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Association between genetic variants in CYP2E1 and CTRC genes and susceptibility to alcoholic pancreatitis: A systematic review and meta-analysis

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ABSTRACT

Background: Genetic predisposition plays an important role in the development of alcoholic pancreatitis (AP), with previous studies suggesting that genetics variants in certain genes, such as*CYP2E1* and *CTRC*, partially explain individual susceptibility to this disease. Therefore, the aim of this work was to conduct a systematic review and meta-analysis of existing studies that analyzed how polymorphisms within *CYP2E1* and *CTRC* genes influence the risk of AP.

Material and methods: We performed a systematic review of studies that analyzed the genotype distribution of *CYP2E1* and *CTRC* allelic variants among patients with AP and a group of controls. A meta-analysis was conducted using a random effects model. Odds ratios (ORs) and their confidence intervals (CIs) were calculated.

Results: The T allele of the*CTRC* 180 C > T variant was significantly more prevalent among patients with AP compared to all controls (OR = 1.79, 95% CI = 1.43–2.24; $P < 0.00001$) and healthy subjects (OR = 1.84, 95% CI = 1.46–2.31; $P < 0.00001$). The Trp variant of *CTRC* Arg254Trp polymorphism was also more prevalent in patients with AP; however, these results were not significant after excluding one study. We found no clear evidence that *CYP2E1*-DraI or of *CYP2E1*-RsaI/PstI polymorphisms modulate the risk of developing AP.

Conclusions: Our meta-analysis supports that the T allele of*CTRC* 180C > T polymorphisms modulates the risk of alcoholic pancreatitis. No clear evidence was found for the remaining SNPs being associated with this disease.

1. Introduction

Excessive alcohol consumption is associated with alcoholic pancreatitis (AP), which can remain as acute AP (AAP) or, often after recurrent episodes, progresses to alcoholic chronic pancreatitis (ACP) (Clemens et al., 2016). In developed countries, alcohol is considered responsible for 25–35% and 40–70% of all cases of acute and chronic pancreatitis, respectively (Conwell et al., 2017; Yang et al., 2008). The pathogenesis of AP is not completely understood, although the direct toxicity of alcohol metabolites to acinar cells damages the pancreas, in addition to its interaction with other immunological, metabolic, and toxic factors (such as tobacco) (Pandol and Raraty, 2007; Apte et al., 2010). Genetic predisposition also plays an important role in both AAP and ACP, and might partly explain why only 5–10% of heavy drinkers ultimately develop ACP.

Accordingly, several polymorphisms within different genes have

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been analyzed as potential candidates to explain susceptibility to ACP (Vonlaufen et al., 2007; Whitcomb, 2013). Out of these, cytochrome P450 2E1 (CYP2E1) is an ethanol-inducible microsomal enzyme that is crucial for the oxidative metabolism of ethanol through the non-alcohol dehydrogenase pathway (Foster et al., 1993; Wacke et al., 1998). Several allelic variants within this highly polymorphic gene have been explored to explain individual susceptibility to AP. These variants include two polymorphisms associated with a modification of enzyme activity, *CYP2E1*-RsaI/PstI, and *CYP2E1*-DraI polymorphism (Hayashi et al., 1991; Uematsu et al., 1991). In addition, chymotrypsin C (CTRC) is a protease that degrades all human trypsin and trypsinogen isoforms. The degradation of trypsin has a protective role against pancreatitis; thus, *CTRC* variants (such as Arg254Trp, K247_R254del, and 180 C > T) are also candidates for AP susceptibility(Beer et al., 2013; Szabó and Sahin-Tóth, 2012).

Several authors have explored how polymorphisms within *CYP2E1* and *CTRC* are associated with AP risk by means of various candidate gene association studies and a recent genome-wide analysis association study (GWAS) of ACP patients (Rosendahl et al., 2018). Existing genetic association studies tend to have small sample sizes and heterogeneous designs, leading to contradictory results. Therefore, the aim of our work was to perform a systematic review and meta-analysis, which finally included 19 studies, of existing genetic association studies focused on polymorphisms within *CYP2E1* and *CTRC* genes and the risk of AP.

2. Material and methods

2.1. Inclusion criteria

To analyze the relationship between the genetic variants of *CYP2E1* and *CTRC*, cross-sectional, case-control, and cohort studies on the genetic distribution of polymorphisms within the stated genes in patients with AP, and at least in a group of controls without pancreatitis, were considered eligible for inclusion. Patients had to be diagnosed according to standard criteria. Studies with overlapping data were excluded (only the study with the largest population was included).

