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Common variants in the *CLDN2-MORC4* and *PRSS1-PRSS2* loci confer susceptibility to acute pancreatitis

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ABSTRACT

Background/Objectives: Acute pancreatitis (AP) is one of the most common gastrointestinal disorders often requiring hospitalization. Frequent aetiologies are gallstones and alcohol abuse. In contrast to chronic pancreatitis (CP) few robust genetic associations have been described. Here we analysed whether common variants in the *CLDN2-MORC4* and the *PRSS1-PRSS2* locus that increase recurrent AP and CP risk associate with AP.

Methods: We screened 1462 AP patients and 3999 controls with melting curve analysis for SNPs *rs10273639* (*PRSS1-PRSS2*), *rs7057398* (*RIPPLY*), and *rs12688220* (*MORC4*). Calculations were performed for the overall group, aetiology, and gender sub-groups. To examine genotype-phenotype relationships we performed several meta-analyses.

Abbreviations: ACP, alcoholic chronic pancreatitis; AP, acute pancreatitis; CI, confidence interval; CLDN2, claudin 2; CP, chronic pancreatitis; CTRC, chymotrypsin C; GWAS, genome wide association study; MORC4, MORC family CW-type zinc finger 4; NACP, non-alcoholic chronic pancreatitis; OR, odds ratio; PRSS1, serine protease 1, cationic trypsinogen; PRSS2, serine protease 2, anionic trypsinogen; RIPPLY1, ripply transcriptional repressor 1; SNP, single nucleotide polymorphism.

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Single nucleotide polymorphisms
Risk factors

Results: Meta-analyses of all AP patients depicted significant (p-value < 0.05) associations for *rs10273639* (odds ratio (OR) 0.88, 95% confidence interval (CI) 0.81–0.97, p-value 0.01), *rs7057398* (OR 1.27, 95% CI 1.07–1.5, p-value 0.005), and *rs12688220* (OR 1.32, 95% CI 1.12–1.56, p-value 0.001). For the different aetiology groups a significant association was shown for *rs10273639* (OR 0.76, 95% CI 0.63–0.92, p-value 0.005), *rs7057398* (OR 1.43, 95% CI 1.07–1.92, p-value 0.02), and *rs12688220* (OR 1.44, 95% CI 1.07–1.93, p-value 0.02) in the alcoholic sub-group only.
Conclusions: The association of CP risk variants with different AP aetiologies, which is strongest in the alcoholic AP group, might implicate common pathomechanisms most likely between alcoholic AP and CP.

Introduction

Acute pancreatitis (AP) is one of the most common gastrointestinal disorders requiring hospital admission worldwide [1]. Accordingly, treatment costs are a major burden for health care systems as demonstrated for the United States of America [2,3]. The course of the disease varies and is more severe when necrosis develops while it is worst in patients with infected necrosis. So far, treatment options are symptomatic since causal interventions are not available.

In a large proportion of patients, alcohol misuse or bile duct stones cause AP, whereas other aetiologies are rare [4,5]. In contrast, to chronic pancreatitis (CP) where several genetic risk factors have been described for alcoholic (ACP) as well as the non-alcoholic form (NACP) there are only a few replicated genetic associations with common variants found in AP. Here, an association with the p.N34S variant in the *SPINK1* gene (serine protease Kazal, Type 1) was found in a large European cohort as well as an association with the c.180C > T variant (p.G60 =) in *CTRC* (Chymotrypsinogen C) [6,7]. Other studies investigating common variants in cytokines, barrier function, and the innate and adaptive immune system did not reveal robust associations [8,9]. Recently, a genome-wide association study (GWAS) in patients with chronic and recurring pancreatitis detected variants in the *CLDN2-MORC4* (claudin 2; RIPPLY1, ripply transcriptional repressor 1; MORC family CW-type zinc finger 4) and *PRSS1-PRSS2* (serine protease 1 and 2, cationic and anionic trypsinogen) loci that were associated with the disease [10]. The results were first replicated in a European cohort and thereafter in Asian cohorts as well [11,12]. Interestingly, the association seems to be strongest in ACP patients, a result which was confirmed in a large European GWAS [13]. As recent studies showed that ACP and NACP most likely share mutual pathomechanisms [11,13], we aimed to investigate whether genetic variants in the reported common risk loci also associate with AP. This hypothesis was further supported by an Indian study in patients with recurring idiopathic AP that demonstrated an association of the *CLDN2-MORC4* and the *PRSS1-PRSS2* variants in this cohort [14]. Here, we present the results of a large-scale association analysis of these variants in an European cohort including 1462 patients with AP of different aetiologies and 3999 healthy controls.

