

Name: Sylvanus Toikumo, Ph.D.

Email: Sylvanus.Toikumo@pennmedicine.upenn.edu

Pain-Specific Cell-Type Insights Inform the Shared Genetic Liability of Chronic Pain and Addiction in >1.2 million Individuals

Chronic pain is a highly prevalent, debilitating condition with a complex genetic basis, yet the mechanisms linking genetic risk to cellular function and comorbid traits are incompletely understood. To define the genetic architecture of chronic pain and its shared liability with addiction, we conducted a meta-GWAS of chronic pain phenotypes in 1,235,695 individuals of European ancestry from the Million Veteran Program, UK Biobank, and FinnGen. We identified 343 independent loci, including 92 novel associations, and integrated multi-omics gene prioritization highlighted 490 genes whose regulation in the brain and blood contributes to pain risk. MiXeR analyses revealed substantial shared genetic liability between chronic pain and substance use traits: risk variants for chronic pain were largely concordant with those influencing opioid use and substance use disorders and contributed to co-occurring psychiatric traits and inflammatory biomarker levels. Sex-stratified analyses identified loci unique to males and females, highlighting potential biological differences in pain susceptibility. To understand these findings mechanistically, we integrated GWAS results with single-cell RNA sequence data from human brain and dorsal root ganglia, and chromatin accessibility data from human brain and mouse dorsal horn. These analyses revealed an enrichment of pain-associated variants in glutamatergic neurons of the prefrontal cortex, hippocampus, and amygdala, and in sensory neurons of the dorsal root ganglia. These results expand the catalog of chronic pain risk loci, clarify the pleiotropic genetic architecture linking pain with addiction and psychiatric traits, and provide cell-type-specific insights to guide mechanistic studies and the development of targeted, non-addictive interventions for chronic pain and comorbid substance use disorders.

Authors:

Submitter: Sylvanus Toikumo, Postdoctoral Researcher, University of Pennsylvania, Philadelphia
Henry Kranzler, M.D., University of Pennsylvania