2.2. Bibliographic search

To identify eligible studies, we searched the PubMed, Web of Science, Scopus, and Embase electronic databases up to October 2019. Potentially relevant articles were searched for using the following terms in combination with Medical Subject Headings (MeSH) terms and text words: “CTRC”, “Chymotrypsin C”, “cytochrome”, “CYP2E1”, “CYP1A1”, “polymorphism”, “mutations”, “variants”, “pancreatitis”, “alcohol”, “alcoholic” and “alcoholism”. No language restrictions were applied. We also scanned the reference lists of the retrieved publications to identify additional relevant articles. The search was supplemented using the MedLine option ‘Related Articles’ and consulting review articles on the topic.

2.3. Data extraction

The bibliographical search and data extraction were performed independently by three investigators (RUM, CC, and INV). Any divergence of opinion was resolved by consensus with the senior authors (AJC and MM). From each study, the following information was extracted: author names and year of publication, in addition to the country, ethnicity, and demographic information (age and sex) of the study population. Genotype frequencies were extracted or calculated from raw data. The reporting of HWE in healthy controls was verified for each eligible study or was calculated from available data. In addition, we recorded the criteria used to diagnose AP, AAP, and ACP. Patients were categorized into the following groups, where information was available: alcoholics with AP (further divided into AAP and ACP groups), alcoholics without AP but with alcoholic liver disease (ALD), alcoholics without known organic disease (“alcoholic controls”), healthy individuals, and patients with acute or chronic pancreatitis of other origin (non-AAP and non-ACP patients, respectively). The corresponding authors of the original studies were contacted if additional data were needed.

2.4. Statistical analysis

The main objective was to compare the distribution of each polymorphism identified in the systematic review among patients with AP as cases versus controls. For this purpose, independent meta-analyses were carried out to compare: a) alcoholics with pancreatitis vs. all controls (alcoholics without pancreatitis and/or healthy subjects combined), b) alcoholics with pancreatitis vs. alcoholics without this disease (alcoholic controls and/or alcoholics with ALD), c) alcoholics with pancreatitis vs. healthy subjects.

Our secondary aims were to analyze the distribution of identified polymorphisms among: a) patients with AAP vs. controls, b) patients with ACP vs. controls, and, c) patients with ACP vs. patients with chronic pancreatitis of other etiology. Additional analysis comparing patients with AAP or ACP vs. controls was performed as previously described for the main objective. Sub-analysis by ethnicity was also performed. Patients with acute pancreatitis due to gallstones were excluded from the comparisons. Meta-analysis was only performed when three or more studies were available.

The meta-analysis was carried out using RevMan 5.0 software, (Review Manager (RevMan), 2014[Computer program]. Version 5.3) as previously described (Chamorro et al., 2014; Marcos et al., 2011). In brief, we used a random-effects model (DerSimonian and Laird method) (Cochrane Handbook for Systematic Reviews of Interventions, 2020) to calculate the odds ratio (OR) and its 95% confidence interval (CI). A P-value < 0.05 was considered statistically significant. Cochran´s Q statistic was used to evaluate heterogeneity with a significant Cochran's Q-statistic ($P < 0.10$) indicating heterogeneity across studies. The I^2 statistic was used to estimate inconsistency in meta-analyses (Higgins et al., 2003). Due to the low, or very low, prevalence of the mutated variant for all analyzed polymorphisms, we only performed the comparisons using a recessive model for the more prevalent allele. Sensitivity analysis was performed by excluding individual studies and by excluding those with deviations in the HWE equilibrium in controls. HWE was assessed by the X^2 test.

3. Results

3.1. Identification and selection of relevant studies

We initially identified 274 candidate articles for inclusion (Fig. 1). After removing duplicates, the abstracts of 125 articles were reviewed, and 66 were excluded for various reasons. Thus, a total of 59 full text articles were assessed for eligibility. From these, 37 full text articles were excluded for different reasons, including overlapping data for two studies,(Chao et al., 1995; Cichoż-Lach et al., 2008) with other studies from the same authors (Chao et al., 1997; Cichoz-Lach et al., 2006). Another study was excluded due to a lack of data on genotypic frequencies (Chao et al., 2000). Finally, three of the 59 studies fulfilled our inclusion criteria, but were excluded because they had analyzed polymorphisms within *CYP2E1* and *CTRC*, which have been investigated in less than three works and were therefore not amenable to integration by means of a meta-analysis (Cartmell et al., 2005; Koziel et al., 2015; Schubert et al., 2014).

