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Pancreas divisum does not cause pancreatitis, but associates with *CFTR* mutations

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Abstract

Bertin *et al*¹ partially dispel arguments that pancreas divisum (PD) causes pancreatitis, but fascinatingly indicate that PD associates with *CFTR* gene mutations predisposing to pancreatitis. This association, however, does not definitely confer a pathophysiological role for PD in pancreatitis but may denote that PD co-mingles with *CFTR* mutations without influencing pancreatitis or *CFTR* mutations influence pancreatic duct embryogenesis. We advise “idiopathic pancreatitis” patients with PD to undergo genetic testing. In lieu of *CFTR* mutations, undertake no endoscopic/surgical procedure; if *CFTR* mutations are found, refer patients for genetic counseling and withhold endoscopic/surgical therapy unless randomized studies show benefit.

Editorial

There is increasing evidence that pancreas divisum (PD) does not cause pancreatitis. Bertin *et al*¹ add further support that PD does not trigger pancreatitis by showing that the prevalence of PD was similar in patients with and without idiopathic pancreatitis and alcoholic pancreatitis (7, 5 and 7%, respectively). Although they concluded that PD by itself does not cause pancreatitis, they found that the prevalence of PD in patients with pancreatitis and *CFTR*, *SPINK1* or *PRSS1* mutations (a term we use broadly to include polymorphisms) was 47, 16 and 16%, respectively, and concluded that PD “acts as a partner of genetic mutations” or cofactor in causing pancreatitis in patients with these mutations. This second conclusion is problematic. Associations do not confer causation.

Another analysis of table 1 of Bertin *et al*¹, which assumes that all 114 patients with and without gene mutations (1st 4 columns) have “idiopathic pancreatitis”, reveals several observations. First, 65% of patients with “idiopathic pancreatitis” had gene mutations (74 of 114) and 91% of the subset with PD had a gene mutation (21 of 23). Considering only *CFTR* mutations, the prevalence of mutations is higher in patients with pancreatitis and PD (61%) than in pancreatitis patients without PD (18%). This latter prevalence data is low, however, compared to the 37% prevalence of *CFTR* mutations reported by Cohn *et al*² in idiopathic pancreatitis without PD. Although a greater proportion of patients with PD may have a *CFTR* mutation than patients without PD, these data are insufficient to claim that PD

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is a partner or cofactor with *CFTR* mutations in causing pancreatitis. Alternative hypotheses that might explain this association are that *CFTR* mutations associated with pancreatitis also alter embryogenesis of the pancreatic duct and/or PD merely co-mingles with *CFTR* mutations without influencing the genetic susceptibility to pancreatitis.

Not all patients with gene mutations (particularly *CFTR* and *SPINK1* mutations) develop idiopathic recurrent pancreatitis or chronic pancreatitis (AR/CP), and it is unknown what the prevalence of PD is in these persons. Collecting PD prevalence data for persons with gene mutations but no pancreatitis might strengthen or weaken the assertion that PD is a cofactor in causing pancreatitis in patients with gene mutations. If persons with gene mutations and no pancreatitis have a similar prevalence of PD (~7%) as the other control populations, the authors' assumption would be strengthened. Finding, however, that the prevalence of PD in this group was similar to patients with the gene mutations and pancreatitis would suggest that PD and gene mutations co-mingle without PD being a co-factor in causing AR/CP.

Background prevalence of PD reported by Bertin *et al*¹ corroborate previous findings. For example, there is wide variability reported in the literature for the prevalence of PD in the normal population. Based on a review and pooling of data from 77 studies³, we reported 4–18% or higher prevalence of PD in patients without pancreatitis. Recent studies report PD prevalence in this range. For example, Choudari *et al*⁴ reported a 10% prevalence and Bertin *et al*¹ report a 5–7% PD prevalence in the control groups (idiopathic pancreatitis, alcoholic pancreatitis and no pancreatic disease).