Methods

Study subjects

The respective medical ethical review committees of all participating centres approved the study protocol and all patients gave written informed consent. The diagnosis of AP was made when at least two of the following criteria were fulfilled: a) typical clinical presentation (upper abdominal pain); b) elevation of serum lipase or amylase levels 3-times above the upper limit; c) imaging studies indicating AP [15]. The aetiology of AP was categorized into alcoholic, biliary, idiopathic, trauma, post-ERCP, hypertriglyceridaemia, hypercalcaemia, medication and drugs, ischemic, anatomic variants, and unknown. Given the limited sample size in these categories, sub-group analyses were performed for the alcoholic, biliary, and idiopathic cohorts only. Further follow-up data of the patients were not available. In total, the study included 1462 AP patients (n = 672 women), derived from Germany (n = 777; 339 women), Italy (n = 164; 86 women), Hungary (n = 501; 245 women), and Poland (n = 20; 2 women). When the patients were stratified according to the revised Atlanta classification the following distribution was observed for the overall AP group with available data (n = 1300), mild cases n = 761; moderately severe cases n = 363; severe cases n = 176 [16]. The detailed distribution of patients and controls is summarized in Table 1.

As controls we used in parts formerly genotyped samples from our recent study [11]. Overall, 3999 samples were used (2220 women) from Germany (n = 3295; 1828 women), Italy (n = 326; 221 women), Hungary (n = 246; 138 women), and Poland (n = 132; 63 women). More details of the controls are provided in Supplementary Table 1.

Genotyping

The detailed methods used for genotyping are summarized in the Online Supporting Information. For quality control we re-genotyped three percent of the samples blinded to the investigator. The concordance rate was 97.4% (453/465). Call rates for *rs10273639*, *rs7057398* and *rs12688220* in the European samples were 99.3% (5421/5461), 98.6% (5383/5461), and 99.3% (5425/5461), respectively.

Statistical analysis

The methodology used for the statistical analyses has been recently described elsewhere [11]. In brief, we assessed the quality of SNP genotypes by study-wise call rate. Hardy-Weinberg equilibrium was calculated for all patients and controls in the *PRSS1-PRSS2* and for females in the *CLDN2-MORC4* locus. SNPs in the *CLDN2-MORC4* locus were analysed separately for female and male patients. Effects of the SNPs were determined by logistic regression analysis using an additive model of inheritance. We used a model of complete X (XIA) and no X inactivation (nXIA) to determine combined effects [16]. Regarding analysis of X-chromosomal SNPs, male genotypes A and B are always coded as 0 and 1, respectively. In the model of X inactivation, female genotypes AA, AB, BB are coded as 0, 0.5, 1, while in the model of no X inactivation, these genotypes are coded as 0, 1, 2. Overall statistics and stratified tests for Hardy-Weinberg disequilibrium were additionally performed [17]. We pooled study-wise effects by standard meta-analysis techniques as implemented in the package “meta” of the statistical software “R

Table 1
Details of the patient and control cohorts.