Therefore, 19 studies that fulfilled inclusion criteria were ultimately included in our meta-analysis to compare the relationship between different genetic variants and the presence of AP. Among *CTRC*, Arg254Trp allelic variant (rs121909293) was analyzed by six studies (Cichoż-Lach et al., 2019; da Costa et al., 2016; Masamune et al., 2013; Phillips et al., 2018; Rosendahl et al., 2008; Zou et al., 2018) and 180

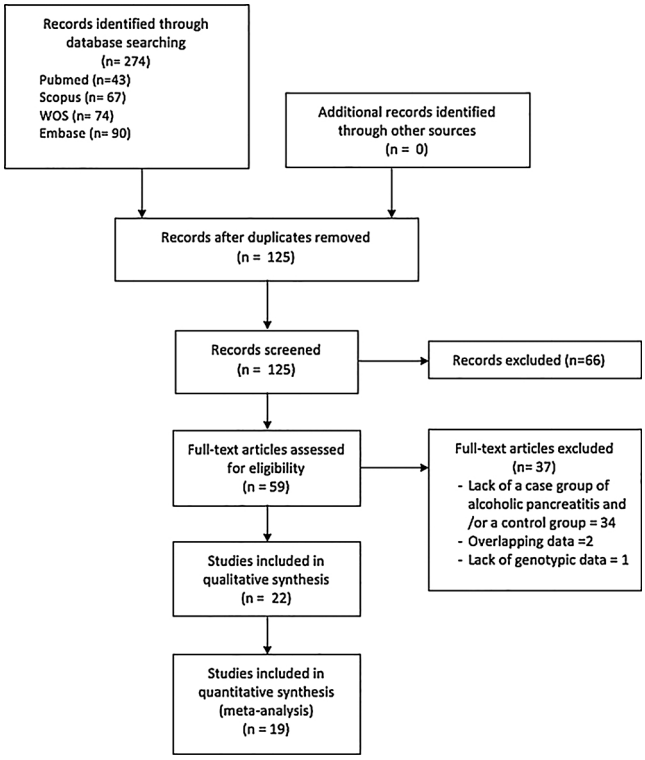

Fig. 1. Flow chart of the studies selected for inclusion in the meta-analysis.

C > T (rs497078) by four studies (Koziel et al., 2017; LaRusch et al., 2015; Masamune et al., 2013; Zou et al., 2018). For *CYP2E1,* 10 studies analyzed RsaI/PstI SNP (rs2031920/rs3813867, with both SNPs being in full linkage disequilibrium)(Burim et al., 2004; Chao et al., 1997; Cichoz-Lach et al., 2006; Frenzer et al., 2002; Gubergrits et al., 2014; Kim et al., 2004; Maruyama et al., 1999; Matsumoto et al., 1996; Verlaan et al., 2004; Yang et al., 2001) and four studies analyzed DraI SNP (rs6413432)(Frenzer et al., 2002; Singh et al., 2015; Verlaan et al., 2004; Yang et al., 2001).

3.2. Study characteristics

Studies included in the meta-analysis included 2244 patients with AP (1980 ACP patients and 264 AAP patients), 582 alcoholic controls without liver or pancreatic disease, 708 patients with ALD, 3638 patients with non-ACP, and 6506 healthy subjects. Detailed population demographics are shown in Supplementary Table 1, and selection criteria for each group are shown in Supplementary Table 2. Tables 1 and 2 present the genotypic distribution of genetic variants included in the meta-analysis of *CTRC* and *CYP2E1*, respectively. All authors used genomic DNA extracted from nucleated peripheral blood cells. There were no statistically significant deviations from HWE in the control groups of any of the studies, except for that of Kim et al. from Korea (Kim et al., 2004).

3.3. Meta-analysis of the association between gene variants in CTRC and susceptibility to alcoholic pancreatitis

The results of the meta-analysis comparing *CTRC* 180 C > T polymorphism and the risk of AP are shown in Fig. 2 and Table 3. The prevalence of the T allele was significantly higher in AP patients and ACP patients compared with all controls (for AP: OR = 1.79, 95% CI = 1.43–2.24, P < 0.00001, Fig. 2A; for ACP: OR = 1.99, 95% CI = 1.49–2.67, P < 0.00001, Fig. 2B). Funnel plots (Supplementary Fig. 1) did not show obvious asymmetry. The T allele of 180 C > T polymorphism was also significantly associated with the presence of AP and ACP versus healthy subjects (for AP: OR = 1.84, 95% CI = 1.46–2.31, $P < 0.00001$; for ACP: OR = 2.10, 95% CI = 1.55–2.84, $P < 0.00001$). However, there was no significant difference between ACP patients and non-ACP patients (Table 3). After sensitivity analysis, the exclusion of individual studies did not alter the significant results in the comparison of AP patients with controls and AP patients with healthy subjects. However, meta-analysis after the exclusion of the study by LaRusch et al.(LaRusch et al., 2015) yielded no significant differences when comparing ACP patients with controls and ACP patients with healthy subjects.

