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COMMENTARY

"TO BE OR NOT TO BE" GWAS Ends the Controversy about the DRD2 Gene as a Determinant of Reward Deficiency Syndrome (RDS)

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Abstract: Since 1990, there have been thousands of published studies on addiction psychiatry. Several from Blum et al showed the clinical relevance of the Genetic Addiction Risk Severity (GARS) test in identifying risk for reward deficiency behaviors in cohorts from polysubstance abuse and pain clinics, post-surgical bariatrics, and DWI offenders facing prison time. Since Blum et al first published in JAMA (1990) concerning the association of the DRD2 gene polymorphism and severe alcoholism, reactions have been mixed. More recently, however, a meta-analysis of 62 studies showed a significant association between DRD2 rs1800497 and Alcohol Use Disorder (AUD). Other studies from Yale University showed that a haplotype block of the DRD2 gene A1 allele was associated with AUD and heroin dependence. GWAS studies of depression and suicide in 1.2 million veterans confirmed the first psychiatric candidate gene study finding from Blum et al 1990; a significant association between the minor DRD2 allele, Taq A1 and severe alcoholism. Additionally, the DRD2 rs1800497 is robustly associated with suicidal behaviors. Furthermore, DNA polymorphic alleles underlying substance use disorder (SUD) with multiple substances were mapped via chromatin refolding, revealing that the DRD2 gene and associated polymorphism(s) as the top gene signal. Based on these investigations, we conclude that GWAS should end the controversy about the DRD2 gene being one determinant of Reward Deficiency Syndrome (RDS) first reported in 1996.

Keywords: GWAS, candidate genes, DRD2 gene, polymorphisms, hypodopaminergia, reward deficiency, addictive and non-addictive behaviors

"To be or not to be?—that is the question" is the first line of arguably the most famous speech in Shakespeare's Hamlet.

Early Evidence and Controversy

In 1990, Kenneth Blum and Ernest Noble set the world on its heels with the publication of their seminal research, the discovery that the A1 allele of the dopamine D2 receptor gene correctly classified 77% of subjects known to have severe Alcohol Use Disorder (AUD) and concurrently was not present in 72% of subjects without AUD.[1] Positive associations with other addictions[2–8] were also found. Blum also pointed out that the DRD2 A1 was reward linked.[1] There is confirming evidence[9] throughout the literature that supports the original objective research by Noble and Blum et al,[10] revealing that independent of alcoholism, carriers of the DRD2 A1 allele progressively reduced (the number of binding

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sites) Bmax in subjects with A2/A2, A1/A2, and A1/A1 alleles, with subjects with A2/A2 having the highest mean values, and subjects with A1/A1, the lowest (up to 40% reduction). These values were confirmed by others.[6,10]

While NIDA scientists excitedly embraced this novel finding by Blum et al,[1] the opposite was true for NIAAA scientists. An editorial by NIAAA scientists,[11] and others accompanying the original JAMA report,[1] while reasonable at the time, initiated the long-standing controversy over the role of the DRD2 TaqA1 allele and its putative association with alcoholism.

The then director of the National Institute of Mental Health (NIMH), Elliot Gershon, published an article in Science Magazine showing a shattered glass castle, suggesting that Blum and Noble live in a glass castle.[12] Along these lines, in 1990, Bolos and others from the section on Genetic Studies, NIAAA did not support a widespread or consistent association between the D2 receptor gene and alcoholism.[13] We attribute this to poorly screened controls.

