



Can Genetic Testing Provide Information to Develop Customized Nutrigenomic Solutions for Reward Deficiency Syndrome?

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We are entering the era of genomic medicine and neuroimaging as it relates to addiction a subset of Reward Deficiency Syndrome (RDS) [1-3]. In 2005 our laboratory received the first USA patent on Nutrigenomics and RDS treatment. This was awarded on the basis of our earlier work showing anti-addiction activity of a nutraceutical consisting of amino-acid precursors and enkephalinase inhibition properties and our discovery of the first polymorphic gene (Dopamine D2 Receptor Gene [DRD2]) to associate with severe alcoholism [4-7]. Prior to the later genetic finding we developed the concept of Brain Reward Cascade which continues to act as blue-print for stratification of addiction risk through neurogenetics [8].

In 1996 our laboratory also coined the term "Reward Deficiency Syndrome (RDS)" to define a common genetic rubric for both substance and non-substance related addictive behaviors [9,10]. Following many reiterations we utilized polymorphic targets of a number of reward genes (serotonergic, Opioidergic, GABAergic and Dopaminergic) to customize KB220 [Neuroaaptogen- amino-acid therapy (NAAT)] by specific algorithms. Identifying 1,000 obese subjects in the Netherlands a subsequent small subset was administered various KB220 formulae customized according to respective DNA polymorphisms individualized that translated to significant decreases in both Body Mass Index (BMI) and weight in

pounds [11]. This was followed up in the USA with similar significant effects [12,13]. Following these experiments we have been successfully developing a panel of genes known as "Genetic Addiction Risk Score [14,15] (GARS_{DX}).™"

In unpublished work, we found that when we selected 10 genes with appropriate variants, a statistically significant association between the ASI- Media Version -alcohol and drug severity scores and GARS_{DX} provided the first validated genetic panel for RDS. This observation was found in 273 patients attending seven diverse treatment centers. This now validated panel could be utilized to provide a personalized approach by coupling gene polymorphisms with potential nutrigenomic solutions.

Independently, a variant of NAAT -KB220Z in abstinent heroin addicts, increased resting state functional connectivity. Specifically we observed enhanced *rs* functional connectivity in a putative network that included the dorsal anterior cingulate, medial frontal gyrus, nucleus accumbens, posterior cingulate, occipital cortical areas, and cerebellum [16]. In other unpublished rat work using a novel segmented rat atlas, we show that KB220Z significantly activates, above placebo, seed regions of interest including the left nucleus accumbens, cingulate gyrus, anterior thalamic nuclei, hippocampus,

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pre-limbic and infra-limbic loci. This response induced by KB220Z demonstrates significant functional connectivity, increased brain volume recruitment and enhanced dopaminergic functionality across the brain reward circuitry. This robust yet selective response implies clinical relevance. These results and other quantitative electroencephalography (qEEG) experiments results suggest a putative anti-craving/anti-relapse role of KB220Z in addiction by direct or indirect dopaminergic interaction [17].

We are now paused to propose a Reward Deficiency System Solution that promotes early identification and stratification of risk alleles by utilizing GARS_{Dx} allowing for customized nutrigenomic targeting of these risk alleles by altering NAAT ingredients as an algorithmic function of carrying these polymorphic DNA –SNPS potentially yielding the first ever nutrigenomic solution for addiction and pain[18]. The concept of dopaminergic activation in the long term is supported by the recent work of Willuhn et al. showing that a deficiency of phasic dopamine causes escalation of cocaine intake in animals. This suggests dopamine agonistic therapy rather than dopamine antagonistic therapy in the long-term treatment with patients presenting with RDS [19].

Certainly, we encourage others to also develop similar addiction algorithms based on reward gene polymorphisms and as therapeutic targets to improve clinical outcomes and long term remission for all RDS addictive behaviors.

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Conflict of Interest

Kenneth Blum, PhD is the holder of a number of US and Foreign patents issued and pending related to Nutrigenomics and Nutraceuticals. Through IGENE LLC., Dr. Blum exclusively licensed the Genetic Addiction Risk Score (GARS)™ to Dominion Diagnostics, LLC. Dr. Blum is also an officer and stock holder of IGENE, LLC, RD Solutions and Victory Nutrition International. He is a paid consultant of Dominion Diagnostics, LLC, IGENE, Malibu Recovery Center. Dr. Blum is a member of the scientific advisory board of Dominion Diagnostics, LLC and is Chief Scientific Advisor of Dominion Diagnostics, LLC; RD Solutions, Inc, Victory Nutrition International, LLC. Gozde Agan and James Fratantonio are employed by Dominion Diagnostics. There are no other author conflicts of interest.

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