Association study on chronic pain from UK Biobank whole-exome sequencing cohort

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INTRODUCTION

Chronic pain is a debilitating health issue; however, genetic foundations of chronic pain remain vague[1,2]. In this study, we aim to study the genetic underpinnings of chronic pain from the large-scale UK Biobank (UKBB) whole exome sequencing (WES) data[3].

OBJECTIVES

1. To identify pain susceptible variants and genes.
2. To investigate pathogenic pathways to pain.

METHODS

We screened among Caucasians for chronic pain samples using the following UKBB fields: field 3571(back pain), 4067(facial pain), 2956(general pain), 3799(headache), 3414(hip pain), 3773(knee pain), 3404(neck or shoulder pain), and 3741(stomach or abdominal pain). Participants who responded with “yes” to these fields were classified as pain cases, while those who checked “none of the above” in field 6159 were considered healthy controls. We further defined three additional pain traits based on the number of pain sites experienced simultaneously(chronic lone pain: one pain site only; chronic overlapping pain: at least two pain sites; chronic multisite pain: number of pain sites.) We conducted both variant-level and gene-level association tests with these pain traits. For the gene-level analysis, we focused on functionally damaging rare variants (minor allele frequency < 0.01). We applied Ensembl Variant Effect Predictor (VEP)[4] and Loss-Of-Function Transcript Effect Estimator (LOFTEE)[5] to classify rare variants into three groups: high-confidence loss-of-function(HC_LoF) variants, deleterious missense(del_mis) variants, and possible damaging missense(posD_mis) variants. We conducted gene-level analyses by SAIGE-GENE+[6]. Finally, we performed a pathway analysis on pain-related genes.

RESULTS

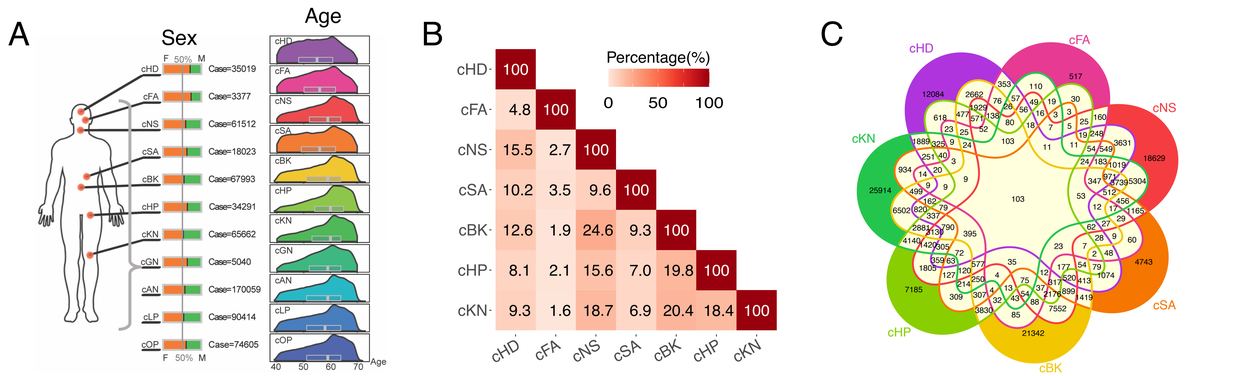

Fig 1. Overview of chronic pain cases. A. Case distribution by body sites. B. Case overlap between two chronic pain conditions (chronic general pain cases were excluded). C. Case overlap among chronic pain conditions (chronic general pain cases were excluded). F: female; M: male; cHD: headache; cFA: facial pain; cNS: neck or shoulder pain; cSA: stomach or abdominal pain; cBK: back pain; cHP: hip pain; cKN: knee pain; cGN: general pain; cAN: any pain; cLP: lone pain; cOP: overlapping pain.

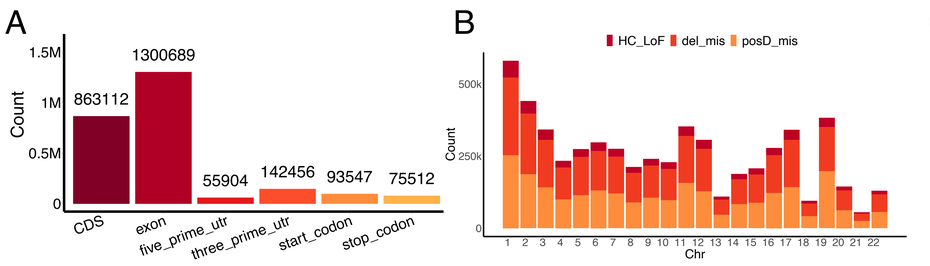

Fig 2. Variant distribution. A. Variant distribution by genomic region. B. Rare variant distribution by functional consequence. C. Overlap between rare variant groups.