The meta-analysis of *CTRC* Arg254Trp polymorphism and the risk of AP are presented in Fig. 3 and Table 3. The Trp allele had significantly higher prevalence for AP patients versus all controls (OR = 2.17, 95% CI = 1.14–4.13, $P < 0.00001$; Fig. 3A) and for ACP patients versus all controls (OR = 1.99, 95% CI = 1.14–4.15, $P < 0.00001$; Fig. 3B). Supplementary Fig. 2 presents funnel plots indicating publication bias due to the lack of studies in the bottom right-hand corner of the plot. The Trp allele of *CTRC* Arg254Trp polymorphism was also significantly associated with the presence of AP when comparing AP patients with healthy subjects (OR = 2.77, 95% CI = 1.36–5.64; $P = 0.005$) and ACP patients with healthy subjects (OR = 2.79, 95% CI = 1.37–5.66; $P = 0.005$). We found no significant association between ACP patients and non-ACP patients (Table 3). After the sensitivity analysis, the exclusion of the study by Rosendahl et al.(Rosendahl et al., 2008) generated a lack of significant results for all stated comparisons. Ethnicity analysis could not be performed in the *CTRC* meta-analyses, due to an insufficient number of studies.

3.4. Meta-analysis of the association between gene variants in the CYP2E1 gene and susceptibility to alcoholic pancreatitis

The meta-analysis for the association of *CYP2E1*-RsaI/PstI polymorphisms with the risk of AP showed a significant association between this SNP and the presence of ACP. The prevalence of the mutated allele (C1C2 and C2C2 genotypes) was significantly higher in ACP patients compared to controls and healthy subjects (Table 4). Ethnicity analysis (including Caucasian individuals) showed that the C1C2 and C2C2 genotypes of *CYP2E1*-RsaI/PstI polymorphisms were significantly associated with the presence of AP in patients versus all controls (OR = 1.91, 95% CI = 1.23–2.98; $P = 0.004$) and healthy subjects (OR = 1.90, 95% CI = 1.19–3.05; $P = 0.008$). It was also significantly associated with the presence of ACP in patients versus all controls (OR = 1.95, 95% CI = 1.24–3.06; $P = 0.004$) and healthy subjects (OR = 1.91, 95% CI = 1.18–3.08; $P = 0.008$).

After the sensitivity analysis, the exclusion of the study by Gubergrits et al.(Gubergrits et al., 2014) generated non-significant results in the two significant comparisons for the overall population (ACP patients vs. controls and vs. healthy subjects) and in the four significant comparisons among Caucasians. The exclusion of both Gubergrits et al. (Gubergrits et al., 2014) and Kim et al.(Kim et al., 2004) (which deviated from HWE) did also yield non-significant results.

CYP3E1-DraI polymorphism showed no significant association with the risk of AP (Table 5). The exclusion of individual studies did not yield a significant result.

4. Discussion

Our systematic review and meta-analysis showed that two SNPs of *CTRC* (Arg254Trp and 180 C > T) were significantly associated with a higher risk of AP. Of interest, the result obtained for SNP 180 C > T (rs497078) was consistent across the various comparisons and all included studies. Indeed, all studies used in our systematic review showed that the T allele of this SNP occurred at a higher frequency among patients with AP, despite marked differences in the frequency of minor alleles due to ethnicity. These results support those of a recently published GWAS, which showed that this SNP is associated with an OR of

Table 1
Genotype distribution of CTRC gene polymorphisms among individuals included in the meta-analysis.

Authors, year	Subject group	180 C > T genotype distribution		Arg254Trp genotype distribution	
		CC	CT + TT	Arg/Arg	Arg/Trp + Trp/Trp
Rosendahl et al. (2008)	Healthy subjects	–	–	2786	18
	ACP patients	–	–	340	8
	ALD patients	–	–	430	2
	Non-ACP patients	–	–	882	19
Masamune et al. (2013)	Healthy subjects	274	0	274	0
	ACP patients	243	1	244	0
	Non-ACP patients	262	0	261	1
LaRusch et al. (2015)	Healthy subjects	804	209	–	–
	ACP patients	154	82	–	–
	Non-ACP patients	236	66	–	–
Da Costa et al. (2016)	Healthy subjects	–	–	296	1
	ACP patients	–	–	109	1
	Non-ACP patients	–	–	38	0
	Alcoholic controls	–	–	109	1
Koziel et al. (2017)	Healthy subjects	334	83	–	–
	AAP patients	216	83	–	–
Phillips et al. (2018)	Healthy subjects	–	–	237	1
	ACP patients	–	–	178	0
	Non-ACP patients	–	–	53	1
	AAP patients	–	–	15	0
	Non-AAP patients	–	–	30	0
Zou et al. (2018)	Healthy subjects	1193	3	1194	2
	ACP patients	204	2	205	1
	Non-ACP patients	841	14	855	0
Cichoz-Lach et al. (2006)	Healthy subjects	–	–	51	1
	ACP patients	–	–	122	2
	Non-ACP patients	–	–	52	0

ACP: alcoholic chronic pancreatitis. AAP: alcoholic acute pancreatitis. Non-ACP: non-alcoholic chronic pancreatitis. ALD: alcoholic liver disease without pancreatitis.

