REVIEW ARTICLE

A 21ST CENTURY PERSPECTIVE ON DEPRESSION, REWARD GENES, AND DNA POLYMORPHIC TARGETED NUTRIGENOMIC RESOLUTION

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ABSTRACT

Mood disorders including major depressive disorder (MDD) are one of the most important causes of disability for human health and the second leading source of disease burden, going beyond cardiovascular diseases, dementia, lung cancer, and diabetes. The comorbidity of depression and substance use disorder (SUD) has been well-established. While there are over 6,000 studies on genes and depression, a definitive human gene map of depression still eludes the field of psychiatric genetics. Certainly, GWAS and candidate approaches are on-going and hold out promise for the future. It is our contention that one approach involves the induction of true "dopamine homeostasis" easier said than done. In this treatise, we are suggesting a novel therapeutic modality that includes DNA genotyping based on a Genetic Addiction Risk Score (GARS) test and concomitant alteration of a Pro-dopamine Regulator (KB220) contents linked to personalized polymorphisms observed in the genes across the brain reward circuitry in the prefrontal cortex and mesolimbic systems.

INTRODUCTION

Most recently, Stein *et al.* (2017), reported on a number of important findings of the comorbidity of depression and substance use disorder (SUD). They found:

- Nearly two out three persons screened for depression, yet only 8.2 % were being treated for depression before their admission

- Screening positive for depression was associated with a 2.95 fold increase in the expected odds of perceived need for depression treatment (PNDT)
- Nearly half of those depressed (48%) did not PNDT
- Approximately 40% of the participants perceived that they were not depressed; of these people, 52 % screened positive for depression.

Stein and associates (Stein *et al.*, 2017) clearly encouraged that patients seeking opioid treatment should be screened for depression and treated accordingly. It is noteworthy that it has been reported earlier that upwards of 90% of patients attending
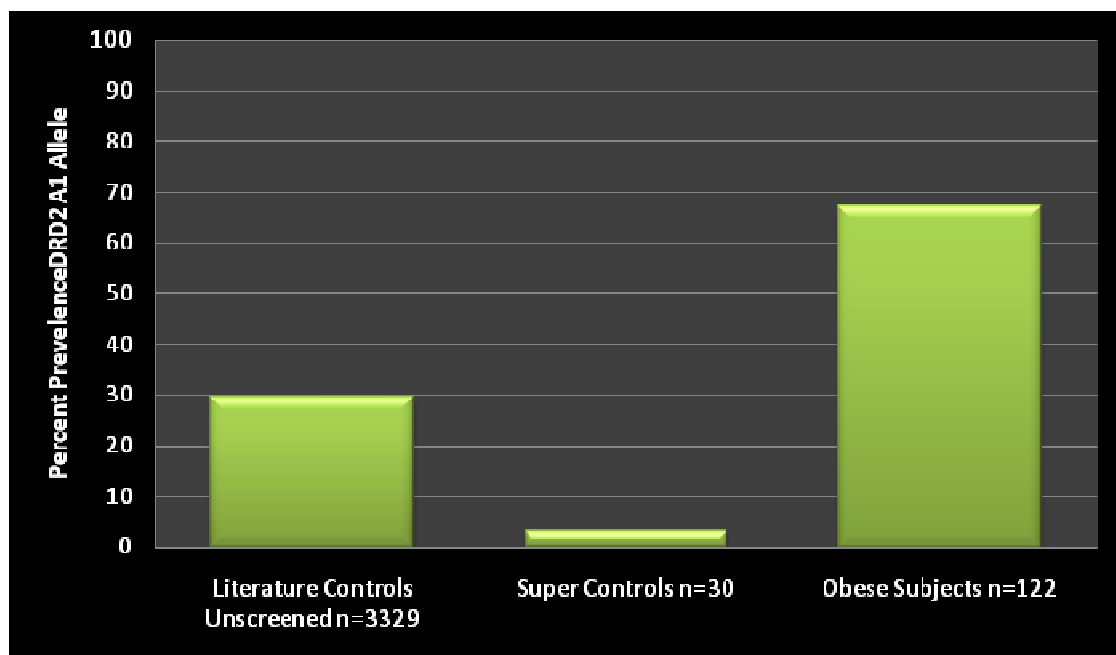
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treatment for SUD diagnose positive for depression, however following residential treatment only one-third of the patients present with a depression diagnosis upon leaving treatment (Staiger *et al.,* 2011; Beaulieu *et al.,* 2012; Blum *et al.,* 1986; Archer *et al.,* 2013; Blum *et al.,* 1988). Furthermore, the rates of depression have been increasing steadily among adolescents especially females since 2011. In a 2015 survey, an estimated three million teens reported having at least one major depressive episode over the past year (Tweeten & Park, 2017). Mood disorders are considered one of the most important causes of disability for human health and the second leading source of disease burden, going beyond cardiovascular diseases, dementia, lung cancer, and diabetes. While genetic risk factors are well established for major affective disorders including depression as a recurrent disorder, little is known about the putative genomic relationship between impulsive, compulsive and addictive behaviors and depression. The important fundamental question of understanding the true nature of depression and resultant comorbidities resides in the genomic expression of polygenes of the mesolimbic pathway and in particular the brain reward cascade (Blum *et al.,* 2000). Related work published in JAMA, in 1990, involving the initial discovery of the dopamine D2 receptor gene and alcoholism, following the considerable controversy and over thousands of published articles, serves today as the cornerstone of understanding the neuronal and synaptic genetics of many reward dependence behaviors including mood and well-being

