Should risk variants at the RIPPLY1-CLDN2-MORC4 and TRPV6 loci be tested in non-alcoholic chronic pancreatitis?

K. Ocskay[1], M. F. Juhász[1], P. Mátrai[2], M. Sahin-Tóth[3], A. Párniczky[1,2]

[1]Heim Pál National Pediatric Institute, Hungary, [2]Institute for Translational Medicine, Medical School, University of Pécs, Medical School, Hungary, [3]Department of Surgery, University of California Los Angeles, United States of America

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Background and aims

Chronic pancreatitis (CP), influenced by both **genetic and environmental factors**, poses a significant health burden with its progressive nature. While excessive alcohol consumption is a prominent risk factor, **non-alcoholic chronic pancreatitis (NACP)** presents challenges due to less overt precipitating factors. We aimed to assess the impact of rs7057398 and rs12688220 variants at the ***RIPPLY1-CLDN2-MORC4*** locus and rare functionally deficient ***TRPV6*** variants in NACP susceptibility in a **systematic review and meta-analysis.**

Methods

Systematic search was conducted on PubMed, Embase, and Web of Science databases on **November 2, 2023**, aiming to assess non-alcoholic acute recurrent pancreatitis (ARP) and CP cases, excluding conference abstracts and preprints.

Utilizing a **random-effect** model with REML estimation, **odds ratios (OR) with 95% confidence intervals (CI)** were computed using the **allelic model** (**rs7057398**: C vs T; **rs12688220**: T vs C) for the total population and hemizygotes as well, the homozygote (rs7057398: CC vs TT; rs12688220: TT vs CC) and heterozygote model (rs7057398: CT vs TT; rs12688220: TC vs CC). **Minor allele frequnecy (MAF)** was calculated for both variants. In the analysis of **functionally deficient** rare **Transient Receptor Potential Vanilloid 6 (*TRPV6*) variants** were collectively pooled and compared to cases without mutations affecting TRPV6 function, calculating OR with 95% CI. Subgroup analysis, stratified by age, set the threshold for early-onset CP at 30 years in all cases.

Statistical heterogeneity was evaluated using **Chi² tests and I² values**. Due to limited study numbers, funnel plots and Egger's test were deemed inappropriate.

Conclusion

Meta-analysis suggests that rs7057398 and rs12688220 variants of the *RIPPLY1-CLDN2-MORC4* locus and functionally deficient *TRPV6* variants are risk factors for non-alcoholic chronic pancreatitis, advocating for screening.

Results

The ***TRPV6* gene**, encoding a calcium-selective channel crucial for epithelial calcium absorption, exhibits high expression in exocrine tissues, particularly in pancreatic ductal and acinar cells.

In a comprehensive analysis involving 2236 cases and 2748 controls, **functionally deficient variants in the *TRPV6* gene** were **associated with a 35-fold increased odds of developing NACP** compared to individuals without these variants (**Figure 1**).