Despite positive reports linking the DRD2 gene Taq A1 allele to some RDS behaviors, the controversy gained steam with negative thinking by not only scientists[14] but science reporters.[15] Gelernter's group[16] from Yale also did not find support for the DRD2 TaqA1 allele and alcoholism. Careful review and reappraisal[2,12] revealed two important caveats which help explain the lack of association.[1] First, the control population was derived from a French Tourette's Cohort.[2] Secondly, subjects with elevated SGOT liver enzyme levels were excluded (leaving not very severe alcoholics). The poor screening of controls (or, the inclusion of hidden RDS behaviors like obesity, ADHD, PTSD, and gambling) may have produced a series of spurious results in gene-based investigations of the role of DRD2 gene polymorphisms and neuropsychiatric disorders. These conflicting results called for "super controls" in the research.[17] The concept of super controls has emerged especially in the field of addiction psychiatry and is an important concept that has not properly been addressed. If one considers the old Plomin idea that one-gene-one-disease or OGOD, elimination of just this one genetic polymorphism in the controls is a simple research task. However, this is not the case when we consider complex polygenic variants with a small effect size for each individual gene polymorphism, as, for example, with an array of addictive behaviors in studies dealing with both substance and non-substance behavioral addictions. In this scenario, there could be multi-genetic loci and accompanying sometimes unobvious when screening for controls, a few RDS-type of behaviors, that must be eliminated from so-called healthy controls. If this is not accomplished the entire experiment may be flawed providing spurious and false results. To be clear, it is like analyzing a disease with a disease instead of controls. In fact, Chen et al[17] revealed that assessment of the DRD2 A1 allele in unscreened or poorly screened controls was found to be 33% compared to elimination of every RDS behavior in the probands and their families, eliminating the RDS disorder in the controls resulting in only 3.3% of the super-controls.

GWAS Ends the Controversy

In 2004, Neville et al found that the DRD2 Taq1A RFLP is a single nucleotide polymorphism (SNP) that causes an amino acid substitution within the 11th ankyrin repeat of ANKK1 (p.Glu713Lys) helped to explain the previously described associations between the DRD2 Taq1A RFLP and neuropsychiatric disorders such as addiction. The polymorphic pattern of this receptor gene suggests that susceptibility to at least one form of alcoholism is conferred by a gene located on the q22-q23 region of chromosome 11.[18] Blum et al also pointed out that the DRD2 A1 allele was not specific for alcoholism but was reward linked.[1]

In 2008, Gelernter's group[19] reported that for both AUD and drug dependence, the ANKK1 exon 8 to DRD2; C957T was significantly associated ($p = 0.0028$) in both samples. Other naysayers like David Goldman became less abrasive, and by 2019,[20] his group reported applying a meta-analysis involving 62 studies of DRD2 and AUD with 16,294 participants and found the rs1800497 SNP associated with AUD (odds ratio, 1.23; 95% CI, 1.14–1.31; $P < 0.001$). They correctly pointed out that the association was attributable to spuriously low allele frequencies in controls in positive studies.[20] Although this appears to be a negative comment, Blum et al have consistently argued that fewer RDS behaviors in controls (thus the lower frequency of DRD2 A1 and other alleles that induce functional hypodopaminergia) are mandatory, expected, and desirable for the accurate candidate and GWAS genetic investigations.[21] Blum's concept of RDS characterizes a group of behaviors associated with the relative failure of the dopaminergic system. RDS behaviors are brain reward mechanisms typified by dopaminergic dysfunction, an acute excess or chronic deficit of dopamine

release in the brain reward circuitry.[22] The reward deficiency behaviors include drug and non-drug addictive, compulsive, and impulsive behaviors.[23,24]

In 2014, Blum's group developed the genetic addiction risk severity (GARS) test of eleven SNPs from ten genes and neurotransmitter pathways hypodopaminergic antecedents to addiction psychiatry.[25] In 2022, 74,566 case-controls AUD were used to statistically validate the selection of the risk alleles measured by GARS and showed significance for DRD2, DRD3, DRD4, DAT1, COMT, OPRM1, and 5HTT at 5%. These alleles captured a post-risk estimate for 8% of the population's alcoholism prevalence.[25,26] Also, over 3000 people presenting with polysubstance abuse from at least one-dozen chemical dependency and behavioral addiction clinics, including general population mixed gender and race, were genotyped, resulting in a GARS score for drug and alcohol risk at over 90% and 72%, respectively.[27]