(Blum *et al.,* 1990). Between the years 1990 to 1995, polymorphisms (genetic variants) of the DRD2 gene as well as other brain reward candidate genes (serotonergic, endo-cannabinergic, enkephalinergic, gabaergic, and dopaminergic) have been associated with a number of impulsive, compulsive and addictive behaviors referred to as Reward Deficiency Syndrome (RDS; Table 1). In fact, in terms of the DRD2 gene variant (A1 form) it has been associated with not only alcoholism but heroin dependence, psychostimulant dependence, nicotine dependence, carbohydrate craving, pathological aggression, pathological gambling, sex addiction, high-risk taking behavior, and certain personality disorders including schizoid avoidance behavior, borderline, impaired executive function of the brain, inability to cope with stress in the family, posttraumatic stress disorder, and most recently excessive internet video gaming (Blum *et al.,* 1995). In an attempt to understand reward dependence behaviors and associated neurogenetic impairments leading to brain reward dysphoria or depression and thus social ineptness, more in-depth research is required. However, our laboratory in 1996 coined the term RDS (Table 1) to describe a standard genetic rubric of impulsive, compulsive and addictive behaviors, which is an important emerging psycho-neurogenetic concept, now being adopted worldwide and is listed as a disorder in SAGE 2017 Encyclopedia of Abnormal Psychology (Blum, 2017). The importance of this topic was highlighted at a meeting of the World Congress of Psychiatric Genetics held in

Table 1. Reward Deficiency Syndrome (RDS) Spectrum

BEHAVIORS					
ADDICTIVE		IMPULSIVE		OBSESSIVE COMPULSIVE	PERSONALITY DISORDERS
Substance	Non-Substance	Spectrum Disorders	Disruptive		
Alcohol	Thrill Seeking	Attention-Deficit	Conduct	Body Dysmorphic	Paranoid
Cannabis	(novelty)	Hyperactivity		Hoarding	Schizoid
Opioids	Sexual Sadism	(ADD/ADHD)	Intermittent Explosive	Trichotillomania	Borderline
Sedatives/Hypnotics	Sexual			(hair pulling)	Schizotypal
Stimulants	Masochism	Tourette and Tic			Histrionic
Tobacco	Hypersexuality	Syndrome	Oppositional Defiant	Excoriation (skin picking)	Narcissistic
Sugar	Gambling				Avoidant
Fat/Salt	Internet	Autism	Exhibitionistic	Non-Suicidal Self-Injury	Dependent
Food	Gaming				

Fig. 1. Differential prevalence of the DRD2 A1 allele under different control and obesity groups (with permission Chen *et al.,* 2012)

New York City, where approximately 60 articles were presented involving genes, depression, and mania. Interestingly, out of these research reports, approximately 20% involved the comorbidity of depression and many related RDS behaviors including substance use disorder (SUD), ADHD, obsessive-compulsive disorder, anxiety, among others. Regarding systematically mapping genes associated with depression alone as well as in association with RDS behaviors, we are proposing genotyping of diagnosed major depressive, and RDS probands compared to a highly screened non-RDS controlled population. To our knowledge, this has only been accomplished by our laboratory concerning the DRD2A1 allele.

