Submitter Name: Renato Polimanti
Submitted email: renato.polimanti@yale.edu
PI Name: Joel Gelernter
PI email: joel.gelernter@yale.edu

Leveraging genome-wide data to investigate differences between opioid use vs. opioid dependence in 41,176 individuals from the Psychiatric Genomics Consortium

Renato Polimanti[1], Raymond K. Walters[2], Emma C. Johnson[3], Jeanette N. McClintick[4], Amy E. Adkins[5], Daniel E. Adkins[6], Silviu-Alin Bacanu[7], Laura J. Bierut[3], Tim B. Bigdeli[8], Sandra Brown[9], Kathy Bucholz[3], William E. Copeland[10], E. Jane Costello[11], Louisa Degenhardt[12], Lindsay A Farrer[13], Tatiana M. Foroud[14], Louis Fox[3], Alison M. Goate[15], Richard Grucza[3], Laura M. Hack[16], Dana B. Hancock[17], Sarah M. Hartz[3], Andrew C. Heath[3], John K. Hewitt[18], Christian J. Hopfer[19], Eric O. Johnson[17], Kenneth S. Kendler[20], Henry R. Kranzler[21], Ken Krauter[22], Dongbing Lai[14], Pamela A. F. Madden[3], Nicholas G. Martin[23], Hermine H. Maes[20], Elliot C. Nelson[3], Roseann E. Peterson[24], Bernice Porjesz[8], Brien P. Riley[7], Nancy Saccone[25], Michael Stallings[18], Tamara Wall[9], Bradley T. Webb[7], Leah Wetherill, the Psychiatric Genomics Consortium Substance Use Disorders Workgroup, Howard J. Edenberg[4], Arpana Agrawal[3], Joel Gelernter[1]

[1]Department of Psychiatry, Yale University School of Medicine; [2]Analytic and Translational Genetics Unit, Department of Medicine, Massachusetts General Hospital and Harvard Medical School; [3]Department of Psychiatry, Washington University School of Medicine; [4]Department of Biochemistry and Molecular Biology, Indiana University School of Medicine; [5]Department of Psychology, Virginia Commonwealth University; [6]Department of Psychiatry, University of Utah; [7]Virginia Commonwealth University Alcohol Research Center, Virginia Institute for Psychiatric and Behavioral Genetics; [8]Department of Psychiatry and Behavioral Sciences, State University of New York Downstate Medical Center; [9]Department of Psychiatry, University of California San Diego; [10]Department of Psychiatry, University of Vermont Medical Center; [11]Department of Psychiatry and Behavioral Sciences, Duke University Medical Center; [12]National Drug and Alcohol Research Centre, University of New South Wales; [13]Department of Medicine (Biomedical Genetics), Boston University School of Medicine; [14]Department of Medical and Molecular Genetics, Indiana University School of Medicine; [15]Department of Neuroscience, Icahn School of Medicine at Mount Sinai; [16]Department of Psychiatry and Behavioral Sciences, Stanford University; [17]Center for Omics Discovery and Epidemiology, RTI International; [18]Institute for Behavioral Genetics, University of Colorado Boulder; [19]Department of Psychiatry, University of Colorado Denver; [20]Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University; [21]Center for Studies of Addiction, University of Pennsylvania Perelman School of Medicine; [22]Department of Molecular, Cellular, and Developmental Biology, University of Colorado Boulder; [23]QIMR Berghofer Medical Research Institute; [24]Department of Psychiatry, Virginia Commonwealth University; [25]Department of Genetics, Washington University School of Medicine

To provide novel insights into the biology of opioid dependence (OD) and opioid use (i.e., exposure, OE), we completed a genome-wide analysis comparing up to 4,503 OD cases, 4,173 opioid-exposed controls, and 32,500 opioid-unexposed controls. Among the variants identified, rs9291211 was associated with OE (a comparison of exposed vs. unexposed controls; z=-5.39,

p=7.2×10-8). This variant regulates the transcriptomic profiles of SLC30A9 and BEND4 in multiple brain tissues and was previously associated with depression, alcohol consumption, and neuroticism. A phenome-wide scan of rs9291211 in the UK Biobank (N>360,000) found association of this variant with propensity to use dietary supplements (p=1.68×10-8). With respect to the same OE phenotype in the gene-based analysis, we identified SDCCAG8 (z=4.69, p=10- 6), which was previously associated with educational attainment, risk-taking behaviors, and schizophrenia. In addition, rs201123820 showed a genome-wide significant difference between OD cases and unexposed controls (z=5.55, p=2.9×10-8) and a significant association with musculoskeletal disorders in the UK Biobank (p=4.88×10-7). A polygenic risk score (PRS) based on a GWAS of risk-tolerance (N=466,571) was positively associated with OD (OD cases vs. unexposed controls, p=8.1×10-5; OD cases vs. exposed controls, p=0.054) and OE (exposed controls vs. unexposed controls, p=3.6×10-5). A PRS based on a GWAS of neuroticism (N=390,278) was positively associated with OD (OD cases vs. unexposed controls, p=3.2×10-5; OD cases vs. exposed controls, p=0.002) but not with OE (p=0.671). Our analyses highlight the difference between dependence and exposure and the importance of considering the definition of controls (exposed vs. unexposed) in studies of addiction.