Genetic Addiction Risk Score (GARS®) as a Predictor of Reward Deficiency Syndrome (RDS): Identifying Predisposition Not Diagnosis

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Blum’s laboratory has dedicated work to develop an accurate genetic test to predict true liability/risk for addiction and Reward Deficiency Syndrome (RDS) behaviors [1,2]. Geneus Health LLC, scientists, in conjunction with their Genomic Testing Center GTC, have successfully developed the first Genetic Addiction Risk Score (GARS®). The actual association to determine risk using a clinical outcome, termed the Addiction Severity Index- Media Version (ASI-MV), was accomplished with the Institute of Behavioral Genetics, University of Colorado, Boulder [3-7] and Dominion Diagnostics. The commercial test has just been awarded a USPTO patent issued on 9/11/2018.

To develop this patented Genetic Addiction Risk Score (GARS), we first selected ten reward candidate genes including Dopamine receptors (DRD1, 2, 3, 4); Dopamine Transporter (DAT1); serotonin transporter, COMT, MAO, GABA, Mu opiate receptor and a number of SNPs and point mutations that influence the net function of dopamine at the brain reward site. The variants or SNPs, including point-mutations, were chosen to reflect a hypodopaminergic trait. This was based on thousands of association studies providing clear evidence of specific risk alleles for all addictions (Figure 1).

After a preliminary selection phase reviewing many reward gene polymorphisms and risk alleles, we selected the following 10 reward genes. This list was compiled from PubMed in 2014 involving 25,620 various reported articles on the GARS gene panel.

Table 1 illustrates the reward genes that have been extensively researched and include but are not limited to D1-D4 receptors; Dopamine Transporter (DAT1); Serotonin transporter (S-HTTLP); Mu opiate receptor (OPRM1); GABA receptor (GABRB3); catechol-o-methyltransferase (COMT) val158met; and MAO-A gene promoter VNTR.

In terms of validation, we partnered with the developers of the Addiction Severity Index- Media Version (ASI-MV), a test mandated in at least 13 states, for both alcohol
and drug severity risk scores [8]. We contacted seven very diverse treatment centers across the United States resulting in a total of 393 subjects that were genotyped using the selected GARS panel. All the data was genotyped and analyzed at the Institute for Behavioral Genetics (IBG) at the University of Colorado Boulder. The results indicate a significant association between a summed score of all GARS panel risk alleles (variant forms) and both the ASI-MV alcohol (p < 0.004) and drug (P < 0.05) severity indices in a total of 273 subjects. Further analysis revealed a clear path to predicting additive behavioral risk. Clearly, carriers of any four risk alleles had a significant prediction of drug severity risk, and carriers of any seven had a significant prediction of alcohol severity risk.

Furthermore, the higher the number of risk alleles, the stronger the prediction of alcohol or drug use severity. Results also demonstrate that family problems, psychological issues and medicalization significantly correlate with risk as well. One important caveat was that if we changed any specific SNP within the GARS panel, the significance was lost. This strongly suggests the importance of the combined GARS panel, with any deviation producing false results as may occur with other commercial tests with little to no validation research. These results are further substantiated by other studies including the work of Blum, et al. [2] revealing that carriers of the DRD2 A1 allele at birth have a 74% chance to become addicted to any one of the RDS behaviors.

The GARS test is indeed a cluster analysis linking these polymorphisms synergistically with an overall expression of DNA predictability to many addictive behaviors as denoted in the Reward Deficiency Syndrome (RDS) concept. In a recent paper published in the journal Science, the researchers measured the amount of genetic overlap across the disorders using genome-wide association studies (GWAS) of 265,218 patients and 784,643 controls. They examined the relationships between

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**Table 1:** Proposed Genetic Addiction Risk Score (GARS™) Panel of Reward Genes.

<table>
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<tr>
<th>Genes</th>
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<tbody>
<tr>
<td>Dopamine D1 Receptor Gene</td>
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<td>Dopamine D3 Receptor Gene</td>
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<td>Dopamine D4 Receptor Gene</td>
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<td>Serotonin Transporter Gene</td>
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<td>Dopamine Transporter Gene</td>
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<td>Mu-opiate Receptor Gene</td>
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<td>GABA-B3 Receptor Gene</td>
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<td>Monoamine Oxidase A Gene</td>
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<td>Catechol-O-Methyltransferase Gene</td>
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**Figure 1:** Illustrates the number of studies per genetic risk allele produced in 2014 and is reproduced with permission from Blum, et al. [7].
brain disorders and 17 physical or cognitive measures, such as years of education, from 1,191,588 individuals. The dataset ultimately included all GWAS consortia studying common brain disorders with sufficient sample sizes identified by the team. Their results demonstrated that psychiatric disorders share many genetic variants, while neurological disorders (such as Parkinson’s or Alzheimer’s) appear more distinct.

The results indicate that psychiatric disorders likely have important similarities at a molecular level, which current diagnostic categories do not reflect[9]. This suggests that using GARS may have predictive relevance for addictive behaviors inclusive of RDS, not as a diagnostic, but as a test to identify predisposition of high addiction risk for substance use disorder (SUD) as well as process addictions.

It is well-known that DNA polymorphisms, in by itself, is impacted by the environment or epigenetics. In fact, it is the known relationship between the two elements whereby the mathematical equation \( P = G = E \) represents the resultant phenotype. We believe that this novel tool could help psychiatrists and other clinical professionals identify people at risk for not only substance use disorder but a remarkable array of Reward Deficiency Syndrome (RDS) behaviors [1]. The importance of early identification with GARS is reflected in people knowing their brain circuitry DNA risk alleles now involving hypodopaminergia as a prophylaxis.

Our take home message is that especially, young people having this objective DNA knowledge will have an edge in knowing what to avoid in the future including powerful pain medications as only one beneficial example. Understanding that GARS is not a diagnostic, but a simple test for one’s predisposition for RDS risk seems prudent. In fact, this knowledge, may help change not only the recovery space, but the future of our precious children, now at least in America a scary place whereby death from opioids loom.

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Conflict of Interest

Kenneth Blum, David Siwicki own stock in Geneus Health, LLC. Dr. Blum is the recipient of a number of USA genetic and neuro-nutrient patents issued and pending. Drs. Baron, Badgaiyan, Modestino, Thanos, Siwicki, Moran, and Simpatico are members of Geneus Health Scientific Advisory Board. There are no other conflicts to report.

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