It was found that while unscreened controls in a number of studies ranged from 16-33%, a highly screened non-RDS cohort including no family history of any RDS behavior resulted in only 3.3% (Chen *et al.,* 2012) (Fig. 1). Utilizing previous work from our laboratory especially on obesity, we evaluated the prevalence of the DRD2 A1 allele under different control and obesity groups. There is a large body of literature showing a relationship between multiple factors including dopaminergic genes, body mass index, obesity, overeating, carbohydrate craving, energy expenditure and low dopamine D2 receptor (D2R) receptor density. In line with this aforementioned literature, there is a paucity of research of dopamine receptor gene (specifically DRD2) variants and the percentage of body fat. In one study, we genotyped 122 obese/overweight (O/OW) Caucasian participants. This group was paired with 30 non-obese Caucasian controls, all of whom we screened for substance abuse as an exclusionary factor. We assessed all participants for their weight, body mass index (BMI; kg m^{-2}), and the percentage of body fat. This last test was accomplished with the use of a dual energy X-ray absorptiometry (DEXA). We separated the participants into two independent groups. The first was those with the Taq1 A1 allele (A1/A1 or A1/A2). The second was those without the A1 allele (A2/A2). The control group had a typical range of body fat (specifically that of 18-25 % for males and 25-31% for females). The O/OW participants had a percent body fat value of over 25% for males and 32% for females. For our O/OW participants, we had a mean BMI of 29.3 ($\pm$ 6.25 kg m^{-2}), with their mean body fat of 42.1 $\pm$ 7.5% and mean weight was 82.7 $\pm$ 21.7 kg. We found the DRD2 and Taq1 A1 allele was in 67% of the O/OW subjects versus 3.3% of super controls (A group), or 33.3% of screened (for obesity and drug abuse) controls (B group), and finally, unscreened literature controls were at 29.4% (P $\leq$ 0.001). When comparing all cases with more than 34% body fat, utilizing a logistic regression analysis revealed the DRD2 A1 allele accounts for approximately 45.9% of the variance in the data. This was found to be statistically significant (χ^2 = 43.47, degrees of freedom (df) = 1, P < 0.0001). The culmination of these results is in agreement with a significant role in obesity for the DRD2 gene, with obesity measured by BMI, weight, and percentage of body fat (Noble, 2003).

The possibility that dopamine–related genetic variants may provide information linked to etiology of depression has been researched extensively. It is widely known that depression is highly heritable and several genetic variants have been found to modulate endogenous dopamine neurotransmission (Nestler and Carlezon, 2006; Lee *et al.,* 2015). While most of the literature favors the role of dopamine and depression (Brown and Gershon, 1993; Opmeer *et al.,* 2010), some association

studies failed to find the significant association (Sherman, 2012). Importantly, when dopamine-related polymorphisms have been studied in the context of genome-wide association studies (GWAS), to date, none have emerged as significantly associated with depression (Rybakowski, 2013).

According to many experts, one likely contributor to these inconsistent findings is that common genetic variants for complex diseases like depression, tend to have small to modest effects. Certainly, tests of association based on a single nucleotide polymorphism (SNP) are unlikely to yield significant effects unless extensive samples are studied. One interesting approach, providing an answer to the ongoing controversy of whether or not a number of polymorphic dopaminergic genes are associated with depressive symptomatology, was published by Pearson-Fuhrhop *et al.* (Pearson-Fuhrhop *et al.,* 2014). They examined the combined sum of five dopamine-related polymorphisms and depressive symptom severity. These included: synaptic dopamine availability (*COMT* and *DAT*) and dopamine receptor binding (*DRD1*, *DRD2*, *and DRD3*). By utilizing this dopamine genetic risk score based on functional polymorphisms, they found a significant association with the degree of depressive symptoms in healthy individuals and with depression severity in persons with major depressive disorder (MDD), supporting the original concept of severity as suggested by Blum *et al.* in terms of alcoholism (Blum *et al.,* 1990). Most importantly, this genetic risk score shows stronger associations with the measures of depression than does any single variant. This provides clinicians with a genetic model for determining the best therapeutic intervention regarding dopaminergic therapies for persons with MDD. There is a plethora of scientific studies suggesting an array of genetic dopaminergic dysfunctions in both medical (Prasad *et al.,* 2008) and psychiatric disorders (Zai *et al.,* 2007). While a number of genes have already been associated with depression to our knowledge, there has never been a large candidate approach covering a plethora of polygenes in a single sample to provide information regarding genetic patterns as potential predictors of depression in humans. Certainly, we are cognizant of genomic array scans to delineate chromosomal areas associated and linked to various forms of affective disorders. However, our approach which does not devalue the genomic array approach may provide the basis for a novel personalized medical treatment to combat depression utilizing polymorphic DNA-directed customization of non-pharmacological antidepressive nutrigenomic solutions. There was a systematic review between 01.01.2004 to 03.28.2014 by the VHL (Virtual Health Library). Their search was completed using descriptor terms. These included "anxiety", "depression", "mutation" and "genetic markers". The articles selected were indexed within MEDLINE. The information pertinent to this study was chosen, categorized and analyzed. Of the 374 articles found, 29 met the eligibility criteria.