Country	Germany	Hungary	Italy	Poland	All
Patients					
Age range years	9–96	11–93	18–87	24–92	9–96
Median	52	58	56	48	54
No. (female)	777 (339)	501 (245)	164 (86)	20 (2)	1462 (672)
Aetiology					
Biliary	315	219	38	8	580
Alcohol	176	80	10	11	277
Idiopathic	168	84	17	0	269
Unknown	43	66	91	0	200
Post-ERCP	33	19	3	1	56
HTG, HCa	13	29	0	0	42
Drugs and medication	15	3	1	0	19
Trauma	12	0	0	0	12
Anatomic variants	2	0	4	0	6
Ischemia	0	1	0	0	1
Controls					
Age range years	18–81	18–89	18–83	16–91	16–91
Median	52	45	35	34	49
No. (female)	3295 (1828)	246 (108)	326 (221)	132 (63)	3999 (2221)
Genotyped in Derikx et al. (2015)	2853	35	326	89	3303

The controls were in parts genotyped previously with the same methodology (Derikx et al., Gut, 2015). Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography; HTG, hypertriglyceriaemia; HCa, hypercalcaemia; No., number.

3.0.1" (ww.r-project.org). Heterogeneity between studies was assessed using Q-statistics. As we occasionally observed study heterogeneity, we calculated random-effect models throughout. We analysed and compared likelihoods of XIA, nXIA and sex interaction for the purpose of model diagnostics. We generated forest-plots using GraphPad Prism (v.6.0a) (San Diego). *P*-values <0.05 were considered statistically significant.

Results

PRSS1–PRSS2 locus (rs10273639)

Our meta-analysis of all AP patients in contrast with all controls revealed a significant association (odds ratio (OR) 0.88, 95% confidence interval (CI) 0.81–0.97, *p*-value 0.01) for the *PRSS1-PRSS2* locus. In the country-specific subgroups this association was significant in Hungarian (OR 0.73, 95% CI 0.59–0.91, *p*-value 0.0043) and German patients (OR 0.89, 95% CI 0.79–0.99, *p*-value 0.044) (Fig. 1). Contrary to male patients (OR 0.83, 95% CI 0.73–0.94, *p*-value 0.004), no significance was observed for the female group of all AP patients (Supplementary Table 2). Next, we analysed the different aetiology subgroups of all patients and detected a significant association for the alcoholic AP subgroup (OR 0.76, 95% CI 0.63–0.92, *p*-value 0.005). This association was also detected in the total male alcoholic AP patients (OR 0.77, 95% CI 0.62–0.95, *p*-value 0.015), but not in the female patients. All other analysis including comparisons of subgroups in females and males as well as between the different aetiology groups were not significant. The results are summarized in Fig. 1, Supplementary Fig. 1 A–C and Supplementary Table 2. Genotype frequencies are shown in Supplementary Table 5.

RIPPLY1 (rs7057398)

Using the model with X-inactivation the meta-analysis of all AP patients compared with all controls revealed a significant association (OR 1.27, 95% CI 1.07–1.5, *p*-value 0.005) for *RIPPLY1* in the *CLDN2-MORC4* locus. In the country specific subgroups from Italy and Poland this association was statistically significant (OR 1.83, 95% CI 1.07–3.15, *p*-value 0.028; OR 6.48, 95% CI 2.24–19.55, *p*-value 0.0006; respectively). Fig. 2 summarizes the results for all patients and the country-specific subgroups. In the gender specific subgroups a statistically significant association was seen for all male patients (OR 1.25, 95% CI 1.02–1.53, *p*-value 0.028) and the male patients from Poland (OR 6.59, 95% CI 2.16–21.2, *p*-value 0.001). In the analysis of the aetiology subgroups a significant association was seen for the overall alcoholic group (OR 1.43, 95% CI

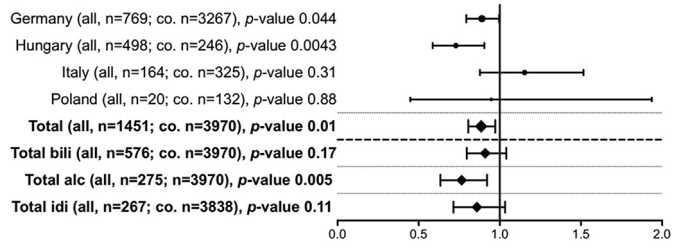

Fig. 1. Results for *rs10273639* (*PRSS1–PRSS2*) for the overall acute pancreatitis cohorts from the different countries and corresponding Meta-analysis results. Separated by the dashed lines, Meta-analysis results of the different aetiologies (biliary = bili, alcoholic = alc, and idiopathic = idi) are shown. Numbers of patients and controls (co.) are given in parentheses. To summarize the single study results, a fixed-effect model was used.

