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Review Article

Genetic Addiction Risk Severity (GARS) Test in Addiction Medicine: Early Identification of Pre-Addiction Phenotype

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Abstract

This expert opinion will detail the gene addiction connection: gene alleles and genetic testing. The Neurogeneticist Kenneth Blum, with Ernest Noble, published the first study to associate an allele of the Dopamine D2 Receptor Gene (DRD2) and severe alcoholism in *JAMA* 1990. This research confirmed an association preempted by a theoretical construct that identified the neurotransmitter interaction leading to dopamine release in the mesolimbic system as the "Brain Reward Cascade" in 1989. Earlier basic research had identified the role endorphins played in alcoholism, the blocking effect of Naloxone, an opioid-receptor antagonist in alcohol dependence, and supported the concept of a common mechanism between alcohol and opiates. Blum., *et al*. also developed a theory based on binding studies and other basic research that identified a "hypodopaminergic" trait/state caused by either genetics, stress, or toxicity as "Reward Deficiency Syndrome" (RDS). Blum's group developed a nutraceutical therapy (scientific code) KB220Z to treat RDS and the Addiction Risk Severity (GARS) test to identify genetic risk for RDS. Reward deficiency syndrome, characterized as a relative failure of the neurotransmitter system in brain reward mechanisms, has been linked to dopaminergic dysfunction, acute excess, or chronic deficit of dopamine release in the brain reward circuitry. The reward deficiency behaviors include drug and non-drug addictive, compulsive, and impulsive behaviors.

Keywords: *Genetic Addiction Risk Severity (GARS); Addiction Medicine; Pre-Addiction Phenotype*

Abbreviations

RDS: Reward Deficiency Syndrome; DRD2: Dopamine D2 Receptor Gene; GARS: The Genetic Addiction Risk Severity

Introduction: The Gene Addiction Connection

Neurotransmitters: The earliest work and discovery

Nerve stimulation experiments on frog hearts carried out by Otto Loewi in 1921 demonstrated the release of a substance that slowed the heart rate. The substance was independently identified as acetylcholine, a neurotransmitter, by Henry Hallett Dale, who shared the Nobel Prize in 1936 for Physiology or Medicine with Otto Loewi. In 1950, Sir Bernard Katz Ulf von Euler and Julius Axelrod contributed to understanding how these "chemical messengers" function in neural communication. The development of electrophysiological techniques allowed researchers to measure the electrical activity of neurons directly [1]. They used this technology to study the effects of chemical messengers on neuronal communication and researched the synthesis, release, and reuptake of neurotransmitters [2].

Arvid Carlsson contributed to understanding the neurotransmitter Dopamine in the 1950s and 1960s. He finally received the Nobel Prize for this work in 2000 [3]. Teleanu., *et al*. recently reviewed the neurological functions of chemical messengers and important neurotransmitters discovered since the turn of the century. They explain the link between disturbances in neurotransmitter homeostasis and some neurological disorders [4].

Receptor discovery

Theories about neurotransmitter receptors developed by Sir Bernard Katz and John Newport Langley helped explain how responses occur when neurotransmitters bind to their specific receptors on target cells. In the 1970s, radioligand binding techniques allowed scientists to identify receptor subtypes more accurately. In the 1980s and 1990s, cloning techniques allowed scientists to clone genes encoding receptors, contributing to a better understanding of the receptor structure and function [5].

Identification of endogenous ligands (Like endorphins and enkephalins)

The common mechanism between alcohol and opiates

Trachtenberg., *et al*. formulated a hypothesis regarding the cause of the physical craving for alcohol, prompted by two key findings [6]. The initial finding revealed that the brain has receptor sites specifically for naturally occurring opiate-like substances, including endorphins, enkephalins, and dynorphins, produced by the nervous system. The second finding showed that opiates, along with alcohol metabolites such as tetrahydroisoquinolines, bind to these receptors in the brain. They also found that the physiological craving for alcohol may be the result of a genetic deficiency of naturally occurring opiatelike substances [7] as well as other neurotransmitter deficits (like dopaminergic, GABAergic, and serotonergic) [6].

"Brain reward cascade"

The neurotransmitter interaction leads to dopamine release in the mesolimbic system.

The brain's reward circuitry involves a complex interplay of neurotransmitters and their receptors. The primary neurotransmitter in the brain's reward system is dopamine, but other neurotransmitters, such as serotonin, GABA, and endorphins, also play crucial roles. The reward circuitry plays a crucial role in managing motivation, reinforcement learning, and the perception of pleasure.