The candidate association of the DRD2 A1 allele initially met with significant controversy[1,13] the gene and associated polymorphisms have now been confirmed in several elaborate GWAS studies. Levey et al,[27] from Yale, reported on a large meta-analysis of depression that used data from 23andMe, the Million Veteran Program, the UK Biobank, the FinnGen biobank, and subjects of European ancestry (n = 1,154,267; 340,591) and African ancestry (n = 59,600; 25,843). Remarkably, transcriptome-wide association study analyses showed significant associations with the expression of NEGR1 (a dopamine regulatory gene) in the hypothalamus and DRD2 in the nucleus accumbens, among others. This extensive investigation underscored the genetic architecture of depression and provided new insight into the interrelatedness of complex psychiatric traits.

Similar work from Kimbrel et al[28] carried out a GWAS that identified gene polymorphic associations in pan-ancestry and ancestry with attempted suicide among veterans. They found a robust pan-ancestry signal at the DRD2 locus (p = 1.77×10-7). Moreover, they also identified and subsequently replicated the association in a large, independent international civilian cohort (p = 7.97×10-4). Of further interest, ancestry-specific genome-wide significant loci were also identified in African Americans, European-Americans, Asian Americans, and Hispanic Americans. A pathway analysis yielded an impressive list of reward gene polymorphisms with high clinical significance, including glutamatergic synapse, dopaminergic synapse, oxytocin signaling, cortisol synthesis and secretion, and circadian rhythm. Most importantly, the authors suggest that their pathway analyses suggest that many commonly impacted biological pathways could inform the development of beneficial therapeutics for suicide prevention. These genetic findings support the RDS construct.[28]

Finally, a new study confirms the RDS construct originally suggested by Blum's group in 1995[23] and 1996[24] and could eventually lead to universal therapies to treat multiple substance use disorders. To help end the three-decade controversy, Hatoum et al[29] observed polymorphic alleles of DNA that underlie SUD with multiple substances, including 19 SNPs associated with general addiction risk and 47 DNA variants linked to the specific drug of abuse: 32 for tobacco, nine for alcohol, five for cannabis, and one for opioids. The DRD2 gene and associated polymorphism were the top gene signal (DRD2 (P = 7.9 × 10–12)), mapped via chromatin refolding. They found that repeated exposures to addictive substances can result in adaptation in the dopamine pathway, effect tolerance, and craving. Importantly, these analyses highlight that the regulation or modulation of dopaminergic gene function, rather than just the presence of variation in dopaminergic genes, is central to general addiction liability. In addition, it is genuinely interesting that gene therapy, as first studied by Panayotis Thanos and Nora D Volkow and others, consistently revealed that increasing the DRD2 receptors via an adenoviral vector delivered into the nucleus accumbens of rats significantly reduced alcohol intake as well as cocaine self-administration.[30–32]

Evidence that dopamine neurotransmission is a top candidate with significant associations in candidate and GWAS studies involving millions of people presenting with depression, suicide ideation, attempted suicide, and SUD is an incontrovertible basis for extensive studies to identify effective treatments for neuropsychiatric diseases.

Disclosure

Dr Kenneth Blum reports personal fees from VNI, ELECTRONICWAVEFORM LABS, during the conduct of the study; grants from NIH, outside the submitted work; in addition, Dr Kenneth Blum is the inventor of the Genetic Addiction Risk Severity (GARS) test and KB220 pro-dopamine variants and through his companies Synaptamine, Inc. and SpliceGen Holdings own all relevant worldwide patents. Dr Kenneth Blum has a patent 10,894,024 with royalties paid to SYNAPATAMINE. The authors report no other conflicts of interest in this work.

