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Spinal cord neuronal subtypes conserved across species are genetically implicated in chronic pain disorders

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Genome Wide Association Studies (GWAS) have identified risk variants for several chronic pain disorders, but these studies do not identify the functional effects on the genome nor the particular spinal cord cell types affected by these variants. As in other polygenic diseases, we expect variants associated with chronic to lie in and around genomic regulatory elements (REs), non-coding DNA sequences that regulate gene expression. For this study, we acquired putative REs by collecting single-nucleus Assay for Transposase-Accessible Chromatin (snATAC-seq), from the dorsal horns of mouse and macaque, and mapped these REs to orthologs in human in order to study their association with risk loci found in GWAS.

Because active REs are highly cell-type-specific indicators, we hypothesized that particular neural subtypes identified by previous knockout experiments will be highly enriched for chronic pain markers in their particular set of regulatory elements. Using LD score regression, we found several excitatory and inhibitory subpopulations enriched for chronic pain markers, which were previously implicated in chronic pain from knockout experiments. Remarkably, the enrichment results of macaque and mouse show high similarity, suggesting that the functional role, and consequences of dysfunction, of these cell types is well conserved across species.

Our results provide genetic evidence for the functional role of particular neural subtypes in chronic pain disorders. Our results hold across mouse and macaque, demonstrating that follow-up studies of these cell types in mouse will have translational relevance for future work in macaque, and potentially later in humans.