Blum and Kozlowski (1989) conducted a review of numerous rigorous research studies, examining how neurotransmitters interact within the brain [8]. A detailed map describing the brain's reward circuitry was developed over many decades by initially embracing the work of Wise and Bozarth [9]. This foundational framework, known as the "Brain Reward Cascade" (BRC), outlines the common neurochemical pathways linked to reward that are shared by all addictive behaviors [10,11]. The core premise of this model is that only the balanced, "homeostatic" release of dopamine at the nucleus accumbens (NAc) results in a sense of well-being. Any deviation from this balance leads to "dopamine resistance" (hypodopaminergia), which can trigger cravings, whether in the form of liking or wanting [12-

14]. Furthermore, an excess of dopamine may contribute to schizophrenia [15], while insufficient dopamine levels can cause feelings of unhappiness, anhedonia, or depression [16].

Neurons in the mesolimbic reward circuitry have three main components: The VTA is a group of neurons in the midbrain that produce the neurotransmitter dopamine, which is involved in motivation, pleasure, and learning. When an individual encounters a rewarding stimulus, dopamine moves across the synapse (the tiny gap between neurons). The VTA sends dopamine projections to the NAc, the PFC, and other brain regions, such as the amygdala, hippocampus, and striatum. The dopamine reward pathway is a neural circuit that mediates the rewarding effects of natural and artificial stimuli, such as food, sex, drugs, and money. or engagement in pleasurable activities such as eating and socializing [17].

The nucleus accumbens (NAc) is a region within the basal forebrain that receives dopamine inputs from the ventral tegmental area (VTA). The NAc is responsible for the hedonic and pleasurable, as well as the motivational and incentive aspects of rewards, and integrates information from other brain regions that modulate reward stimuli's value (salience) [18].

The PFC is located at the front of the brain and receives dopamine inputs from the VTA. The PFC involves the cognitive or executive aspects of reward, such as planning, decision-making, goal setting, and self-control. The PFC also regulates the activity of the VTA and the NAc and can inhibit or enhance the rewarding effects of stimuli [19].

The dopamine reward pathway is not a static or fixed circuit but rather a dynamic and adaptive one that changes in response to experience and learning. For example, repeated exposure to a rewarding stimulus can lead to sensitization, an increased response to the same stimulus, or tolerance, a decreased response to the same stimulus. Moreover, factors such as stress, mood, hormones, drugs, and genetic variations that can alter the function and expression of dopamine receptors and transporters can influence the dopamine pathway [12].

The dopamine reward pathway is essential for survival and well-being, but it can also be involved in maladaptive behaviors and disorders, such as addiction, obesity, eating disorders, depression, and schizophrenia. These disorders can result from dysregulation or dysfunction of the reward pathway due to environmental (epigenetic) or DNA (genetic) factors or a combination of both. Understanding the neurobiology of the dopamine reward pathway is foundational to the development of better treatments and interventions for these conditions [20].

Neurotransmission

Neurotransmitter systems in the brain play vital roles in regulating various physiological and pathological processes. These systems involve complex interactions between neurons and are crucial for maintaining proper brain function table 1.

System	Role	Some pathological processes
Dopaminergic	Reward and pleasure, motivation, motor control, mood regulation, and cognitive function	Conditions include Parkinson's disease, schizophrenia, addiction, and attention deficit hyperactivity disorder (ADHD).
Serotonergic	Regulates mood, appetite, and sleep; contributes to emotional stability and stress response	It is associated with disorders like depression and anxiety, as well as conditions like obsessive-compulsive disorder (OCD) and eating disorders.
Noradrenergic	Arousal, attention, mood regulation, and stress response	Mood disorders, anxiety disorders, and conditions like attention deficit hyperactivity disorder (ADHD).
Cholinergic	Learning, memory, attention, and muscle control	Impairments observed in Alzheimer's disease and other cognitive and movement disorders
GABAergic	Major inhibitory neurotransmitter regulates anxiety, stress response, and overall excitability in the brain.	It is implicated in anxiety disorders, epilepsy, and sleep disorders.

Glutamatergic	Major excitatory neurotransmitter; crucial for learning, memory, and synaptic plasticity	Associated with neurodegenerative disorders, schizophrenia, and mood disorders
Endorphin (Opioid System)	Pain modulation, reward, and pleasure	Chronic pain conditions, addiction, and mood disorders.
Histaminergic	Regulates wakefulness and arousal.	Narcolepsy and other sleep disorders
Endocannabinoid	Modulates mood, appetite, sleep, and pain perception	Associated with mood disorders, chronic pain, and neurodegenerative conditions.
Peptidergic	Various neuropeptides (e.g. substance P, neuropeptide Y) have diverse roles in regulating mood, stress response, pain, and appetite.	They are associated with conditions such as chronic pain, mood disorders, and eating disorders.