References

1. Blum K, Noble EP, Sheridan PJ, et al. Allelic association of human dopamine D2 receptor gene in alcoholism. *JAMA*. 1990;263:2055–2060. doi:10.1001/jama.1990.03440150063027
2. Comings DE, Comings BG, Muhleman D, et al. The dopamine D2 receptor locus as a modifying gene in neuropsychiatric disorders. *JAMA*. 1991;266:1793–1800. doi:10.1001/jama.1991.03470130073032
3. Ishiguro H, Arinami T, Saito T, et al. Association study between the −141C Ins/Del and TaqI A polymorphisms of the dopamine D2 receptor gene and alcoholism. *Alcohol Clin Exp Res*. 1998;22:845–848.
4. Arinami T, Itokawa M, Komiyama T, et al. Association between severity of alcoholism and the A1 allele of the dopamine D2 receptor gene TaqI A RFLP in Japanese. *Biol Psychiatry*. 1993;33:108–114. doi:10.1016/0006-3223(93)90309-2
5. Noble EP, Blum K, Khalsa ME, et al. Allelic association of the D2 dopamine receptor gene with cocaine dependence. *Drug Alcohol Depend*. 1993;33:271–285. doi:10.1016/0376-8716(93)90113-5
6. Volkow ND, Fowler JS, Wolf AP, et al. Effects of chronic cocaine abuse on postsynaptic dopamine receptors. *Am J Psychiatry*. 1990;147:719–724. doi:10.1176/ajp.147.6.719
7. Comings DE, Flanagan SD, Dietz G, Muhleman D, Knell E, Gysin R. The dopamine D2 receptor (DRD2) as a major gene in obesity and height. *Biochem Med Metab Biol*. 1993;50:176–185. doi:10.1006/bmmb.1993.1059
8. Noble EP, St Jeor ST, Ritchie T, et al. D2 dopamine receptor gene and cigarette smoking: a reward gene? *Med Hypotheses*. 1994;42:257–260. doi:10.1016/0306-9877(94)90127-9
9. Thompson J, Thomas N, Singleton A, et al. D2 dopamine receptor gene (DRD2) Taq1 A polymorphism: reduced dopamine D2 receptor binding in the human striatum associated with the A1 allele. *Pharmacogenetics*. 1997;7:479–484. doi:10.1097/00008571-199712000-00006
10. Noble EP, Blum K, Ritchie T, Montgomery A, Sheridan PJ. Allelic association of the D2 dopamine receptor gene with receptor-binding characteristics in alcoholism. *Arch Gen Psychiatry*. 1991;48:648–654. doi:10.1001/archpsyc.1991.01810310066012
11. Gordis E, Tabakoff B, Goldman D, Berg K. Finding the gene(s) for alcoholism. *JAMA*. 1990;263:2094–2095. doi:10.1001/jama.1990.03440150102034
12. Blum K, Noble EP. The sobering D2 story. *Science*. 1994;265(5177):1346–1347. PMID: 7802784. doi:10.1126/science.7802784
13. Bolos AM, Dean M, Lucas-Derse S, Ramsburg M, Brown GL, Goldman D. Population and pedigree studies reveal a lack of association between the dopamine D2 receptor gene and alcoholism. *JAMA*. 1990;264:3156–3160. doi:10.1001/jama.1990.03450240058040
14. Holden C. Alcoholism research. A cautionary genetic tale: the sobering story of D2. *Science*. 1994;264:1696–1697. doi:10.1126/science.8209249
15. Horgan J. D2 or not D2. A barroom brawl over an "alcoholism gene". *Sci Am*. 1992;266(29):32. doi:10.1038/scientificamerican0292-32
16. Gelernter J, O'Malley S, Risch N, et al. No association between an allele at the D2 dopamine receptor gene (DRD2) and alcoholism. *JAMA*. 1991;266:1801–1807. doi:10.1001/jama.1991.03470130081033
17. Chen TJ, Blum K, Mathews D, et al. Are dopaminergic genes involved in a predisposition to pathological aggression? Hypothesizing the importance of "super normal controls" in psychiatricgenetic research of complex behavioral disorders. *Med Hypotheses*. 2005;65:703–707. doi:10.1016/j.mehy.2005.04.037
