Pancreatology 19 (2019) 479–480

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Editorial

# Carboxyl ester lipase (*CEL*) hybrid genes and chronic pancreatitis. The saga continues

In this issue of *Pancreatology* Oracz et al. analyzed the hybrid allele of carboxyl-ester lipase (*CEL-HYB1*) in a Polish pediatric cohort of chronic pancreatitis cases [1]. The presence of the *CEL-HYB1* allele has been previously reported to increase the risk for chronic pancreatitis in northern European cohorts [2], however the Polish group could not replicate the original finding in the presented study raising questions about the true effect of the *CEL-HYB1* variant.

Inflammatory diseases of the pancreas often result from the interplay of environmental and genetic risk factors [3]. Since the groundbreaking discovery that mutations in the human cationic trypsinogen gene (*PRSS1*) cause hereditary pancreatitis [4], genetic and functional studies revealed the pathological essence of the disease, in which premature trypsinogen activation plays a central role [5]. In 2013 it became clear that beside the trypsin-dependent pathway, mutation induced misfolding of digestive proteases and consequent endoplasmic reticulum (ER) stress can contribute to disease onset and progression in a number of cases [6]. Although the role of the misfolding-dependent pathological pathway in the development of chronic pancreatitis had been proposed in a subset of *PRSS1* variants earlier [7], the discovery of the association between carboxypeptidase A1 (*CPA1*) variants and early-onset chronic pancreatitis clearly demonstrated its importance [6]. Moreover, a recent study in mice carrying the most frequently found human CPA1 p.N256K variant further corroborated the role of protein misfolding and consequent ER stress in acinar cell damage and pancreatitis [8].

In 2015, a recombined allele of the carboxyl-ester lipase (CEL) and its pseudogene CELP has been reported to confer susceptibility to chronic pancreatitis [2]. The carrier frequency of this *CEL-HYB1* allele in familial CP cases of 71 German subjects was 14.1% in comparison to 1% in control population (OR = 15.5) and in case of non-alcoholic chronic pancreatitis patients from Germany and France the enrichment was ~5-fold (3.7% in patients versus 0.7% in controls, OR = 5.2). *In vitro* experiments showed a secretion defect due to intracellular retention of the hybrid protein suggesting possible involvement of the misfolding-dependent pathway as unveiled previously for certain *PRSS1* and *CPA1* variants. Furthermore, also in case of single base pair deletions in the VNTR region of the *CEL* gene causing maturity-onset diabetes of the young (CEL-MODY) functional studies showed that the mutant CEL variant is retained inside the cell leading to ER stress and consequent acinar cell damage [9]. Zou et al. attempted to replicate the *CEL-HYB1* association in a cohort of chronic pancreatitis patients from China, Japan and India [10]. However, instead of the originally described *CEL-HYB1* allele they found a novel hybrid allele (*CEL-HYB2*), without association with the disease (allele frequency 1.7% in patients versus 1.7% in controls). Functional data were consistent with these findings as the authors demonstrated that the *CEL-HYB2* allele resulted in significantly reduced mRNA expression and decreased intracellular CEL protein amount due to nonsense-mediated messenger RNA decay. Also, this study highlighted that the *CEL-HYB1* risk allele might be ethnic-specific and warranted further investigations of this risk allele in other populations.

Surprisingly, in the present Polish cohort study Oracz et al. did not find a significant difference in the carrier frequency of the *CEL-HYB1* allele between patients and controls (4.8% versus 2.4%), although a two-fold trend for enrichment of the risk allele in patients was observed [1]. However, in familial cases the *CEL-HYB1* allele appeared with similar frequency as it was observed in the initial German discovery cohort (15% versus 14%). How can we reconcile the previously reported results with the lack of significant association in this European cohort? There are several points to consider.

*Winner's curse.* In genetic association studies, researchers tend to focus on genetic effect sizes of variants that yield significant evidence for association, leading to estimates that are upwardly biased. Thus, initial reports are more likely to exaggerate the impact of genetic variants. Consequently, if the sample size calculation for a replication study is based on an overestimated effect size, it will probably be underpowered and more likely to fail.

*Sample size.* The frequency of the *CEL-HYB1* risk allele in controls (2.4%) was unexpectedly ~ 3-fold higher than described in the original article (0.7%), while in patients (4.8%) it was comparable to the findings in the German and French cohort (3.7%) [1,2]. It follows that to prove any significant association in the Polish cohort, larger sample size is needed. However, why is the frequency of the risk allele in Polish controls overrepresented remains an open question. One explanation might be due to a genetic drift, but false positivity during the genetic testing cannot be entirely ruled out as well.

*Pediatric versus adult cohorts.* While Fjeld et al. investigated the *CEL-HYB1* allele status in familial, non-alcoholic and alcoholic chronic pancreatitis patients, the Polish cohort consisted of pediatric patients with early disease onset [1,2]. Whether there is a difference in the frequency of *CEL-HYB1* between ethnically matched adults with chronic pancreatitis and children needs to be determined. It is possible that other environmental or genetic factors are needed to provoke the disease and these factors may act differently in childhood and adulthood.

*Familial versus sporadic cases.* An interesting finding of the Polish replication study was, that despite the lack of significant association in the entire cohort, a stronger trend was seen in familial cases (3/20), similarly to the initial German discovery cohort (10/71). These observations raise the possibility that only certain types of

https://doi.org/10.1016/j.pan.2019.05.463

*CEL-HYB1* alleles are pathogenic, perhaps due a yet unknown mutation linked with the allele. Under this scenario, pathogenic *CEL-HYB1* alleles may be more likely to occur in familial cases where penetrance is stronger. The presence of such linkage would explain why among three CP families the *CEL-HYB1* allele co-segregated with the disease in one only. In the two other familial cases in the absence of the true pathogenic *CEL-HYB1* allele yet unknown susceptibility factors may contribute to the disease.

In any event, the negative results presented by Oracz et al. highlight the need for additional investigations into the role of CEL in chronic pancreatitis. Undoubtedly, the CEL saga continues.

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Available online 31 May 2019