Table 1: *Here are some key neurotransmitter systems and their roles.*

Notably, these neurotransmitter systems often interact, and imbalances or dysregulation in one system can impact others, contributing to the complexity of various neurological and psychiatric conditions. Understanding these systems is crucial for developing targeted treatments for neurotransmitter dysfunction disorders [21].

Neurotransmitters bind to specialized receptors on the surface of neighboring neurons. Binding initiates a series of cellular events inside the receiving neuron. This process is known as signal transduction. Different intracellular signaling pathways are triggered when the receptor is activated, influencing the neuron's activity. In the reward system, the key receptors are the dopamine receptors, particularly D1 and D2 receptors. For example, when dopamine binds to a neuron, dopamine receptor activation initiates change in electrical activity in the neuron. D1 receptor binding may increase neuronal firing, while D2 receptor binding may have inhibiting effects.

An early instance of mRNA gene expression related to substance use disorder (SUD) was presented by the Noble., *et al*. [22] discovery. It showed that there were differences in the binding affinity and the number of binding sites for the dopamine D2 receptor in the caudate nucleus between alcoholic and non-alcoholic subjects. Alcoholics exhibited lower binding affinity and fewer binding sites for the D2 receptor compared to non-alcoholics. Additionally, individuals with the A1 allele who also had alcoholism exhibited a significant reduction in dopamine D2 receptor sites. The number of these receptor sites decreased progressively as the presence of the A1 allele increased, transitioning from the A2/A2 to A2/A1 and finally to A1/A1 genotypes. Subjects with the A2/A2 genotype had the highest quantity of dopamine D2 receptor sites, while those with the A1/A1 genotype had the lowest. In fact, individuals with the A1/A1 genotype showed a decreased protein expression correlating with a 30–40% reduction in dopamine D2 receptors. This differential expression of dopamine D2 receptors, related to the polymorphic patterns of the dopamine D2 receptor gene, supports the role of the dopamine system in the vulnerability to a specific subtype of severe alcoholism.

After release, neurotransmitters like dopamine are not left in the synapse indefinitely. They are broken down by enzymes or removed when transporters on the presynaptic neuron reabsorb (reuptake) the neurotransmitter, terminating the signal. There are specific dopamine transporters that recycle dopamine back into the presynaptic neuron.

Neurotransmitters, such as serotonin GABA and endorphins, modulate the brain reward circuitry and interact with dopamine in complex ways by activation, inhibition, and disinhibition, see figure 1.

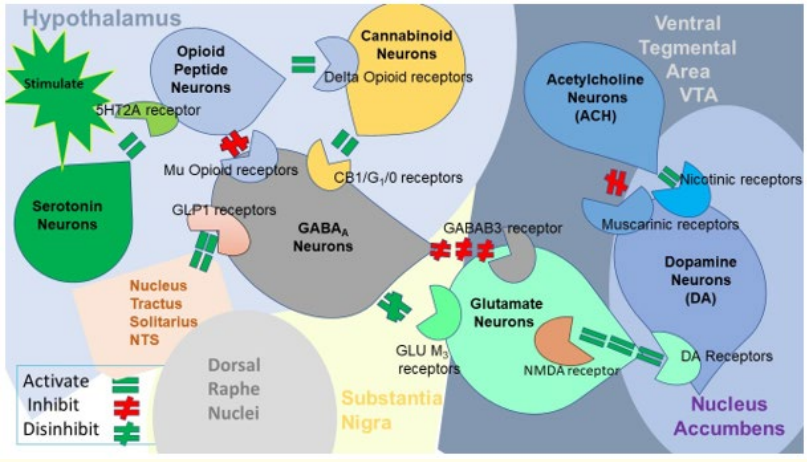

Figure 1: *The mesolimbic brain reward cascade.*

This cartoon illustrates the interaction of some well-known brain reward cascade (BRC) neurotransmitter pathways. Environmental stimulation triggers the release of serotonin in the hypothalamus, which then activates the subsequent release of opioid peptides from opioid peptide neurons through mechanisms involving 5-HT2A receptors. Subsequently, in the substantia nigra, the opioid peptides bind to two distinct opioid receptors, each producing different effects. One is through the mu-opioid receptor that inhibits (red hash sign) GABAA neurons (possibly via an opioid peptide like enkephalins). The second stimulates cannabinoid neurons (for example, the Anandamide and 2-arachidonoylglycerol) (green equal sign) through beta-endorphin-linked delta receptors, which inhibit GABAA neurons. When activated, cannabinoids, primarily the 2-arachidonoylglycerol neurons, can disinhibit (green hash sign) GABAA neurons indirectly by G1/0 coupled to CB1 receptor activation. Glutamate neurons in the dorsal raphe nuclei (DRN) indirectly disinhibit GABAA neurons in the substantia nigra through the activation of GLU M3 receptors (23). When disinhibited, GABAA neurons strongly inhibit (red hash signs) the glutamatergic drive from the VTA via GABAB3 receptors. In the nucleus accumbens, acetylcholine (ACh) neurons can inhibit (red hash sign) muscarinic receptors while stimulating nicotinic receptors (green hash). Glutamate neurons in the VTA project to dopamine neurons through NMDA receptors (green equal sign), ultimately leading to the release of dopamine in the nucleus accumbens (NAc).