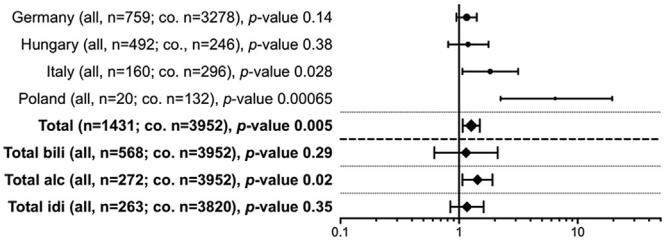

Fig. 2. Results for *rs7057398* (*RIPPLY1*) for the overall acute pancreatitis cohorts from the different countries and corresponding Meta-analysis results. Separated by the dashed lines, Meta-analysis results of the different aetiologies (biliary = bili, alcoholic = alc, and idiopathic = idi) are shown. Numbers of patients and controls (co.) are given in parentheses. A fixed effect meta-analysis assuming complete X-inactivation was performed.

1.07–1.92, *p*-value 0.02), only. The results are summarized in Fig. 2, Supplementary Fig. 2 A-C and in detail including all aetiology as well as gender specific subgroups in Supplementary Table 3 A. The associations under the non X-inactivation model were comparable (Supplementary Table 3 B). The genotype (for females) and allele frequencies (for males) are shown in Supplementary Tables 6 and 7.

MORC4 (rs12688220)

Furthermore, for the model of X-inactivation a statistically significant association was found for the group of all AP patients (OR 1.32, 95% CI 1.12–1.56, *p*-value 0.001) investigating MORC4. A significant association was also seen in the country specific subgroups from Italy (OR 2.1, 95% CI 1.2–3.69, *p*-value 0.0094) and Poland (OR 5.9, 95% CI 2.05–17.63, *p*-value 0.001). Fig. 3 summarizes the results for all patients and the country-specific subgroups. In the aetiology subgroups, association with all alcoholic AP patients (OR 1.44, 95% CI 1.07–1.93, *p*-value 0.02) was found only. In gender specific subgroups no significant associations were present, apart from the overall AP male patient group (OR 1.33, 95% CI 1.08–1.63, *p*-value 0.006) and the male alcoholic AP group (OR 1.47, 95% CI 1.07–2.01, *p*-value 0.02). The results are summarized in Supplementary Fig. 3 A-C and in detail including all aetiology as well as gender specific subgroups in Supplementary Table 4 A. The associations in the non X-inactivation calculations were similar (Supplementary Table 4 B). The genotype (for females) and allele frequencies (for males) are shown in Supplementary Tables 8 and 9.

Analysis of aetiologies and disease course

The strength of the associations differed numerically between the aetiology subgroups. However, when subgroups were analysed no significance was obtained (data not shown). Additionally, we compared the severity sub-groups categorized with the revised Atlanta classification (mild, moderately severe, severe) [18], but did not detect a significant association (data not shown).

Discussion

The main mechanism for the pathogenesis of CP seems to depend on premature intra-pancreatic trypsin activation or its diminished inhibition. This pathophysiological concept is supported as several genetic associations have been described in genes encoding proteases or anti-proteases of the digestive enzyme cascade [19]. For the first time our results demonstrate an association of a common protective variant in the *PRSS1-PRSS2* locus with AP. Functional studies of this variant indicate a lower intra-pancreatic trypsinogen level, which would fit in the proposed concept [20]. However, the strength of the association in AP (all

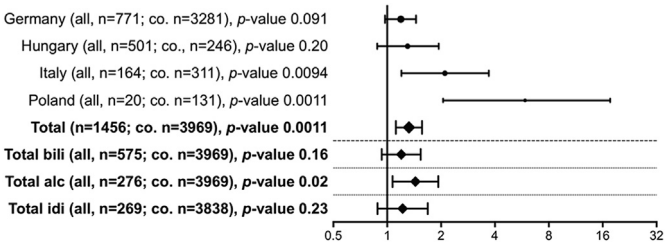

Fig. 3. Results for *rs12688220* (*MORC4*) for the overall acute pancreatitis cohorts from the different countries and corresponding Meta-analysis results. Separated by the dashed lines, Meta-analysis results of the different aetiologies (biliary = bili, alcoholic = alc, and idiopathic = idi) are shown. Numbers of patients and controls (co.) are given in parentheses. A fixed effect meta-analysis assuming complete X-inactivation was performed.