1.5–2 for ACP vs. healthy individuals or alcoholic controls (similar to the OR obtained in our analysis) (Rosendahl et al., 2018). This SNP was also in strong linkage disequilibrium ($R^2 = 0.97$) with SNP 52 G > A rs545634, which was the lead polymorphism found at *CTRC* in the GWAS. This 180 C > T allele is also associated with chronic pancreatitis of other causes (Derikx et al., 2009; Paliwal et al., 2013) and our meta-analysis detected no differences between patients with ACP and non-ACP for the distribution of this SNP. Thus, the 180 C > T SNP of *CTRC* might be a common genetic risk marker of pancreatitis. This could be similar to the association of rs738409 SNP in the adiponutrin/patatin-like phospholipase domain-containing 3 gene (*PNPLA3*) for liver disease (Chamorro et al., 2014).

The association of this SNP of *CTRC* with a higher risk of pancreatitis is biologically plausible. CTRC is a protease that has a protective role against pancreatitis through trypsin degradation. Loss-of-function variants (such as 180 C > T and 52 G > A) are able to disrupt nucleotide binding sites, potentially increasing the risk of pancreatitis (Beer et al., 2013; LaRusch et al., 2015). Therefore, our result and accumulated evidence support that the T allele of 180 C > T CTRC polymorphism represents a risk factor for the development of alcoholic pancreatitis. Given the relatively high prevalence of the T allele in the Caucasian population, the presence of this mutation in patients of this genetic background might be of clinical use for identifying alcoholic patients at a higher risk of developing severe pancreatic damage.

In contrast, although our results show that the Trp allele of the Arg254Trp polymorphism (rs121909293) increases the risk of AP, this finding is highly dependent on a single study (Rosendahl et al., 2008) and was not consistent in all works included in our meta-analysis. The Trp allele might increase the risk of pancreatitis in conjunction with other variants in this gene (such as K247_R254del variant, which could not include in the meta-analysis due to the low number of available studies) or the SNPs of other genes. Therefore, its potential pathogenic role in AP cannot be clearly established from our data or from the recently published GWAS in CP (Rosendahl et al., 2018). The low frequency of mutated alleles of these variants makes it difficult to ascertain their effects, and would also be a limitation for its clinical use.

CYP2E1 encodes a crucial enzyme involved in ethanol metabolism, with it being hypothesized that SNPs in this gene are involved in AP susceptibility. In addition, *CYP2E1*-RsaI/PstI and *CYP2E1*-DraI polymorphisms are associated with an altered enzyme activity (Hayashi et al., 1991; Uematsu et al., 1991; Watanabe et al., 1994). However, 11 studies on the role of *CYP2E1*-RsaI/PstI polymorphisms and four studies on *CYP2E1*-DraI polymorphism were included in the meta-analysis, with no clear differences in their genotypic distribution being detected among alcoholics, non-ACP patients, alcoholic controls, and healthy subjects. A previous meta-analysis with minor methodological differences suggested that *CYP2E1*-RsaI/PstI polymorphism affects the non-Asian population or patients with chronic pancreatitis; however, we were not able to confirm that these polymorphisms contribute to AP risk based on our sensitivity analysis and additional comparisons (Wu et al., 2018). The lack of association of this gene with the risk of pancreatitis in the recently published GWAS reinforces our conclusion.

Our meta-analysis provides a comprehensive evaluation of this topic; however, there were some limitations. Considering general limitations of meta-analysis of genetic association studies, conflicting results and heterogeneity among included studies is quite common and may reflect true genetic heterogeneity across different samples or occult population stratification. Regarding publication bias, the exclusion of negative unpublished studies may undoubtedly affect the validity of the analysis (Zintzaras and Lau, 2008). Regarding our work, only a small number of studies were eligible for inclusion in our systematic review. Furthermore, several of the included studies had low sample sizes, with almost every study comparing different groups with different selection criteria for cases and controls (see Supplementary Table 2). This low number of studies and design heterogeneity limited the number of comparisons possible (e.g., separate analysis for AAP), and made it difficult to assess publication bias or evaluate the role of ethnicity. The heterogeneity of study designs in this field needs to be addressed, as it precludes the clinical applicability of these genetic markers. The low number of studies also partly explains the lack of significant results

Table 2
Genotype distribution of CYP2E1 gene polymorphisms among individuals included in the meta-analysis.