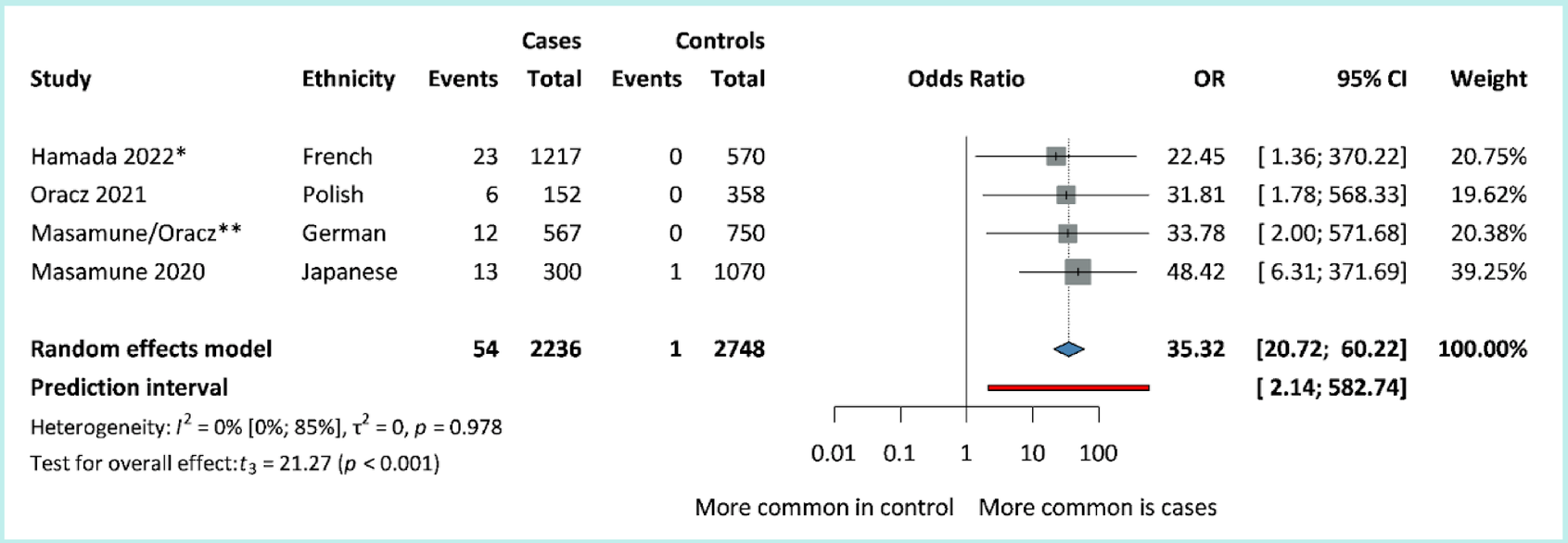


Fig.1. Association of functionally deficient TRPV6 variants and NACP

The ***RIPPLY1-CLDN2-MORC4* locus on the X chromosome** was identified as a **significant risk modifier** for acute pancreatitis and **NACP** through a GWAS pinpointing SNPs **rs7057398 and rs12688220**. **CLDN2**, which is crucial for **tight junction** integrity is mainly expressed in **pancreatic ductal cells. During stress and inflammation** (as pancreatitis), claudin 2 **expression increases in acinar cells.**

At the individual study level, MAF was significantly elevated in cases compared to ethnically matched controls (**Figure 2**). MAF was notably higher in Indian and Asian studies compared to European cohorts. In the **allelic model, minor allele carriers** displayed **significantly increased odds for NACP** (OR 1.54, CI 1.17 to 2.01, p=0.009) (**Figure 3**). The risk allele was siginificantly associated with NACP in homo-, hetero- and hemizygotes as well.

For rs12688220, the allelic model yielded an OR of 1.64 (CI 1.10 to 2.45, p=0.025) (**Figure 3**). The association between rs12688220 and NACP exhibited distinct ORs across genotypes, with statistically significant results. **Limited data** was available **on early-onset cases**, therefore definitive conclusions cannot be drawn.

SNP	Group	Cohorts	Events	Total	MAF	95% CI	I2 [95% CI]
rs7057398	Cases	6	1424	3049	0.49	0.31;0.67	98% [97;99]
	Controls	6	2884	8803	0.38	0.27;0.50	98% [98;99]
rs12688220	Cases	6	1589	3396	0.46	0.27;0.67	99% [98;99]
	Controls	6	3418	10405	0.35	0.24;0.47	99% [99;99]

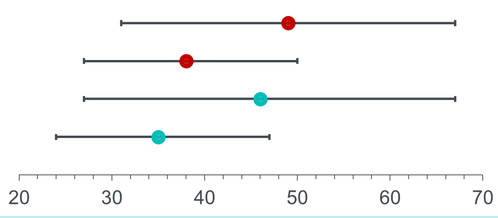
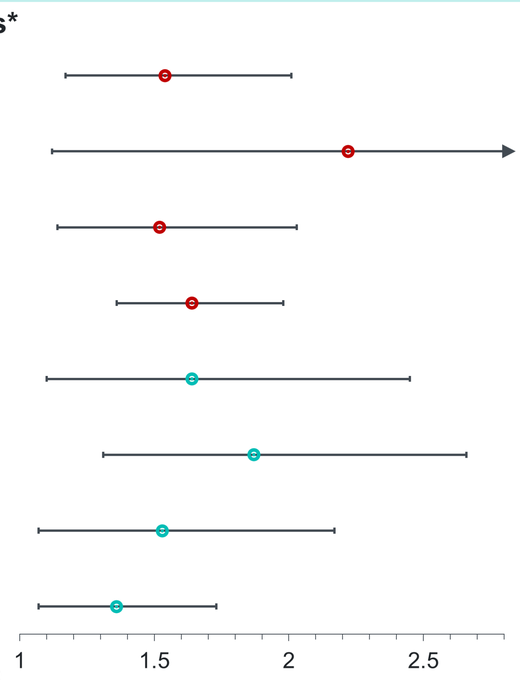


Fig.2. Minor allele frequency of RIPPLY1-CLDN2-MORC4 variants and NACP

SNP	Model	Cohorts	Cases*	Controls*	OR	95% CI	I2 [95% CI]
rs7057398	Allelic	6	1424/ 3049	2884/ 8803	1.54	1.17;2.01	75% [44;89]
	Homozyg	6	200/ 506	361/ 1830	2.22	1.12;4.42	63% [10;85]
	Hemizyg	6	577/ 1153	935/ 2689	1.52	1.14;2.03	51% [0;80]
	Heterozyg	6	447/ 753	1227/ 2696	1.64	1.36;1.98	0% [0;75]
rs12688220	Allelic	6	1589/ 3396	3418/ 10405	1.64	1.10;2.45	92% [85;96]
	Homozyg	5	146/ 502**	287/ 1834**	1.87	1.31;2.66	30% [0;71]
	Hemizyg	5	497/ 1333**	807/ 3275**	1.53	1.07;2.17	69% [28;87]
	Heterozyg	5	367/ 723	1131/ 1678	1.36	1.07;1.73	0% [0;79]



*events/total; ** one study reportin OR not shown here

Fig.3. Association of RIPPLY1-CLDN2-MORC4 variants and NACP

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