To understand the enormous work ahead the genes involved in this proposed investigation includes, but not limited to, neurotransmitter synthesis, neuronal vesicle storage, synaptic and neuronal metabolism as well as neuronal release. We must mimic the entire brain reward cascade involving serotonergic, enkephalinergic, gabaergic, dopaminergic, adrenergic and cholinergic pathways. These include: dopaminergic (DAT, DRD, COMT), serotonin (5-HTTLPR, HTR1A, HTR2A), interleukins, MCR1, HCN (potassium channel), neurorregulinas, GABAergic (GABA, GAD, DBI) DBI, GABA (GABA$_A$)

receptors and GAD genes (GAD1, GAD2); all of these appear to contribute, or to generate, the condition of depression or anxiety-like. Mutations in mitochondrial DNA in 124pb allele of D2S2944 in ofil 1 and 2 loci which are located on chromosomes 4 and 7, respectively, and the chromosomes 8p, 17p and 15q appear to be associated with the origin of depression or anxiety (Lacerda-Pinheiro *et al.,* 2014). Moreover, there are a number of known candidate genes and chromosomal loci that have already been documented to associate with depression and include the following short list: 3Q27.2; 12q24; 4Q35; 13Q14; 3Q35; 13Q14.4; 15Q28; 15Q26; DISC1; CIT; GRIN2A; SIPA1L1; PACAP; AKT1; CCL13 chemokine; POLG; PPARD; CREB1; AANAT; BCL2; 3'UTR; NRID1; MTHFR; CHRM2; cadherin FAT; SCNI8; NPAS3; ST8SIA2; FKBP5; HPA; HTR2A; G72/G30; TPH2; EMID2; PFTKI; TFR2; SMURF1; PBEFI; ACN9; LHFPL3; PILRB; AVPR1B; P2RX7; GLM460ARG; ILORA; DDC; DAT; IL28R; PAPLN among other genes to be studied.

Summary

To date, research in neuropsychiatric genetics, due to limited resources and funding, has resulted in very truncated and in some cases erroneous knowledge. This in by itself has prevented to some degree real progress in both the prevention and treatment of the societal devastation accompanying all forms of mood disorders. The work of Heller *et al.* (2014) found that the methylation of histone, or an acetylation, taking place at the Fosb locus in nucleus accumbens in reference to transcription. This was sufficient to change drug- and stress-evoked transcriptional and behavioral responses via interactions with the endogenous transcriptional machinery, the true landscape of both neurogenetics and epigenetics is in its infancy and it is the – "the tip of the iceberg." With appropriate funding, we will be able to make significant strides leading to a candidate genomic map of depression in humans. This will be the first step in developing evidence-based personalized medical solutions not only for depression but for RDS which accounts for uncontrollable addictive behaviors affecting over 100 million people (33% of the US population carries the DRD2 gene A1 form that associates with low dopamine D2 receptors and aberrant substance seeking behavior) in the United States alone (Noble *et al.,* 1991). It is our hypothesis that systematic evaluation of the genome via genome-wide scan analysis will be useful for future directions; however, our candidate approach may have a high initial impact to provide DNA targets for possible prevention and treatment of depression (Braverman *et al.,* 2006 & 1996).

Our laboratory is embarking on studies related to what we have termed "Precision Medicine" by using the pro-dopamine regulator known as KB220 whereby its content will be determined by a targeted genetic addiction risk panel (Blum *et al.,* 2016 & 2015; Febo *et al.,* 2017). Finally, it is noteworthy, the search for novel antidepressant agents without dangerous side effects continues in light of recent data indicating suicide ideation. The U.S. Food and Drug Administration has recently extended the Black Box warning on antidepressants regarding pediatric suicidality to include young adults (Leon *et al.,* 2014). This decision was influenced by results from meta-analyses of 372 antidepressant studies (randomized controlled clinical trials) of adults. However, within these studies, most suicide attempts were unsuccessful.

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