Authors, year	Subject group	CYP2E1-RsaI/PstI genotype distribution		CYP2E1-DraI genotype distribution	
		C1C1	C1C2 + C2C2	DD	DC + CC
Matsumoto et al. (1996)	ACP patients	9	2	–	–
	Alcoholic controls	39	23	–	–
Chao et al. (1997)	Healthy subjects	56	44	–	–
	AAP patients	30	18	–	–
	ALD patients	42	33	–	–
	Alcoholic controls	12	7	–	–
	Non-AAP patients	18	14	–	–
Maruyama et al. (1999)	ACP patients	30	23	–	–
	Alcoholic controls	30	16	–	–
	Non-ACP patients	19	11	–	–
Yang et al. (2001)	Healthy subjects	150	5	129	26
	AAP patients	18	1	16	3
	ACP patients	37	1	29	9
	Alcoholic controls	42	4	33	13
Frenzer et al. (2002)	Healthy subjects	188	12	170	30
	ACP patients	65	6	54	17
	ALD patients	56	1	48	9
	Alcoholic controls	54	3	46	11
Burim et al. (2004)	Healthy subjects	197	24	–	–
	ACP patients	11	3	–	–
	ALD patients	59	6	–	–
	Alcoholic controls	37	4	–	–
Kim et al. (2004)	Healthy subjects	51	49	–	–
	AP patients	17	12	–	–
	ALD patients	17	5	–	–
Verlaan et al. (2004)	Healthy subjects	122	6	112	16
	ACP patients	75	7	78	4
	Alcoholic controls	88	5	81	12
	Non-ACP patients	60	0	58	2
Cichoz-Lach et al. (2006)	Healthy subjects	54	0	–	–
	ACP patients	42	2	–	–
	ALD patients	53	4	–	–
	Alcoholic controls	43	0	–	–
Gubergrits et al. (2014)	Healthy subjects	55	25	–	–
	ACP patients	36	36	–	–
Singh et al. (2015)	Healthy subjects	–	–	68	22
	AP patients	–	–	61	11
	Alcoholic controls	–	–	33	7
	Non-AP patients	–	–	63	12

ACP: alcoholic chronic pancreatitis. AAP: acute alcohol pancreatitis. Non-ACP: non-alcoholic chronic pancreatitis. Non-AAP: non-alcoholic acute pancreatitis. ALD: alcoholic liver disease without pancreatitis. AP: alcoholic pancreatitis (acute or chronic).

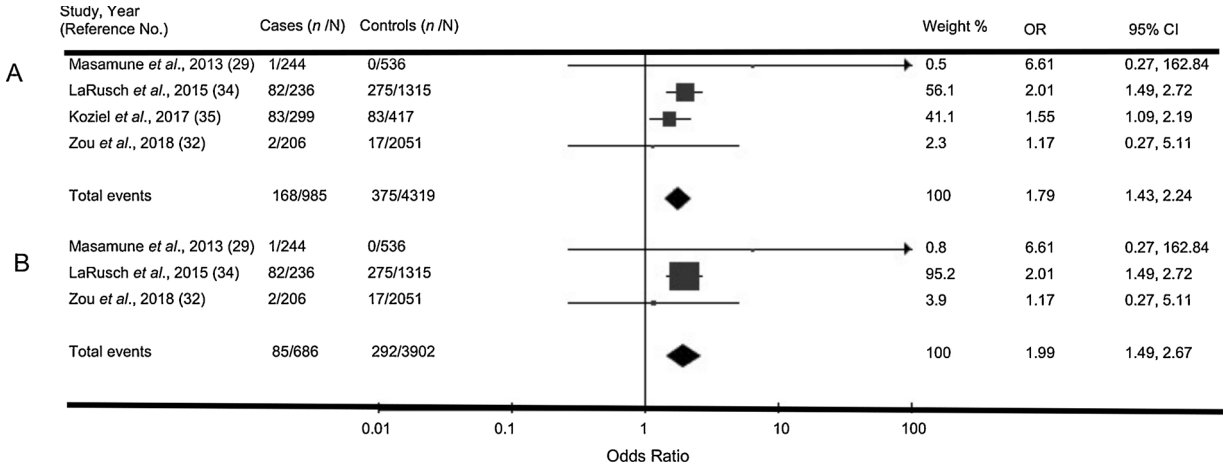

Fig. 2. Meta-analysis of the association of *CTRC* 180C > T polymorphism and alcoholic pancreatitis. (A) Patients with alcoholic pancreatitis vs. all controls. Test for overall effect: Z = 5.12 ($P < 0.00001$). Test for heterogeneity: $\chi^2 = 2.23$ ($P = 0.53$), $I^2 = 0\%$ (B) Patients with alcoholic chronic pancreatitis vs. all controls. Test for overall effect: Z = 4.62 ($P < 0.00001$). Test for heterogeneity: $\chi^2 = 1.04$ ($P = 0.59$), $I^2 = 0\%$. Each study is shown by an OR estimate with the corresponding 95% CI.

Table 3
Summary of meta-analysis results for the association of *CTRC* polymorphisms with alcoholic pancreatitis.

