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Guest Editorial

Evidence Based Clinical Analytics Supporting the Genetic Addiction Risk Severity (GARS) Assessment to Early Identify Probands in Preaddiction

Kenneth Blum[1-6,14]*, Abdalla Bowirrat[1], Panayotis K Thanos[7,8], Colin Hanna[7], Jag Khalsa[8], David Baron[2], Igor Elman[9], Rajendra D Badgaiyan[10], Catherine Dennen[11], Eric R Braverman[2], Paul Carney[12], Kai-Uwe Lewandrowski[13,14], Alireza Sharafshah[15] and Mark S Gold[16]

[1]*Department of Molecular Biology and Adelson School of Medicine, Ariel University, Ariel, Israel*

[2]*Center for Sports, Exercise, Global Mental Health, Western University Health Sciences, Pomona, CA, USA*

[3]*The Kenneth Blum Behavioral & Neurogenetic Institute, LLC., Austin, TX, USA*

[4]*Institute of Psychology, ELTE Eötvös Loránd University, Budapest, Hungary*

[5]*Department of Psychiatry, University of Vermont School of Medicine, Burlington, VY, USA*

[6]*Department of Psychiatry, Wright University, Boonshoff School of Medicine, Dayton, OH, USA*

[7]*Behavioral Neuropharmacology and Neuroimaging Laboratory, Department of Pharmacology and Toxicology, Jacobs School of Medicine and Biomedical Sciences, Clinical Research Institute on Addictions, University at Buffalo, Buffalo, NY, USA*

[8]*US National Institute on Drug Abuse, NIH, Medical Consequences of Drug Abuse and Infections Branch, National Institute on Drug Abuse, NIH, Bethesda, Maryland, USA*

[9]*Cambridge Health Alliance, Harvard Medical School, Cambridge, MA, USA*

[10]*Department of Psychiatry, Case Western Reserve University School of Medicine, Cleveland, OH, USA*

[11]*Department of Family Medicine, Jefferson Health Northeast, Philadelphia, PA, USA*

[12]*Division Pediatric Neurology, University of Missouri, School of Medicine, Columbia, MO, USA*

[13]*Department of Orthopaedics, Fundación Universitaria Sanitas, Bogotá, DC, Colombia*

[14]*Center for Advanced Spine Care of Southern Arizona, Tucson, AZ, USA*

[15]*Cellular and Molecular Research Center, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran*

[16]*Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA*

***Corresponding Author:** Kenneth Blum, Center for Sports, Exercise, Global Mental Health, Western University Health Sciences, Pomona, CA, USA.

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The first ever confirmed candidate psychiatric genetic association study was performed by Kennth Blum and Ernest Noble and their team, whereby they discovered a significant association of the minor *DRD2 allele Taq A1 (rs 1800497 C>T)* and severe alcoholism published in *JAMA* (1990) [1]. While this seminal finding has been the subject of significant controversy, it has been now confirmed in a number of high end and elaborate recent GWAS studies related to depression and suicide in 1.2 million veterans [2,3]. In the latter case, the DRD2 rs1800497 was significantly associated with suicide behaviors at $P = 1.77 \times 10^{-7}$.

Moreover, in a recent meta-analysis Goldmans group reported on 62 studies showing a significant association with the DRD2 rs 1800497 and Alcohol Use Disorder (AUD) [4]. Gelernter's group at Yale, clearly showed an association of a haplotype block of the DRD2 gene A1 allele to associate with AUD and heroin dependence [5].

In 1996, our group using Bayesian theorem revealed a Predictive Value (PV) of 74.4% whereby carriers of the rs 1800497 will express one or more of "Reward Deficiency Syndrome" (RDS) behaviors (e.g. SUD, gambling, overeating, etc [6]. In 2004, Nevile., *et al*. reported that the DRD2 rs 1800497 is a single nucleotide polymorphism (SNP) that causes an amino acid substitution within the 11th ankyrin repeat of ANKK1 (p.Glu713Lys), which, while unlikely to affect structural integrity, may affect substrate-binding specificity [7].

In 2014, our group developed the GARS test consisting of ten genes and eleven SNPs across the finite neurotransmitter pathways representative of the Brain Reward Circuitry DNA hypodopaminergia antecedents to addiction psychiatry [8]. In 2022, involving 74,566 case-controls (AUD) we statistically validated the selection of these risk alleles measured by GARS, and showed significance for DRD2, DRD3, DRD4, DAT1, COMT, OPRM1, and 5HTT at 5% and these alleles captured post-risk for 8% estimation of the population's alcoholism prevalence post-risk for 8% estimation of the population's alcoholism prevalence [9].

Over 33 years as of 12-17-23, a PUBMED search using "dopamine genes" revealed 11,495 articles mostly related to addiction psychiatry. Since 1990 and 2022, our laboratory published a number of studies showing the positive clinically relevant analyses of utilizing GARS to help identify not only AUD (N = 393); SUD (N = 110,241 cases and 122,525 controls; high Opioid risk in pain clinics (121 chronic opioid users); identified eating expectancy and other RDS behaviors in a bariatric post -surgical cohort (N = 34); also utilized in drug Court to help convert DWI offenders facing prison time to rehabilitation based on genetic determinism rather than free will (N = 31) saving over 225 prison time to mandated probation [10]. We genotyped over 3,000 people presenting with polysubstance abuse from at least one-dozen chemical dependency and Behavioral addiction clinics including general population mixed gender and race that resulted in a GARS score for drug and alcohol risk at over 90% and 72% respectively [11,12].

It is indeed noteworthy that since 1990 the first study on psychiatric genetics [1] and as of 12-17-23 there are 30,637 PUBMED listed articles related to the new field of Psychiatric Genetics. Blum's group revealed through intensive investigations the important clinical relevance of a candidate approach referred to as GARS test. Most recently, DNA polymorphic alleles linked to substance use disorder (SUD) with multiple substances were mapped via chromatin refolding, showing that the DRD2 gene and associated polymorphism(s) as the top gene signal [13].

In summary, these results over 3 decades indicate that not only the DRD2 gene, but other polymorphic reward genes measured in GARS (5HTTLPR, MUOR, GABABR3, DRD1-4, DAT1, COMT, AND MAOA) have an important role in the unwanted induction of RDS behaviors. While we encourage the scientific community to perform additional required larger studies (GWAS and Candidate approaches), we believe we have found a very useful tool to help identify addiction risk even at birth not to label but inform parents of potential danger ahead.

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Author Contribution

KB developed the initial manuscript then edited by MAM, followed by approval and comments by AB, PKT, DB, IE, CD, ERB, PC and MSG.

Conflict of Interest

KB holds patents both domestic and foreign related to pro-dopamine regulation complexes and genetic testing for addiction risk. Through his company Synaptamine inc., licensed patents on KB220Z to Victory nutrition international, LLC., There are no other conflicts to report.

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