patients, OR 0.88, 95% CI 0.81–0.97) is lower compared to the first report in patients with CP or recurrent AP (OR range from 0.71-0.748) or to European ACP patients (OR 0.63, 95% CI 0.55–0.72) [10,11]. Of note, the effect size of the SNPs was strongest in the alcoholic AP group. As such, one might argue that our observed association is explained by the fact that alcoholic AP progresses to ACP in up to 38% of the patients [21]. When we compared contrasts of the associations between aetiology groups no significant differences were obtained indicating that our observed association is not driven by the alcoholic AP sub-group. As patient numbers in the subgroups were small we, however, might have missed the effect in this comparison. Nevertheless, it is conceivable that the trypsin-mediated pathomechanism is also relevant for the development of AP in patients with different aetiologies. Here, the disturbed balance of proteases and anti-proteases seems to represent the initiating event in pancreatitis development, whereas the mechanisms important for the disease course or the development of CP still need to be elucidated.

Apart from the trypsin-mediated pathway associations of variants in the X-chromosomal *CLDN2-MORC4* locus with AP were found. The strength of the association for the overall cohorts was comparable for the *RIPPLY* SNP (*rs7057398*) and the *MORC4* (*rs12688220*) variant (OR 1.27, 95% CI 1.07–1.5; OR 1.32, 95% CI 1.12–1.56). Compared to the initial GWAS (1.21–1.49) the association of *rs7057398* was similar, whereas it was slightly stronger in female European ACP patients (OR 1.57) and male ACP patients (OR 2.26) formerly reported [10,11]. Again, for the *MORC4 rs12688220* variant the association (OR 1.33) was comparable to that reported in the GWAS (1.24–1.61), but weaker than in European ACP patients (female, OR 1.71; male, 2.66).

In our study, no significant differences in female and male subgroups were found and models with or without X-inactivation showed no differences. This implies that the variants do not have a gender specific effect. As mechanism of action of the *CLDN2-MORC4* risk variants, changes in the localization of claudin-2 were discussed, which would represent a new disease causing mechanism [10]. Nevertheless, further functional studies are warranted to better understand the contribution of these variants to pancreatitis development. Summarized, our findings demonstrate that additional pathways seem to be important for AP development, as it is the case for CP.

As the disease course in AP can vary dramatically, we wondered whether the investigated SNPs might influence severity of the disease in our patients. When we compared the associations of the variants in patients with mild, moderately severe, and severe AP classified according to the revised Atlanta classification no such correlation was seen. Again, this result implicates that variants in both loci may trigger disease onset, but do not influence the disease course.

A limitation of our study is the small sample size in some of the aetiology sub-groups. This entails that in these cohorts interpretation of the data requires caution. On the other hand, associations in the *CLDN2-MORC4* locus revealed homogenous results indicating reliability of the results. Although the comparison of the frequencies of the three SNPs between the aetiology subgroups did not identify that the association is driven by the alcoholic subgroup only, the association is strongest in this group and might be a replication of the results in chronic and recurrent acute pancreatitis. Additionally, we have no follow-up data of the patients with alcoholic AP that might have developed chronic pancreatitis in the meantime. Therefore the effect seen in our analysis might be influenced by such a subgroup.

In conclusion, our study for the first time demonstrates an association of common CP SNPs with AP. This observation shows that the acute and the chronic form of the disease might share common

pathomechanisms. This motivates the search for therapeutic approaches addressing common mechanisms rather than different aetiologies. However, it remains unclear, which genetic factors influence the disease course as well as the progression to CP.

Competing interests

There are no competing interests to be stated by any of the authors.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.pan.2018.05.486.

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