Healthy happiness depends on the set point of the homeostatic dopamine tone [24-26]. Unhappy feelings occur when dopamine release is low (endorphin deficiency). Many hypotheses stem from continuing discoveries in basic neuroscience research that increase understanding about neurotransmitter interactions within this brain reward circuitry [27] and what is known will accelerate.

The neuronal activity contributes to the processing of reward-related information and reinforcement learning. The individual learns to associate certain stimuli or behaviors with the release of dopamine, reinforcing the likelihood of engaging in those behaviors in the future. These processes collectively contribute to one's ability to respond to rewarding stimuli, learn from experiences, and regulate motivated behavior.

"Reward deficiency syndrome" (RDS)

The quest to comprehend the role of neurotransmitter systems in all addictive behaviors and pathologies led to the conceptualization of Reward Deficiency Syndrome (RDS). After Blum's exploration of the neurochemical mechanisms of alcohol and opioids from the 1970s to the mid-1990s, the concept of Reward Deficiency Syndrome (RDS) was published by The Royal Society of Medicine in 1996 [28,29].

RDS refers to a relative deficiency in the dopaminergic system, which is crucial for the brain's reward mechanisms. This "hypodopaminergic" trait or state accounts for various behavioral patterns, especially those related to addiction and other impulsive and

compulsive behaviors. The conceptualization suggests that some individuals may have a neurotransmitter deficiency in the brain's reward system, making them more prone to seeking out rewarding stimuli, such as substances or behaviors, to compensate for this deficiency.

The syndrome encompasses dopaminergic dysfunction acute excess, leading to a deficit of dopamine release in the brain reward circuitry when addiction becomes chronic. The theory suggests that variants of the genes that support the functioning of the reward circuitry determine RDS. The product of the brain reward cascade, which involves many neurotransmitter pathways, see figure 1, is the release of dopamine. Individuals with RDS have lower-than-normal dopamine release, the neurotransmitter associated with pleasure and reward, in their brains. As a result, they may be more susceptible to engaging in activities that stimulate the release of dopamine (acute excess), such as drug use, gambling, or overeating, to experience pleasure and satisfaction. Indeed, many neuropsychiatric behaviors, when they become chronic, develop a dopamine release deficit. Reward deficiency behaviors encompass a range of addictive behaviors, both drug-related and non-drug-related, as well as compulsive and impulsive actions.

One better-known attribute of dopamine is the presynaptic increase in function, dopamine release during the *acute* administration of all addictive substances, and the performance of all non-substance addictive behaviors like gambling [30]. In contrast, in animal models and in humans, measured dopaminergic tonic activity is drastically reduced when addictive behaviors are chronic. Many reviews and experiments strongly support the concept of hypodopaminergic trait/state [31,32]. Dopamine depletion (hypodominergia) in chronic substance seeking is well documented in cocaine [33], alcohol [34], cannabis [35] and morphine abuse [36], and non-substance behaviors like gambling [37,38] and internet gaming [39] (Table 2).

Addictive Behaviors		**Impulsive Behaviors**		**Obsessive Compulsive Behaviors**	**Personality Disorders**
Substance-Related	**Non-Substance Related**	**Spectrum Disorders**	**Disruptive Impulsive**		
Alcohol	Thrill-seeking (novelty)	Attention-deficit Hyperactivity	Anti-social	Body Dysmorphic	Paranoid
Cannabis	Sexual Sadism	Tourette and Tic Syndrome	Conduct	Hoarding	Schizoid
Opioids	Sexual Masochism	Autism	Intermittent Explosive	Trichotillomania-mania (hair pulling)	Borderline
Sedatives/ Hypnotics	Hypersexual		Oppositional Defiant	Excoriation (skin picking)	Schizotypal
Stimulants	Gambling		Exhibitionistic	Non-suicidal Self-Injury	Histrionic
Tobacco	Internet Gaming				Narcissistic
Glucose					Avoidant
Food					Dependent

Table 2: *The table of reward deficiency behaviors includes substance and non-substance addictive, compulsive, impulsive behaviors, and personality disorders.*

Dysfunction in the reward circuitry can contribute to conditions like addiction and other mental health disorders that are associated with dopamine deficiency, whether due to genetic factors, environmental influences, or substance toxicity [27].

