Title: RNA profiling of human dorsal root ganglia reveals sex-differences in mechanisms promoting neuropathic pain

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Neuropathic pain is a major cause of chronic pain affecting millions of adults. Although females represent a greater proportion of chronic pain suffers, little is known about the underlying molecular mechanisms that might contribute to such disparate representation. The study by Ray and colleagues quantified whole transcriptome RNA abundances using RNA-seq in human dorsal root ganglia (DRG) from pain and non-pain patients undergoing thoracic vertebrectomy surgery. Upon analyzing fifty human DRGs, distinct sexually dimorphic gene expression patterns were identified. In particular, in males, signaling genes such as IL1B, TNF, CXCL14 and OSM were increased, while CCL1, CCL21, PENK, and TLR3 expression were identified in females. Distinct cytokine signaling characteristics were associated with neuropathic pain in males and females, with FOS-JUN-driven cytokine profiles dominant in males, while type I and II interferon signaling dominant in females. Many molecular studies for neuropathic pain have focused on examining inflammatory cytokines. Based on the findings of this report, greater attention to interferon-stimulated gene and signaling changes are needed to understand female-specific mechanisms better. Although neuropathic pain phenotype may be similar between males and females, fundamental molecular mechanisms associated with neuropathic pain are distinct between the sexes, which notes the importance of sex-specific mechanisms for characterizing neuropathic pain and developing strategies for treating the condition.