SNP	Comparison	N	OR	95% CI	*P* (random effects model)	I^2 (%)	*P* (heterogeneity)
180C > T	AP patients (n = 985) vs. all controls (n = 4319)	4	1.79	1.43-2.24	< 0.00001	0	0.53
	AP patients (n = 985) vs. healthy subjects (n = 2900)	4	1.84	1.46-2.31	< 0.00001	0	0.53
	ACP patients (n = 686) vs. all controls (n = 3902)	4	1.99	1.49-2.67	< 0.00001	0	0.53
	ACP patients (n = 686) vs. healthy subjects (n = 2483)	3	2.10	1.55-2.84	< 0.00001	0	0.75
	ACP patients (n = 686) vs. non-ACP patients (n = 1419)	3	1.61	0.85-3.06	0.15	16	0.30
Arg254Trp	AP patients (n = 1225) vs. all controls (n = 7595)	6	2.17	1.14-4.13	< 0.00001	0	0.75
	AP patients (n = 981) vs. healthy subjects (n = 4587)	5	2.77	1.36-5.64	0.005	0	0.59
	ACP patients (n = 1210) vs. all controls (n = 7595)	6	1.99	1.14-4.15	< 0.00001	0	0.75
	ACP patients (n = 966) vs. healthy subjects (n = 4587)	5	2.79	1.37-5.66	0.005	0	0.61
	ACP patients (n = 1210) vs. non-ACP patients (n = 1609)	6	1.01	0.45-2.27	0.99	0	0.42

SNP: single nucleotide polymorphism. OR: odds ratio. CI: confidence interval. AP: alcoholic pancreatitis. ACP: alcoholic chronic pancreatitis. ALD: alcoholic liver disease. N: number of studies included in each meta-analysis (only comparisons with N ≥ 3 were included). n: number of individuals in each group.

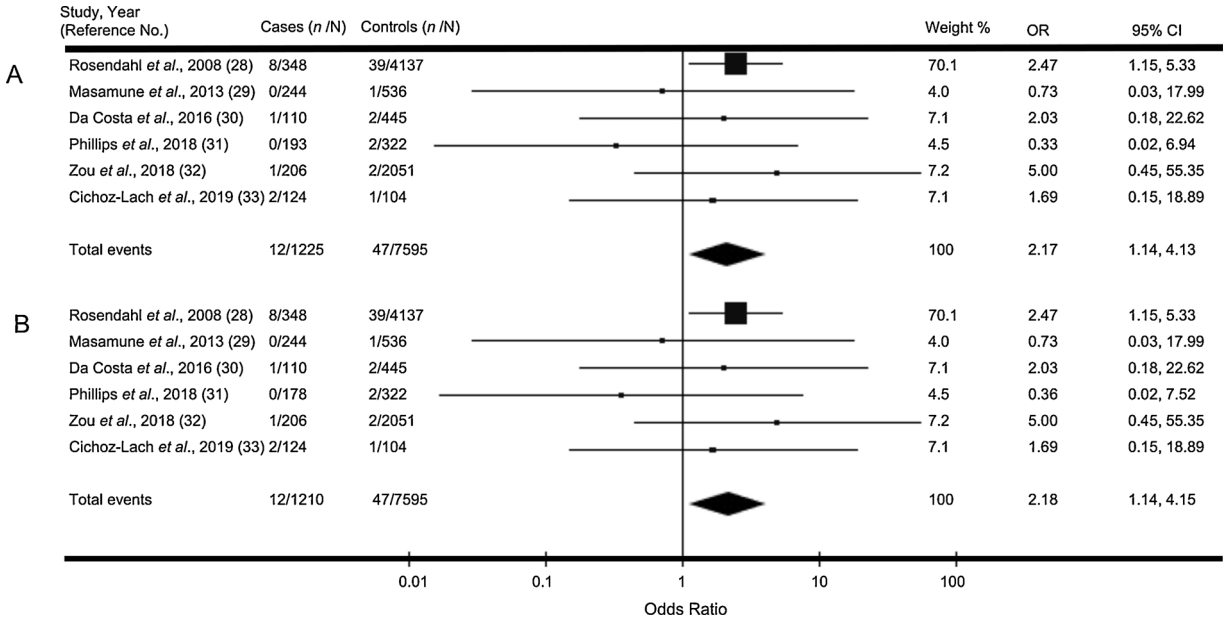

Fig. 3. Meta-analysis of the association between *CTRC* Arg254Trp polymorphism and alcoholic pancreatitis. (A) Patients with alcoholic pancreatitis vs. all controls. Test for overall effect: Z = 2.36 (*P* = 0.02). Test for heterogeneity: $\chi^2 = 2.65$ (*P* = 0.75), $I^2 = 0\%$ (B) Patients with alcoholic chronic pancreatitis vs. all controls. Test for overall effect: Z = 2.37 (*P* = 0.02). Test for heterogeneity: $\chi^2 = 2.52$ (*P* = 0.77), $I^2 = 0\%$. Each study is shown by an OR estimate with the corresponding 95% CI.