Genetic predisposition

One of the most studied of several genes implicated in the development of Reward Deficiency Syndrome is the dopamine D2 receptor gene (DRD2). The AI allele variation impedes the production of sufficient DRD2 receptors. Another is the dopamine transporter (DAT) gene, implicated in ADHD, which removes excessive amounts of dopamine from the synapse during reuptake. The variable number of

tandem repeats (VNTR) in the DAT1 gene regulates dopamine transporter density *in vitro*. Some DAT gene VNTR remove dopamine faster than others, the fastest causing hypodopaminergia resulting in RDS behaviors such as ADHD [40-42].

Bannon., *et al*. observed that *in vitro*, the 3′-UTR of sequence-defined DAT alleles differentially influenced the level of reporter gene expression in HEK-293 cells transfected with two distinct luciferase expression vectors or reporters). The 3′-UTR of sequence-defined DAT alleles had a differential impact on the level of reporter gene expression in HEK-293 cells that were transfected with two different luciferase expression vectors or reporters. These findings provided robust evidence that the 9R length in the 3′-UTR of the DAT gene conceivably is associated with increased DAT protein in the human brain compared with the 10R sequence and that variability in the length of the sequence of the 3′-UTR of the DAT gene influences DAT protein expression in the brain [41].

Spencer., *et al*. [43] investigated the relationship between dopamine transporter (DAT) binding in the striatum of individuals with and without ADHD, focusing specifically on the 3′-untranslated region (3′-UTR) and the intron 8 variable number of tandem repeats (VNTR) polymorphisms of the DAT (SLC6A3) gene. Their findings suggest that some of the dysregulation of the dopamine transporter (DAT) in ADHD may be attributed to an over-representation of the 9R allele associated with the 3′-UTR risk polymorphisms of the SLC6A3 gene, enhancing the understanding of ADHD risk genes and DAT expression in humans.

Additionally, some documented dysregulation of dopamine and the dopamine transporter gene in ADHD cannot be explained by stimulant use alone. This DAT dysregulation is linked to the 9R carriers (VNTR) of the 3′-UTR of SLC6A3 [43]. However, ADHD itself also contributes independently to DAT binding, indicating the presence of an unidentified genetic or nongenetic mechanism underlying this phenomenon.

Epigenetic causes of RDS

Stress, for example, vulnerability to PTSD can be enhanced in people with genetic RDS [44]. Prolonged stress has long-lasting effects on cognition [45]. Alterations within the mesofrontal circuit confer executive functioning deficits in animal models of prolonged stress. Van Wingen., *et al*. found that midbrain activity and integrity were reduced by combat stress and associated with an attentional deficit. However, these functional and structural changes normalized within 1.5 years, but reduced functional connectivity between the midbrain and prefrontal cortex persisted [46].

Toxicity, for example, chronic hypodopaminergic trait/ state, triggers drug/behavioral seeking. Habitual substance use disorder (SUD) or behaviors can induce hypodopaminergia in a person with or without predisposing genetics. Long-lasting hypersensitivity to both substance and non-substance behavioral "wanting" [12,13] confers neuroplastic changes in the reward neural circuitry, accumulating vulnerability to RDS behaviors, including addictions [47].

Methods: Treatments for RDS

The effectiveness of each intervention may depend on the individual's genetics and the specific context or epigenetics involved in their situation.

The goal, regulation of either an acute hyperdopaminergia or chronic hypodopaminergic trait or state, is "dopamine homeostasis". In fact, only a small percentage of treatment centers currently pursue this goal by providing dopamine-boosting modalities.

There are several ways to modulate the activity of the reward circuitry, including:

- Pharmacological interventions: Drugs that target specific neurotransmitter systems, such as dopamine, can modulate the activity of the reward circuitry. For example, drugs that block dopamine receptors reduce the rewarding effects of drugs of abuse, while drugs that enhance dopamine release can increase the rewarding effects of food, sex, and other natural rewards [48-51].

