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Pre-print

Sex-Stratified GWAS of Multisite Chronic Pain in UK Biobank

- **Past genetic work in chronic pain often focuses on specific pain sites or syndromes – may be more powerful to study chronic pain as a complex trait in its own right**
- **Sex as a biological variable has wide-ranging effects, including on resultant phenotype, in many complex traits [1,2]**
- **Chronic pain is twice as prevalent in women compared to men [3-5]**
- **Recent work in animal and cell models highlights sex differences in immune-cell modulation of pain mechanisms [6-8]**

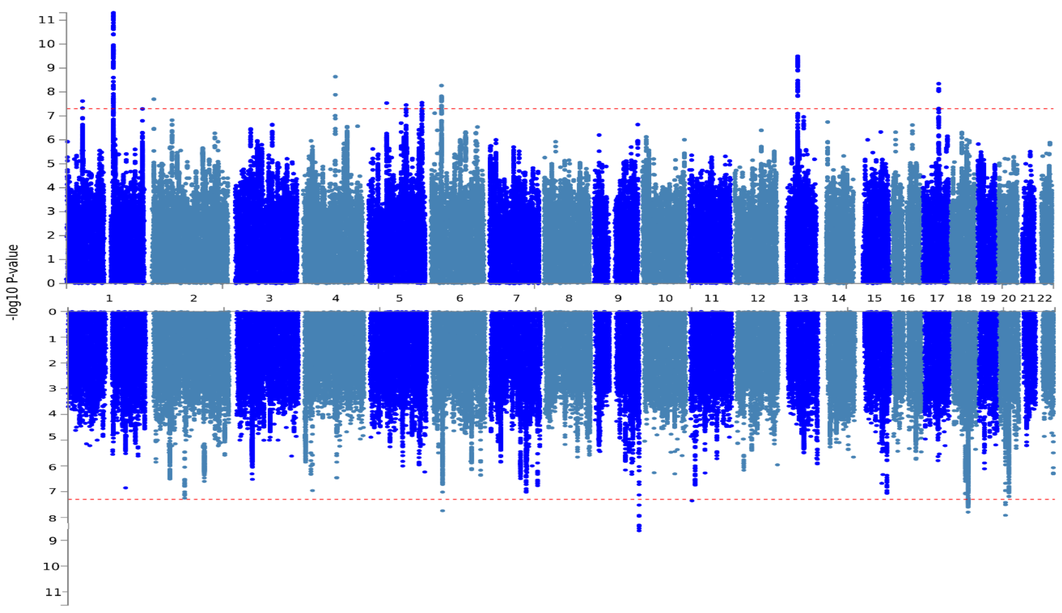

Figure 1: Manhattan Plot. Upper panel: female sex-stratified GWAS, lower panel: male sex-stratified GWAS.
X-axis = chromosome
Y-axis = log-transformed p value for SNP association with MCP

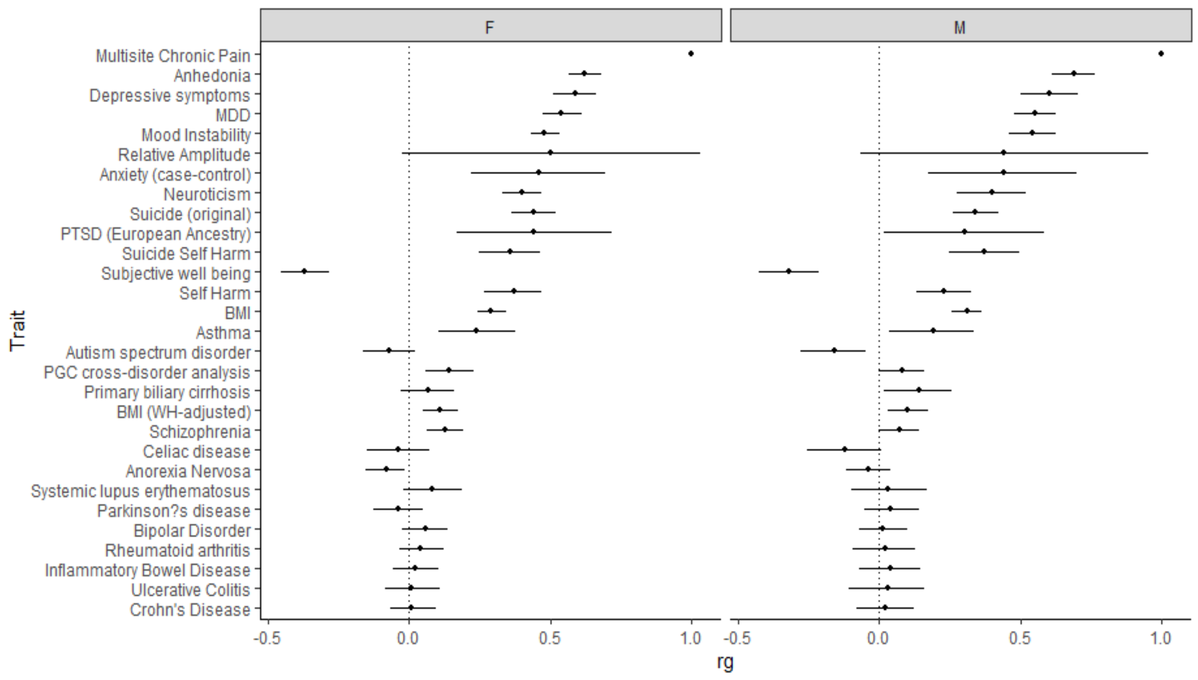

Figure 2: LD Score regression (genetic correlation). r_g = genetic correlation coefficient value. M = male MCP, F = female MCP. 95% confidence intervals for r_g shown. NB trait Multisite Chronic Pain = non-stratified MCP

Methods Summary:

- **Sex stratified BOLT-LMM GWAS of Multisite Chronic Pain, followed by GWAS meta-analysis (N: 209,093 F, 178,556 M)**
- **MAGMA gene-based testing, LD-score regression**
- **MCP-associated gene expression across range of tissues (GTEx), DRG tissue samples, and neural & non-neural human and mouse samples (scRNA)**
- **Polygenic risk score analysis of female and male MCP and chronic widespread pain**

Conclusions:

- *Some differences in male and female MCP were observed at the SNP, gene, genetic-correlation and transcript abundance level, but male and female MCP are highly genetically correlated and patterns of genetic correlation with other traits are qualitatively similar between men and women*
- *Results support a strong central nervous-system component to chronic pain in both sexes, & highlight a role for the DRG and nociception.*

Results:

- Male and female MCP are complex, polygenic traits of moderate SNP-heritability (~10% M vs ~12% F)
- Genetic correlation between male and female MCP was high but significantly lower than 1 (r_g = 0.92)
- *DCC* was the only gene found to be associated with both male and female MCP
- sex-differential patterns of pleiotropy were observed – some may be due to sample size and sex-ratio issues, but some (PTSD, SCZ) may represent greater shared genetic factors between female MCP and particular psychiatric traits
- 11 novel loci (in addition to 76 previously found via sex-combined GWAS) associated with MCP
- sex-differential pleiotropy with female MCP, PTSD and schizophrenia was observed
- almost all sex-differential MCP-associated genes were expressed in the DRG, in addition to the brain
- One male-enriched MCP gene, *AMIGO3* was DRG-specific in terms of expression amongst the tissues assessed in human and mouse samples
- Several MCP-associated loci in both sexes linked to immune function
- Polygenic risk for MCP in both sexes is associated with chronic widespread pain

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