Table 4
Summary of meta-analysis results for the association of CYP2E1-RsaI/PstI polymorphisms with alcoholic pancreatitis.

Comparison	N	OR	95% CI	*P* (random effects model)	I^2 (%)	*P* (heterogeneity)
AP patients (n = 481) vs. all controls (n = 1843)	10	1.32	0.95-1.84	0.10	17	0.28
AP patients (n = 409) vs. alcoholic patients without pancreatitis (n = 683)	9	1.42	0.20-6.48	0.30	10	0.35
AP patients (n = 380) vs. alcoholic controls (n = 407)	8	1.24	0.78-1.96	0.37	0	0.54
AP patients (n = 417) vs. healthy subjects (n = 1038)	8	1.33	0.90-1.98	0.16	18	0.28
AP patients (n = 206) vs. ALD patients (n = 276)	5	1.43	0.69-2.97	0.34	33	0.20
ACP patients (n = 385) vs. all controls (n = 1495)	8	1.68	1.17-2.40	0.004	0	0.55
ACP patients (n = 313) vs. alcoholic patients without pancreatitis (n = 567)	7	1.37	0.83-2.26	0.22	4	0.40
ACP patients (n = 313) vs. alcoholic controls (n = 388)	7	1.32	0.79-2.21	0.29	0	0.45
ACP patients (n = 321) vs. healthy subjects (n = 838)	6	1.94	1.24-3.05	0.004	0	0.89

OR: odds ratio. CI: confidence interval. AP: alcoholic pancreatitis. ACP: alcoholic chronic pancreatitis. ALD: alcoholic liver disease. N: number of studies included in each meta-analysis (only comparisons with N ≥ 3 were included). n: number of individuals in each group.

Table 5
Summary of meta-analysis results for the association of CYP3E1-DraI polymorphism with alcoholic pancreatitis.

Comparison	N	OR	95% CI	*P* (random effects model)	I^2 (%)	*P* (heterogeneity)
AP patients (n = 282) vs. all controls (n = 1001)	4	0.95	0.56-1.63	0.86	49	0.12
AP patients (n = 282) vs. alcoholic controls (n = 237)	4	0.78	0.46-1.31	0.34	12	0.33
AP patients (n = 282) vs. healthy subjects (n = 573)	4	0.90	0.45-1.80	0.76	65	0.03
ACP patients (n = 191) vs. all controls (n = 796)	3	1.08	0.52-2.23	0.84	57	0.10
ACP patients (n = 191) vs. alcoholic controls (n = 196)	3	0.77	0.37-1.61	0.49	39	0.20
ACP patients (n = 191) vs. healthy subjects (n = 483)	3	1.10	0.46-2.63	0.84	67	0.05

OR: odds ratio. CI: confidence interval. AP: alcoholic pancreatitis. ACP: alcoholic chronic pancreatitis. AC: alcoholic controls. N: number of studies included in each meta-analysis (only comparisons with N ≥ 3 are included). n: number of individuals in each group.

after the sensitivity analysis in some sub-analysis and it is of relevance that the exclusion of one single work (Rosendahl et al., 2018) yielded non-significant results regarding CTRC Arg254Trp meta-analysis. Also, potential confounding factors (like age, tobacco use, and gender) could not be evaluated, as they were not reported in all studies. Nevertheless, our approach of analysing all cases with AP (AAP and ACP combined), plus ACP patients separately, is appropriate considering that acute, recurrent acute, and CP potentially represent a disease continuum (Machicado and Yadav, 2017). The comparison with a pool of controls without pancreatitis (healthy individuals and/or alcoholics) has also been used by other authors (Rosendahl et al., 2018).

5. Conclusions

This meta-analysis advances our current understanding of how *CYPE21* and *CTRC* influence susceptibility to AP, providing moderate evidence that possession of the T allele of 180C > T genetic variant of *CTRC* increases the risk of AP. Our meta-analysis provided no clear evidence that the other analyzed SNPs within *CTRC* of *CYPE21* were associated with this disease. Further research with homogeneous design should be performed to improve our current understanding of the genetics of AP, and to establish the clinical applicability.

Contributors

AJC and MM designed the study protocol. RUM, CC and INV independently performed the literature searches and extraction of data. SHP collaborated with literature searches and extraction of data of CYP2E1 polymorphisms. RUM performed statistical analysis. All authors contributed to interpretation of data. RUM and MM drafted the manuscript. CC, INV, AJC and MM provided critical revision of the draft for important intellectual content.

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Declaration of Competing Interest

No conflict declared

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2020.107873.

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