- Behavioral interventions: Cognitive-behavioral therapy (CBT) and trauma therapy can modulate the activity of the reward circuitry by changing the way the brain processes rewarding stimuli. For example, CBT can help individuals with addiction learn to associate drug-related cues with adverse outcomes, which can reduce the reinforcing effects of drugs [52,53].
- Brain stimulation: Sound Therapy, Deep brain stimulation (DBS), and transcranial magnetic stimulation (TMS) can modulate the activity of the reward circuitry by altering the patterns of neuronal firing in specific brain regions. For example, TMS can reduce the craving for drugs of abuse by decreasing the activity of the reward circuitry [54,55].
- Lifestyle changes: Lifestyle changes such as exercise, meditation, and social support can modulate the activity of the reward circuitry by promoting the release of endogenous opioids and other neurotransmitters associated with pleasure and well-being. For example, regular exercise can increase the sensitivity of the reward circuitry to natural rewards such as food and sex, which can reduce the risk of addiction [33]. Although, due to a lack of research, little direct evidence for dopamine boost has been linked to many holistic approaches, dopamine-enhancing foods like low glycemic foodstuffs, like fish oils, are known to boost dopamine function [56] and a 65% increase in neuronal dopamine has been demonstrated from Yoga and Meditation [57].
- Awareness Integration Theory (AIT) is a versatile psychotherapeutic model that delves deep into self-awareness, emotional healing, and personal transformation developed by Dr. Foojan Zeine. The Adaptive Integrative Therapy (AIT) approach integrates various evidence-based therapeutic modalities, including Cognitive Behavioral Therapy (CBT), Existential Psychotherapy, Person-Centered Therapy, Emotion-Focused Therapy (EFT), Mind-Body Interventions, Eye Movement Desensitization and Reprocessing (EMDR), and Clinical Hypnotherapy, Eye Movement Desensitization and Reprocessing (EMDR), and Hypnosis. AIT recognizes behavior as a product of internal and external influences shaped by learning experiences and cognitive schemas developed in childhood and adolescence. Challenging and reframing these maladaptive beliefs and behavioral patterns empowers individuals to take control of their emotions, thoughts, and actions, leading to greater fulfillment and well-being [58,59].

- Research has established a correlation between parenting style, including parenting practices, and a child's risk-taking behavior, such as substance abuse. Longitudinal studies have highlighted other factors, such as peer pressure, delinquencies, and parental substance use, as determining factors in promoting risk-taking behavior. Parenting styles have been important indicators of children's tendency to substance use [60].
- These molecular epigenetic alterations underlie the long-lasting, often tissue-specific transcriptional and behavioral effects of cannabinoids, which have been observed not only within an individual's lifetime but also across subsequent generations [60].
- Epigenetic modifications can trigger a cascade of neuroendocrine alterations, contributing to subclinical and behavioral changes that may serve as precursors to the clinical onset of Substance Use Disorder (SUD) [61].
- Treatment with a pro-dopamine agonist KB220 enhances and helps repair functional connectivity and restore dopamine homeostasis [62-64].

The United States is currently facing a high prevalence of substance use disorders, predominantly driven by the misuse of both legal and illicit opioid. Between 2000 and 2016, there was a staggering 3000% increase in the number of individuals seeking treatment for substance use disorders. Currently, the treatment of opioid use disorder predominantly involves opioid replacement therapy using potent agonists, which primarily aims at harm reduction rather than achieving true prophylaxis or complete remission. A single dose of the potent dopamine D2 receptor agonist, bromocriptine, has been shown to significantly reduce cocaine cravings, as reported by Nobel., *et al*. [65]. Nobel., *et al*. conducted a placebo-controlled study using bromocriptine to treat individuals with Alcohol Use Disorder (AUD) [66]. However, chronic administration of this potent D2 agonist resulted in significant down-regulation of D2 receptors, ultimately negating its clinical usefulness [67]. Research utilizing the Reward Deficiency Syndrome (RDS) model has demonstrated that DNA-directed compensatory overexpression of DRD2 receptors, a form of gene therapy, leads to a significant reduction in alcohol-craving behaviors [34] and decreased self-administration of cocaine [68] in alcohol-preferring rodent models.

KB220 Formulations to treat RDS.

Blum., *et al*. propose an alternative, mild therapeutic, neuro-nutrient formulation that could accomplish D2 receptor agonism to help attenuate RDS [65], increase human mRNA expression to proliferate D2 receptors [63,64], reduce craving, and attenuate stress [24]. Fortunately, ongoing discoveries have served as a crucial catalyst for the evolution, expansion, and scientific acknowledgment of nutrigenomics and its remarkable potential to enhance human health and well-being. In contrast to many treatment strategies that focus on dopaminergic receptor blockade or the attenuation of dopamine release [69], Blum., *et al*. propose an alternative approach: in most circumstances, the use of amino acid precursors to modulate positive dopaminergic activation is a better alternative [64].