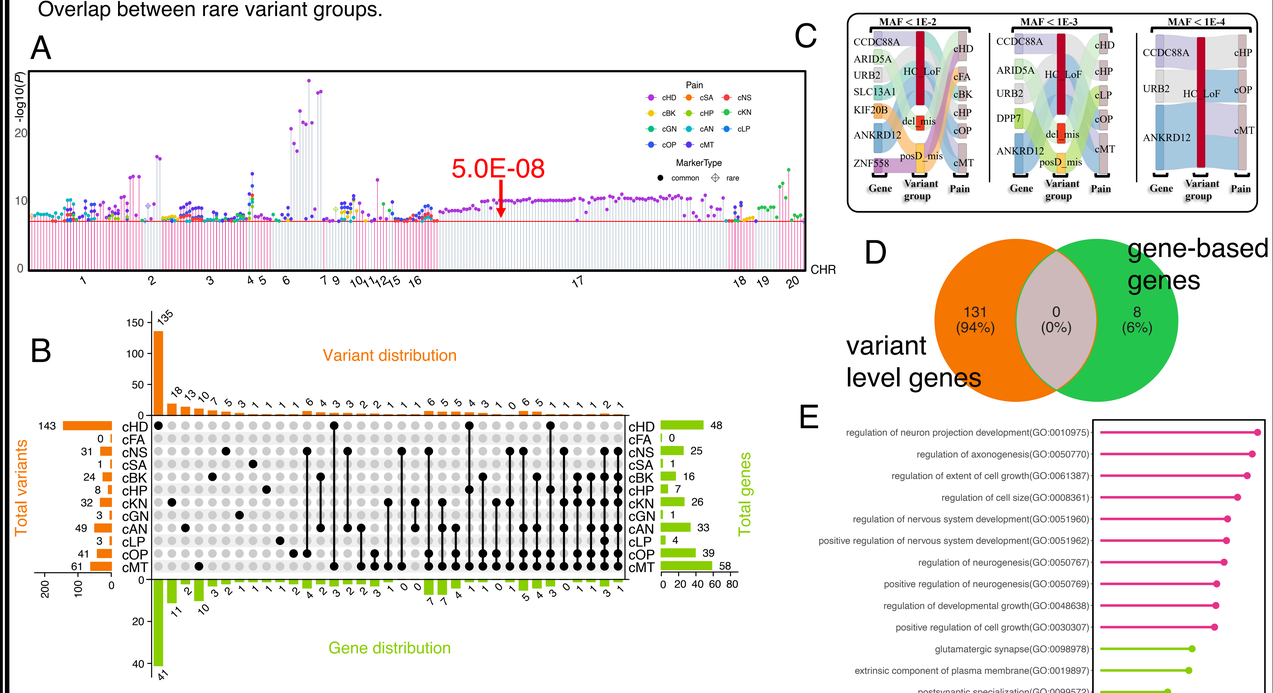

Fig 3. Investigation of pain susceptible loci and pathways. A. Overview of significant variants to chronic pain. B. Distribution of significant variants by pain trait. C. Overview of significant genes from gene-based analysis. D. Gene overlap between variant-level and gene-level analysis. E. Pathway analysis of significant genes from both analyses.

CONCLUSION

1. We discovered 396 variant-pain pairs surpassed the genome-wide significance threshold ($P < 5E-08$); major signals were from common variants(n=392).
2. The largest significant variants were detected from chronic headache (n=143) and no significant variants were detected for chronic facial pain, suggesting that chronic headache is the most heritable trait among all pain conditions[7] examined in the study.
3. Most of these significant variants are unique to chronic headache, implying distinct pathogenic pathways for this condition.
4. From gene-based analysis of functional rare variants, we identified eight genes. Notably, half of these genes are implicated in cell cycle regulation(ARID5A and UBR2 involved in cell growth regulation; CCDC88A in cell migration regulation; and KIF20B in cell proliferation regulation).
5. We found no overlap between genes identified from variant-level tests and those from gene-level test; indicating the distinct roles of common and rare variants in chronic pain.
6. Our pathway analysis further underscored the importance of nervous system in chronic pain[8].
7. Further research is required to specify the unique/common pathogenic pathways/tissues involved in the development of chronic pain.

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