Rare variant associations of chronic pain conditions in the UK Biobank 450K Whole Exome Sequencing

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Abstract

Background: Chronic pain is a complex disease condition with varying aetiology, clinical manifestation, and polygenic architecture.

Objective: Identify and characterize rare genetic variants associated with pain conditions in the 450K WES UK Biobank using novel pain questionnaire data, recalibrated principal component analysis, optimized control cohorts, and epistasis analyses.

Methods & Results: We performed rare variant association analyses of a broad spectrum of pain phenotypes using uncorrected whole exome sequencing data from 450K UK Biobank participants. We investigated associations with pain conditions based on ICD-10 codes and novel pain-specific questionnaire data. For that purpose, we recalibrated principal components to account for population stratification and designed control cohorts to minimize bias and variability in identified associations. For complex regional pain syndrome (UKBB data-field 120004) we found several genome wide significant associations like a causal rare missense variant in sialic acetyl esterase (SIAE R479C, p-value 3.34E-08, odd ratio 7.1, MAF 1e-04) which has been reported to have a defective enzyme activity and known causal links to autoimmune diseases (e.g. rheumatoid arthritis). For the discovery of potential novel targets, we focus on protective rare missense variants and found I480M (rs61749251) in Mammary Analogous Zinc Finger 2 (MAML2, p-value 6.57E-06, odd ratio 0.62, MAF 0.015) which acts as a transcriptional cofactor for Notch proteins. To further investigate the related blood vessel pathophysiology, we search for genetic interaction with SIAE R479C by epistasis calculations and found the mutation V366E in JCAD (beta 3.4, CHISQ 20.4, OR 29.9, p-value 6.39E-06) reported to play a key role in coronary artery disease. Finally, we found a protective rare variant in Lipoprotein associated calcium independent phospholipase A2 (PLA2G7, S388P, beta -2.1/OR 0.12, CHISQ 12.9, p-value 3.16E-04) which is involved in phospholipid catabolism during inflammatory and oxidative stress response and protects against accumulation of oxylipins in the vascular wall.

Conclusions: This study provides valuable insights into the genetic architecture of pain conditions by leveraging rare variant analysis in a large-scale population cohort. Our study identified a realm of novel statistically significant associations of rare protective and causal variants in the 450K WES data for all

pain conditions defined by ICD-10 codes and novel pain questionnaire data within the UK Biobank. Our findings implicate novel genes and regulatory pathways in pain susceptibility, paving the way for future research on personalized pain management and therapeutic targets. As an example, we present our results for complex regional pain syndrome suggesting novel mechanistic insights into the autoimmune and blood vessel pathophysiology. We also identified novel protective rare variants that may offer insights into potential roles in pain resilience mechanisms, pain sensitivity and modulation. Epistasis analysis revealed significant interactions between rare variants in different genes, highlighting their cooperative effects on pain susceptibility.

Keywords: UK Biobank, genetics, rare variants, pain, epistasis, complex regional pain syndrome

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