Supplemental Ingredient	Restored Brain Chemical	Addictive Substance Abuse	Amino Acid Deficiency Symptoms	Expected Behavior Change
D-Phenylalanine or DL-Phenylalanine is a known Enkephalinase inhibitor.	Enkephalins, Endorphins	Heroin, Alcohol, Marijuana, Sweets, Starches, Chocolate, Tobacco	Sensitivity to physical and emotional pain is a characteristic of most Reward Deficiency Syndrome (RDS) conditions. People with RDS crave comfort and pleasure and desire certain foods or drugs.	Reward stimulation. Anti-craving. Mild anti-depression. Mild improved energy and focus. D-phenylalanine promotes pain relief and increases pleasure.
L-Phenylalanine or L-Tyrosine	Nor-epinephrine, Dopamine	Caffeine, Speed, Cocaine, Marijuana, Aspartame, Chocolate, Alcohol, Tobacco, Sweets, Starches	Most RDS conditions. Depression, low energy. Lack of focus and concentration. Attention-deficit disorder.	Reward stimulation. Anti-craving. Anti-depression. Increased energy. Improved mental focus.
L-Tryptophan or 5 hydroxy-tryptophan (5HTP)	Serotonin	Sweets, Alcohol, Starch, Ecstasy, Marijuana, Chocolate, Tobacco	Low self-esteem. Obsessive-compulsive behaviors. Irritability or rage. Sleep problems. Afternoon or evening cravings. Negativity. Heat intolerance. Fibromyalgia. Seasonal affective disorder.	Anti-craving. Anti-depression. Anti-insomnia. Improved appetite control. Improvement in all mood and other serotonin deficiency syndromes.
Gamma-aminobutyric acid (GABA)	GABA	Valium, Alcohol, Marijuana, Tobacco, Sweets, Starches	Feelings of being stressed out. Nervous. Tense muscles. Trouble relaxing.	GABA promotes calmness and relaxation.
(69)L-Glutamine	GABA (mildly enhanced energy). The fuel source for the entire brain	Sweets, Starches, Alcohol	Stress. Mood swings.	Anti-craving, anti-stress. and (mild mood enhancement). Fuel source for the entire brain.

Table 3: *Amino acid nutrition therapy [69].*

With permission [69].

These formulae with the scientific name KB220 also contain Rhodiola rosea, a known catechol-O-methyl transferase (COMT) inhibitor, which provides more synaptic dopamine in the VTA/NAc [70]. Chromium salts were incorporated into the formulation to improve insulin sensitivity and subsequently increase brain concentrations of serotonin. Due to its polar nature and limited capacity to cross the blood-brain barrier, GABA (gamma-aminobutyric acid) faces constraints in its therapeutic application. To prevent excessive inhibition of enkephalin degradation and the consequent suppression of GABAergic spiny neurons in the substantia nigra, a low concentration of glutamate is utilized.

Does KB220 work?

Clinical support

Vulnerability to relapse

KB220 has been extensively studied in numerous clinical trials, providing substantial evidence for its efficacy in addressing substance use disorders and related conditions. The research highlights its potential in reducing vulnerability to relapse, making it a promising option for individuals seeking recovery. Evidence indicates that individuals carrying the A1 allele of the DRD2 gene are at an elevated risk for relapse [71] and have a higher likelihood of discontinuing treatment against medical advice (AMA). However, research has shown that with the use of KB220Z, there is a significant reduction in AMA rates and reduced relapse [72].

Neuroimaging support

Lack of functional connectivity

In a resting state, the brain of an individual with typical genetic traits or epigenetic (environmental) influences exhibits background working connections, referred to as resting state functional connectivity (rsFC). Certainly, Reward Deficiency Syndrome (RDS) and various addictive behaviors-both drug-related and non-drug-related, such as gambling, compulsive sexual behavior, overeating, and attention-deficit/hyperactivity disorder (ADHD)—are associated with reduced resting state functional connectivity (rsFC) [73-77]. The research conducted by Eric J. Nestler and others has paved the way for understanding the epigenetic changes that occur when environmental factors influence DNA gene expression [78]. Blum., *et al*. also contribute to this body of knowledge by exploring related mechanisms.

The Blum., *et al*. group used quantitative electroencephalogram (qEEG) analysis to show that KB220 formulations (induced homeostasis) significantly regulated the prefrontal cortices, particularly in the cingulate gyrus (a region for drug relapse) in abstinent psychostimulant users [79] alcoholics and opiate addicts [80]. Sophisticated quantitative EEG (qEEG) software, such as Low-Resolution Brain Electromagnetic Tomography (LORETA), measures deep brain structures by analyzing data from electrodes placed on the scalp. This technique is analogous to locating the epicenter of an earthquake using measurements taken at the surface. LORETA neurofeedback correlates significant data from quantitative EEG (qEEG) with neural networks in the brain that are associated with various clinical symptoms. The neuro-nutrient formulation provoked changes observed using LORETA in the neurological function of an adult with symptoms of ADHD [81].

Gentle dopamine activation produced by the KB220 formulation observed using rsfMRI increased functional connectivity and induced dopamine homeostasis across the brain reward circuitry one hour after oral administration in abstinent heroin users [36]. The putative dopamine D_2 agonist therapy with KB220Z overcame qEEG abnormalities during protracted abstinence in male psychostimulant, polydrug abusers [82]. Furthermore, advanced functional MRI (fMRI) measurements have shown that the pro-dopaminergic agent KB220Z induces increases in dopamine levels, as well as enhanced functional connectivity and volume between cognitive and reward centers in the brains of naive rodents [64,83]. Ongoing research is necessary to demonstrate that long-term dopamine agonist therapy with a variant of KB220 may facilitate essential "dopamine homeostasis," which is a crucial component in addressing all Reward Deficiency Syndrome (RDS) behaviors, encompassing both substance and non-substance addictions.