Genetic data of Bertin *et al*¹ correspond to previous observations, particularly in terms of the association between PD and pancreatitis patients with *SPINK1* or *PRSS1* gene mutations¹. Gene mutations, most commonly *CFTR* and *SPINK1*, associate in up to 50% of AR/CP patients^{5–7}. The majority of idiopathic AR pancreatitis patients likely have early onset idiopathic CP because *CFTR* and *SPINK1* mutations do not associate with single attacks of acute pancreatitis^{8,9} and the results of natural history studies of patients with idiopathic AR pancreatitis indicate that most develop CP^{10–12}. In India the prevalence of *SPINK1* mutations (range 36–43%) is similar in pancreatitis patients with and without PD¹³. *PRSS1* mutations R122H and N291 have a high disease penetrance (80 and 93 percent)^{14,15} and should not be considered cofactors.

Recent results reported by Japanese investigators¹⁶ differ from the observations by Bertin *et al*¹. To reduce biases associated with referral centers, these investigators used diagnostic magnetic resonance cholangiopancreatography in a community setting to detect PD in 46 patients with idiopathic pancreatitis (8 acute, 23 CP, 15 AR) and in 504 healthy controls. PD prevalence was 2.6% in the control group and significantly higher in the idiopathic AR/CP groups (33% and 43%) but not the acute pancreatitis group (13%). Unfortunately, the investigators did not report genetic data so it is impossible to discern whether there was an association between the increased PD prevalence in the idiopathic AR/CP groups and *CFTR* mutations. In a future study, these investigators may address this limitation by performing genetic testing.

Cigarette smoking is an etiologic factor that Bertin *et al*¹ overlooked and may have influenced their results. Smoking is emerging as major risk for AR pancreatitis and CP^{17,18}, a proposal dating to Claessen in 1842¹⁹ or earlier. Chronic cigarette smoking impairs *CFTR* ion channel conductance in pancreatic ductal cells²⁰, one possible mechanism predisposing to idiopathic pancreatitis, particularly in persons carrying a *CFTR* mutation. Thus, stratification of the data of Bertin *et al*¹ by smoking status may have uncovered whether PD and smoking co-associate or co-mingle in “idiopathic pancreatitis”, similar to analyses of

PD and *CFTR* mutations in idiopathic pancreatitis. Future studies examining the etiology of idiopathic pancreatitis should consider stratification by cigarette smoking.

Bertin *et al*¹ commented that PD obstructs flow of pancreatic juice through the accessory papilla and induces pancreatitis, particularly if there are underlying gene mutations predisposing to pancreatitis. This hypothesis is tantalizing, because *CFTR* mutations increase juice viscosity²¹. We caution, however, that *CFTR* and other mutations have additional sensitizing effects on the pancreas^{22, 23} and there is no experimental evidence (to our knowledge) showing that obstruction in the presence of these gene mutations increase susceptibility to pancreatitis. Based on the hypothesis that PD obstructs flow of pancreatic juice through the accessory papilla, endoscopic and surgical procedures have been advocated to alleviate this presumed obstruction. As we recently updated²⁴ and reviewed³, however, there is no standardized method for assessing a functionally significant obstruction of the minor papilla that predicts endoscopic or surgical response. Although there are a myriad of studies to investigate whether these procedures alleviate pancreatitis, none, including a recent systematic review of uncontrolled endoscopic and surgical studies of patients with PD²⁵, are of sufficient quality to show that either surgical or endoscopic therapy is beneficial (see recent update²⁴ and review³).

This paper has several important research and clinical implications. First, to understand whether PD participates with genetic cofactors in idiopathic pancreatitis it is necessary to determine the frequency of PD in the subgroup of patients with *CFTR* mutations who do not have pancreatitis. Second, patients with “idiopathic pancreatitis” and PD should undergo genetic testing for *CFTR* mutations. If no gene mutations are found, no endoscopic or surgical procedure should be undertaken to alter the accessory sphincter. Third, if gene mutations are found, we recommend referring patients for genetic counseling and withholding endoscopic or surgical therapy unless properly designed studies show these therapies benefit patients. Finding that there possibly is an association between PD and gene mutations (namely *CFTR* mutations) in causation of pancreatitis affords the opportunity to perform randomized studies to determine if accessory sphincter alteration really benefits these patients.

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