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Can We Combat Reward Deficiency Behaviors (RDS) including Substance Use Disorder (SUD) through Genetic Risk Screening coupled with Precision Pro-Dopamine Regulation by Algorithmic matched Polymorphic Allelic Risks

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Research into the neurogenetic basis of addiction identified and characterized by Reward Deficiency Syndrome (RDS) [1] includes all drug and non-drug addictive, obsessive and compulsive behaviors. We are proposing herein that a new model for the prevention and treatment of RDS behaviors based on objective biologic evidence should be given serious consideration in the face of a drug epidemic [2]. Currently, research directed toward improving treatment for highly drug-dependent patients in underserved populations represents one example of adoption of this bold concept and is under study through a NIH grant [3]. The grant explores utilization of the patented Genetic Addiction Risk Score (GARS®) and the neuronutrient pro-dopamine regulator KB220.

The development of GARS followed seminal research in 1990, whereby, Blum's group identified the first genetic association with severe alcoholism published in JAMA [4]. The non-invasive GARS test identifies and measures the total numberof risk alleles of genes and catabolic enzymes affecting an individual's neurochemical hypodopaminergic function, and has been associated in hundreds of studies with RDS behaviors [5].

While the entire molecular biological community is interested in genetic risk for alcohol and substance addiction, and personalized medicine, presently, many are not aware of a known patented genetic panel that demonstrates significant predictability to clinical risk. To this aim, we are highlighting this rather new and unique genetic test to provide this community an up-to date knowledge base. We are briefly summarizing herein the unpublished first study of an association between the Genetic Addiction Risk Score (GARS) and the Addiction Severity Index -Media Version (ASI-MV) among patients from treatment facilities.

The initial sample of 393 individuals who provided saliva for genotyping, was drawn, from eight geographically dispersed treatment centers in the United States. The available sample size of 273 (69%) consisted of individuals who had also completed the ASI-MV questionnaire [6]. The alcohol, and drug severity scores in the ASI-MV were determined using a proprietary algorithm developed by Inflexxion. A laboratory located at the

Institute for Behavioral Genetics (University of Colorado Boulder) performed standard genotyping for specific polymorphic risk alleles derived from a panel of reward genes [7]. The subjects, participating in the pilot phase of the GARS analysis self-reported their race as White at 88.1% (n=244) and were 57.8% (n=160) male. The average age of the of subjects was 35.3 years (SD=13.1, maximum age=70, minimum age=18). This study is a statistical analysis that compared a number of risk alleles to the ASI-MV alcohol and drug severity score of each subject.

Among the ASI analysis sample the number of risk alleles detected ranged from 3 to 15, and the average was 7.97 (SD=2.34) with a median of 8.0. Preliminary examination of the relationship between GARS genotype panel and the Alcohol Risk Severity Score using the Fishers Exact Test revealed a significant predictive relationship (X^2=8.84, df=1, p=0.004, 2 tailed) which remained significant after controlling for age [Hardy-Weinberg Equilibrium intact]. Both age and genetic addiction risk scores were predictive of higher alcohol severity scores as assessed with the ASI-MV. To account for non-normality in the distribution, drug scores were transformed to (Log_{10}) before analysis of the relationship between the GARS panel and ASI-MV Drugs Risk Severity Score. The relationship between the GARS panel and the drug risk severity score was found to be similar but less robust than the observation for the alcohol risk severity. Preliminary examination revealed a nominally significant relationship (B=-0.122, t=-1.91, p=0.057 -2 tailed) in this study, following a priori hypothesis of an association of GARS and ASI predictability of risk in which a one-tailed analysis revealed (P=0.028) for the drug severity. The predictive value of GARS was more robust for alcohol risk severity (a score equal or greater that 7) and for drug risk severity (a score equal or greater that 4). A limitation of this study relates to the attempt of matching an objective score (genes) with a score from a subjective self-report (ASI).

These results show the GARS test to be a useful predictor of susceptibility to problematic substance use. In future studies using highly screened cohorts eliminating all Reward Deficiency Syndrome (RDS) behaviors, LOD scores will be analyzed for each risk allele to determine weighted associations that could lead to even more accurate predictability of the GARS test. These data have allowed for the current utilization of precise genetic guided therapy coined "Precision Behavioral Management" (PBM®).

Simply, "Precision Behavioral Management" (PBM®) uses the GARS to customize KB220PAM formulations to deliver putative dopamine homeostasis based on developed algorithms matched to polymorphic results. To date there is evidence derived from animal and human studies using BOLD neuroimaging and behavioral methodologies, support homeostatic activation of brain dopamine in the reward circuitry by KB220PAM, as well as anti-substance seeking and modification of RDS behaviors [8-12]. RDS encompasses behaviors like PTSD, ADHD, over-eating, shopping, hoarding and related RDS cognitive insults. Combating the drug crisis requires PBM across ethnic groups, to induce dopamine homeostasis to those born with RDS predisposition [13].

It is the goal through this novel model that by using PBM the addiction field will have a synergistic tool along with MAT or even alone, to overcome dopamine dysregulation either surfeit (adolescents) or deficit (adults) by the induction of " dopamine homeostasis"[14].

Author Contributions

The original concept was developed by KB. The original draft was provided by KB to all co –authors. The entire paper was carefully vetted by all co-authors and approved.

Conflict of Interest Statement

KB and DS through Igene LLC, own stock in Geneus Health, LLC., and in some companies holding patents on genetic testing and KB220PAM. KB is Chairman of the Genus Health LLC Board of Directors and Scientific Advisory board and CSO, DS is a member of the Genus Health Scientific Advisory board and President. DB, MG-L, and RDB are members of the Genus Health LLC scientific advisory board. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. MH is Vice President of Dominion Diagnostics LLC whereby Dominion Diagnostics is a licensee to sell GARS in the addiction and pain space but not KB220zPam.

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