Submitter Name: Kenneth Blum Submitter Email: drd2gene@Gmail.com

# Preaddiction Phenotype is Associated with Dopaminergic Dysfunction: Pharmacogenomic Evidence from 88.8M GWAS-Based Samples

Kenneth Blum[-1-3], Alireza Sharafshah[3], Kai-Uwe Lewandrowski[4], Panayotis K. Thanos[5], Jean Lud Cadet[6], Eliot I. Gardner[7], Igor Elman[8], Keerthy Sunder[9] Marjorie C. Gondre-Lewis[10], Gene Jack Wang[11], Marlene Oscar Berman[12], Eric R. Braverman[3], David Baron[1], Jag Khalsa,[13*]J Wesson Ashford,[14] Mark S. Gold[15]

[1]Division of Addiction Research & Education, Center for Sports, Exercise, and Mental Health, Western University of Health Sciences, Pomona, CA., USA; [2]Department of Molecular Biology, Adelson School of Medicine, Ariel University, Ariel, Israel ; [3]Division of Clinical Neurology, The Blum Institute of Neurogenetics & Behavior, Austin, TX., USA ; [4]Department of Orthopaedics, Fundación Universitaria Sanitas Bogotá D.C. Colombia; [5]Behavioral Neuropharmacology and Neuroimaging Laboratory on Addictions, Clinical Research Institute on Addictions, Department of Pharmacology and Toxicology, Jacobs School of Medicine and Biosciences, State University of New York at Buffalo, Buffalo, NY, USA; [6] Molecular Neuropsychiatry Research Branch, NIDA Intramural Research Program, Baltimore, MD., USA; [7]Neuropsychopharmacology Section, Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health, Baltimore, MD., USA; [8]Department of Psychiatry, Harvard Medical School, Cambridge, MA., USA; [9] Department of Psychiatry, University of California Riverside, Riverside Ca., USA ; [10]Neuropsychopharmacology Laboratory, Department of Anatomy, Howard University College of Medicine, Washington, DC., USA; [11]Laboratory of Neuroimaging, National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD, USA; [12]Department of Anatomy and Neurobiology, Boston University School of Medicine, Massachusetts, USA; [13]US National Institute on Drug Abuse, NIH; Medical Consequences of Drug Abuse and Infections Branch, National Institute on Drug Abuse, NIH, Bethesda, Md., USA (*Special Volunteer*); [14] Department of Psychiatry and Behavioral Sciences, Stanford University, Palo Alto, CA, USA; War Related Illness & Injury Study Center, VA Palo Alto Health Care System, Palo Alto, CA, USA; [15]Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA.

Recently, McLellan, Koob, Volkow (2022), urged the addiction biology and clinical field to consider the concept of Preaddiction as missing term in the treatment of Substance Use Disorder (SUD). Facing a similar situation, the diabetes field increased treatment penetration and impact by identifying and intervening with early-stage diabetes, termed *prediabetes*. Blum's group (*we have*) published a series of articles suggesting that all addictive behaviors and genetic vulnerability thereof may be due to dopaminergic dysregulation and coined the term Reward Deficiency Syndrome (RDS). Thus, the rationale of the current investigation strategically considered the possibility that the actual phenotype of preaddiction is indeed dopaminergic dysregulation, that could be early identified with the Genetic Addiction Risk Severity (GARS) test involving 10 specific polymorphic reward genes. This study explores the concept of "Pre-Addiction" within addiction biology through a comprehensive in silico analysis of 88,788,381 GWAS-based samples from 1,373 studies, identifying 18 significant genes (e.g., APOE with p-value=1.0E-126) linked to Opioids, Pain, Aging, and Apoptosis pathways. It aims to correlate these genes with GARS highlighting the most connected genes like MAOA, COMT, APOE, and SLC4A6 through a STRING-MODEL. The analysis expanded to 27 unique genes, emphasizing significant interactions with hsa-miR-16-5p and hsa-miR-24-3p, especially noting SLC6A4. Through PGx mining, 1,173 variant annotations were identified for these genes. Enrichment Analysis and Meta-analysis further solidified these findings, illustrating the pivotal role of dopaminergic pathways in connecting addictive behaviors and depressive symptoms, proposing reward deficiency syndrome (RDS) as the fundamental preaddiction phenotype, with pain, opioid dependence, aging, and apoptosis as critical endophenotypes. WC250