PRSS1 copy number variants and promoter polymorphisms in pancreatitis: common pathogenetic mechanism, different genetic effects

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We have read with interest three related papers that were recently published in this journal.[1-3] Taken together, the findings reported in these papers (summarized in online supplementary note) suggest that loss-of-function *PRSS1* promoter variants can protect against pancreatitis. The other side of the coin is however that gain-of-function *PRSS1* promoter variants predispose to pancreatitis. It therefore follows that the risk-associated [rs4726576C; rs10273639C] allele shares a common pathogenetic mechanism with the previously reported trypsinogen duplication and triplication copy number variants (CNVs)[4,5] since both types of variant predispose to pancreatitis by increasing *PRSS1* expression; this mechanism is quite distinct from either the increased activation and/or stability of trypsin(ogen) or misfolding-induced endoplasmic reticulum stress caused by disease-associated *PRSS1* missense mutations.[6] However, despite both serving to increase *PRSS1* expression, the promoter variant and the CNVs differ significantly in terms of the relative strength of their genetic effects. The risk-associated [rs4726576C; rs10273639C] allele (whose frequency was found to be 0.54 and 0.57 respectively in healthy French individuals of European ancestry[3] and controls from the North American Pancreatitis Study 2[7]) had only a modest genetic effect, defined as having an Odds Ratio of <1.5 in accordance with ref. 8, with respect to the clinical phenotype. By contrast, the *PRSS1* duplication/triplication CNVs, which have never been reported in normal populations, can be classified as disease-causative.

Despite their evident clinical importance, *PRSS1* CNVs have not so far been analysed by many research groups. Apart from the technical difficulties inherent in detecting CNVs, particularly those characterized by an increased copy number, there may be another reason viz. the *PRSS1* duplication and triplication CNVs found in French Caucasian patients with hereditary, familial or sporadic chronic pancreatitis[4,5] arose from a common founder chromosome.[9] However, a *PRSS1* CNV was also identified in one of 75 Chinese children with idiopathic chronic pancreatitis.[10] Although the breakpoints of this CNV have not yet

been characterized, the Chinese data provided the first evidence that pathogenic *PRSS1* CNVs have more than one independent origin. Indeed, during our routine screening of young French patients with chronic pancreatitis or acute recurrent pancreatitis (see methods in online supplementary note), we identified and characterized four novel and non-identical *PRSS1* duplication CNVs (figure 1): #2 in a Caucasian patient with a family history of the disease; #3 in a *Maghrebian* patient with sporadic pancreatitis; #4 in a Caucasian patient plus two family members (brother and father); and #5 in a sporadic pancreatitis patient from *French Guiana*. Not surprisingly, all four novel duplication CNVs involved the entire PRSS1 gene, as well as the entire anionic trypsinogen (PRSS2) gene.

In summary, the recent publications on common *PRSS1* promoter variants[1-3] and the ongoing discovery of rare *PRSS1* CNVs serve to emphasize the key role of increased *PRSS1* expression in the aetiology of pancreatitis. Our new findings demonstrating multiple independent origins for *PRSS1* CNVs, taken together with the earlier Chinese findings[10], suggest that, irrespective of their ethnogeographic origin, *PRSS1* CNVs could be present in those pancreatitis patients in whom a genetic risk factor has not yet been identified. Routine screening for this important type of disease-causing variant is therefore warranted in pancreatitis.

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Competing interests None.

Patient consent Obtained.

Ethics approval Ethical Committee of the University of Brest.

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Figure legend

Figure 1 Schematic illustration of the *PRSS1* (as well as *PRSS2*) duplication CNVs whose breakpoints have been characterized at the nucleotide sequence level. The start and end positions of each duplicated segment are indicated in accordance with human GRCh38/hg38. The critical region contained within these duplicated sequences is indicated by vertical dotted lines. Whereas #3, #4 and #5 are simple duplications, #1 and #2 are complex duplications. In #1, only the functionally relevant duplicated segment is shown; this duplicated allele gave rise to the previously known triplication allele.[9] In #2, an insertion was present in the aberrant chromosomal junction. Sequences spanning the aberrant chromosomal junctions of the four novel *PRSS1* duplication CNVs are provided in supplementary figure S1.