRSS1, protease serine 1; SPINK1, serine protease inhibitor Kazal-type 1; CFTR, cystic fibrosis transmembrane conductance regulator; CTRC, trypsinogen-degrading enzyme chymotrypsin C; 6-MP, 6-mercaptopurine

Significant p values are highlighted

Table 3

Imaging Study Findings in Children with ARP or CP by PD Status

	Pancreas Divisum=Yes (n=52)	Pancreas Divisum=No (n=307)	p-value
Imaging studies performed			
ERCP	37 (71%)	158 (51%)	**<0.01**
Number ERCP (range)	(1–12)	(1–9)	
1	21	88	
2	7	36	
3	5	14	
≥4	4	20	
CT scan	27 (52%)	150 (49%)	0.68
MRI	35 (67%)	226 (74%)	0.34
EUS	9 (17%)	39 (13%)	0.36
Findings (any imaging)			
Focal Acute Pancreatitis	5/36 (14%)	33/240 (14%)	1.0
Inflammatory changes	14/36 (39%)	84/242 (35%)	0.62
Enlarged Pancreas	7/36 (19%)	55/242 (23%)	0.65
Cysts/Pseudocysts	10/52 (19%)	49/307 (16%)	0.55
Peripancreatic inflammation/fat stranding	16/39 (41%)	82/246 (33%)	0.34
Gallstones/Sludge	3/36 (8%)	16/241 (7%)	0.72
Pancreatic Atrophy	11/37 (30%)	70/245 (29%)	0.88
PD stricture	15/49 (31%)	70/295 (24%)	0.30
PD irregularities	20/36 (56%)	97/245 (40%)	0.07
PD dilatation	21/36 (58%)	101/246 (41%)	0.05
Calcifications	4/37 (11%)	24/243 (10%)	0.77
CBD stricture	2/51 (4%)	18/305 (6%)	0.75
CBD dilatation	8/52(15%)	58/306 (19%)	0.53
CBD stones	1/52 (2%)	25/307 (8%)	0.14
Intraheptic biliary dilatation	4/36 (11%)	27/245 (11%)	1.0
Abnormal Side Branches	18/50 (36%)	80/296 (27%)	0.19
Changes suggestive of cirrhosis and/or portal hypertension	2/36 (6%)	13/241 (5%)	1.0
Main Pancreatic Duct - Abnormal	33/52 (63%)	160/303 (53%)	0.15
Intraductal filling defects of calculi	9/52 (17%)	57/300 (19%)	0.77

ARP: Acute Recurrent Pancreatitis; CP: Chronic Pancreatitis; PD, pancreas divisum; ERCP, endoscopic retrograde cholangiopancreatography; CT, computed tomography; MRI, magnetic resonance imaging; EUS, endoscopic ultrasound; CBD, common bile duct

Significant p values are highlighted

Table 4

Treatments Utilized in Children with ARP or CP by PD Status

	Pancreas Divisum=Yes (n=52)	Pancreas Divisum=No (n=307)	p-value
Medical Therapies			
Pain medications	20/49 (41%)	121/274 (44%)	0.66
Pancreatic enzymes	20/50 (40%)	105/273 (38%)	0.83
Vitamins/antioxidants	17/50 (34%)	118/276 (43%)	0.24
Steroids	0/50 (0%)	8/276 (3%)	0.61
Diabetic medications	3/50 (6%)	22/277 (8%)	0.77
Endoscopic Therapies			
Any ERCP	31/50 (62%)	152/305 (50%)	0.11
Biliary sphincterotomy	2/49 (4%)	66/299 (22%)	**<0.01**
Pancreatic sphincterotomy	27/50 (54%)	83/298 (28%)	**<0.001**
Pancreatic duct stent placement	17/50 (34%)	80/301 (27%)	0.27
Biliary stent placement	1/50 (2%)	17/301 (6%)	0.48
Pancreatic duct stone removal	6/50 (12%)	47/300 (16%)	0.50
Surgical Therapies			
Any Pertinent Surgeries	12 (23%)	81/305 (27%)	0.59
Cholecystectomy	4 (8%)	41/304 (13%)	0.24
Celiac nerve block	1 (2%)	5/304 (2%)	1.0
Cyst/pseudo-cyst operation	1 (2%)	13/304 (4%)	0.70
Lateral pancreaticojejonstomy	2 (4%)	14/304 (4%)	1.0
Partial pancreatectomy	0 (0%)	2/304 (1%)	1.0
TPIAT	5 (10%)	34/304 (11%)	1.0

ARP: Acute Recurrent Pancreatitis; CP: Chronic Pancreatitis; PD, pancreas divisum; PERT, pancreatic enzyme replacement therapy; ERCP, endoscopic retrograde cholangiopancreatography; TPIAT, total pancreatectomy with islet auto-transplantation

Significant p values are highlighted

Table 5

Disease Burden in Children with ARP or CP by PD Status

	Pancreas Divisum=Yes (n=52)	Pancreas Divisum=No (n=307)	p-value
Pattern of abdominal pain	(n=49)	(n=276)	
- no abdominal pain	4 (8%)	35 (13%)	0.65
- usually pain free; episodes of mild-moderate pain	9 (18%)	40 (14%)	
- constant mild-moderate pain	2 (4%)	15 (5%)	
- usually pain free; episodes of severe pain	16 (33%)	93 (34%)	
- constant mild-moderate pain+ episodes of severe pain	15 (31%)	76 (28%)	
- constant severe pain	3 (6%)	17 (6%)	
Constant Pain score	(n=45)	(n=261)	
Median (IQR)	0 (0–17)	0 (0–0)	0.21
Range	0–92	0–100	
With any level of constant pain	16 (36%)	62 (24%)	
Episodic Pain score	(n=40)	(n=254)	
Median (IQR)	66.5 (33–79.5)	60 (9–84)	0.98
Range	0–100	0–100	
With any level of episodic pain	34 (85%)	195 (77%)	
Number of ER visits – lifelong (average/yr)	(n=36)	(n=206)	
Median (IQR)	1.7 (1.0–3.7)	1.6 (0.5–2.9)	0.40
Range	0–25	0–18	
Number of ER visits – past year	(n=45)	(n=261)	
Median (IQR)	2 (1–3)	2 (0–3)	0.20
Range	0–12	0–30	
Number of hospitalizations – lifelong (average/yr)	(n=41)	(n=205)	
Median (IQR)	1.6 (1.0–3.6)	1.5 (0.5–2.8)	0.29
Range	0–25	0–18	
Number of hospitalizations – past year	(n=45)	(n=263)	
Median (IQR)	2 (1–3)	1 (0–3)	0.38
Range	0–13	0–23	
Days missed school past month	(n=38)	(n=221)	
Median (IQR)	3 (0–10)	1 (0–6)	0.11
Range	0–30	0–180	
Abdominal pain related to pancreatitis	36/48 (75%)	247/299 (83%)	0.20
Exocrine insufficiency	4/45 (9%)	70/277 (25%)	**0.01**
Endocrine insufficiency	4/50 (8%)	21/297 (7%)	0.76

	Pancreas Divisum=Yes (n=52)	**Pancreas Divisum=No (n=307)**	**p-value**
Number of acute pancreatitis attacks per year	(n=37)	(n=225)	
Median (IQR)	1.4 (0.6–2.0)	1.8 (0.9–3.4)	**0.02**
Range	0–25	0–66	

ARP: Acute Recurrent Pancreatitis; CP: Chronic Pancreatitis; ER: Emergency Room; IQR: interquartile range