18. Neville MJ, Johnstone EC, Walton RT. Identification and characterization of ANKK1: a novel kinase gene closely linked to DRD2 on chromosome band 11q23.1. *Hum Mutat*. 2004;23:540–545. doi:10.1002/humu.20039
19. Yang BZ, Kranzler HR, Zhao H, Gruen JR, Luo X, Gelernter J. Haplotypic variants in DRD2, ANKK1, TTC12, and NCAM1 are associated with comorbid alcohol and drug dependence. *Alcohol Clin Exp Res*. 2008;32:2117–2127. doi:10.1111/j.1530-0277.2008.00800.x
20. Jung Y, Montel RA, Shen PH, Mash DC, Goldman D. Assessment of the association of D2 dopamine receptor gene and reported allele frequencies with alcohol use disorders: a systematic review and meta-analysis. *JAMA Netw Open*. 2019;2:e1914940. doi:10.1001/jamanetworkopen.2019.14940
21. Blum K, Baron D, Lott L, et al. In search of reward deficiency syndrome (RDS)-free controls: the "holy grail" in genetic addiction risk testing. *Curr Psychopharmacol*. 2020;9:7–21. doi:10.2174/2211556008666191111103152
22. Blum K, Bowirrat A, Gondre Lewis MC, et al. Exploration of epigenetic state hyperdopaminergia (Surfeit) and genetic trait hypodopaminergia (Deficit) during adolescent brain development. *Curr Psychopharmacol*. 2021;10. doi:10.2174/2211556010666210215155509
23. Blum K, Wood RC, Braverman ER, Chen TJ, Sheridan PJ. The D2 dopamine receptor gene as a predictor of compulsive disease: Bayes' theorem. *Funct Neurol*. 1995;10:37–44.
24. Blum K, Sheridan PJ, Wood RC, et al. The D2 dopamine receptor gene as a determinant of reward deficiency syndrome. *J R Soc Med*. 1996;89:396–400. doi:10.1177/014107689608900711
25. Blum K, Han D, Gupta A, et al. Statistical validation of risk alleles in genetic addiction risk severity (GARS) test: early identification of risk for alcohol use disorder (AUD) in 74,566 case-control subjects. *J Pers Med*. 2022;12:1385. doi:10.3390/jpm12091385
26. Blum K, McLaughlin T, Bowirrat A, et al. Reward deficiency syndrome (RDS) surprisingly is evolutionary and found everywhere: is it "blowin' in the wind"? *J Pers Med*. 2022;12:321. doi:10.3390/jpm12020321
27. Levey DF, Stein MB, Wendt FR, et al. Bi-ancestral depression GWAS in the million veteran program and meta-analysis in >1.2 million individuals highlight new therapeutic directions. *Nat Neurosci*. 2021;24:954–963. doi:10.1038/s41593-021-00860-2
28. Kimbrel NA, Ashley-Koch AE, Qin XJ, et al. A genome-wide association study of suicide attempts in the million veterans program identifies evidence of pan-ancestry and ancestry-specific risk loci. *Mol Psychiatry*. 2022;27:2264–2272. doi:10.1038/s41380-022-01472-3
29. Hatoum AS, Colbert SMC, Johnson EC, et al. Multivariate genome-wide association meta-analysis of over 1 million subjects identifies loci underlying multiple substance use disorders. *Nature Mental Health*. 2023;1:210–223. doi:10.1038/s44220-023-00034-y
30. Thanos PK, Volkow ND, Freimuth P, et al. Overexpression of dopamine D2 receptors reduces alcohol self-administration. *J Neurochem*. 2001;78:1094–1103. doi:10.1046/j.1471-4159.2001.00492.x
31. Thanos PK, Rivera SN, Weaver K, et al. Dopamine D2R DNA transfer in dopamine D2 receptor-deficient mice: effects on ethanol drinking. *Life Sci*. 2005;77:130–139. doi:10.1016/j.lfs.2004.10.061
32. Thanos PK, Michaelides M, Umegaki H, Volkow ND. D2R DNA transfer into the nucleus accumbens attenuates cocaine self-administration in rats. *Synapse*. 2008;62:481–486. doi:10.1002/syn.20523