The "pro-dopamine regulator (KB220)" has the potential to optimize gene expression, restore the balance of neurotransmitter systems within the Brain Reward Cascade, and prevent relapse by promoting dopamine homeostasis. Additionally, it targets DNA polymorphic reward genes to influence mRNA genetic expression [84].

The genetic addiction risk severity (GARS) test

Genetic testing for preaddiction

There is an urgent need for innovative therapies and reliable, safe, and effective screening methods. Despite decades of federal funding aimed at the research, development, and implementation of innovative therapies for individuals with severe addictions, treatment penetration rates have remained below 20% [85,86].

The diabetes field encountered a similar challenge but successfully improved treatment penetration and impact by identifying individuals at risk for diabetes and implementing interventions during the early stages of the disease, such as prediabetes [87]. The concept of prediabetes has proven effective in slowing the progression of diabetes, leading to improved efficiency in early detection and expedited initiation of treatment.

Similarly, the innovative concept of "preaddiction" has been proposed for inclusion in the DSM to identify individuals with mild to moderate substance use disorder (SUD) or those at risk of developing severe addictive behaviors [86].

While prediabetes is viewed as a manifestation of disrupted endocrine, excretory, and digestive homeostatic functions [88], preaddiction may be more closely associated with hedonistic derailments [89], specifically characterized by hypodopaminergia within the mesolimbic brain reward circuitry [16]. Screening for preaddiction could be accomplished through molecular genetic testing to identify predisposition to Reward Deficiency Syndrome (RDS) behaviors [90], as well as utilizing other neuropsychiatric assessments, such as Memory (CNSVS), Attention (TOVA), Neuropsychiatric Evaluation (MCMI-III), and Neurological Imaging techniques (qEEG/P300/EP) [91]. The concept of preaddiction, when combined with standardized and objective diagnostic screening and testing, could help curb the increasing prevalence of Substance Use Disorder (SUD) and overdose rates through early detection and timely intervention.

The development of the genetic addiction risk severity (GARS) test

Blum., *et al*. set about developing a test to identify preaddiction early in life [90]. In earlier work, Comings and Blum [28,92] developed a biogenic model with the hypothesis that specific genetic variants can cause neurotransmission dysfunctions: genetic hypodopaminergia, and reward deficiency in the brain reward cascade (See figure 1) [29]. Blum then searched the literature for polymorphisms of genes that might impede the production of dopamine in the brain reward circuitry. Each polymorphism included in the Genetic Addiction Risk Severity (GARS) test was selected based on its association with Substance Use Disorder (SUD), a subset of Reward Deficiency Syndrome (RDS) that is linked to reduced dopaminergic (hypodopaminergic) functioning within the brain's reward circuitry [93]. The gene polymorphisms that most adversely impact dopamine release at the brain's reward center were selected from thousands of association studies, providing robust evidence of specific genetic risks associated with various addictions. The detailed list of these polymorphisms is presented in table 4.

Gene	Polymorphism	Location	Risk Allele(s)
Dopamine D1 Receptor DRD1	rs4532 SNP	Chr 5	A
Dopamine D2 Receptor DRD2	rs1800497 SNP	Chr 11	A
Dopamine D3 Receptor DRD3	rs6280 SNP	Chr 3	C
Dopamine D4 Receptor DRD4	rs1800955 SNP	Chr 11	C
	48 bases Repeat VNTR	Chr 11, Exon 3	7R,8R,9R,10R,11R
Catechol-O-Methyltransferase COMT	rs4680 SNP	Chr 22	G
Mu-Opioid Receptor OPRM1	rs1799971 SNP	Chr 6	G
Dopamine Active Transporter DAT1	40 bases Repeat VNTR	Chr 5, Exon 15	3R, 4R, 5R, 6R, 7R, 8R
Monoamine Oxidase A MAOA	30 bases Repeat VNTR	Chr X, Promoter	3.5R, 4R
Serotonin Transporter SLC6A4 (5HTTLPR)	43 bases Repeat INDEL/VNTR plus rs25531 SNP	Chr 17	LG, S
GABA(A) Receptor, Alpha-3 GABRB3	CA-Repeat DNR	Chr15 (downstream)	181

Table 4: *Selected gene polymorphisms, chromosome location, risk variants.*

The Institute of Behavioral Genetics at the University of Colorado, Boulder, conducted the first study utilizing a clinical outcome measure, the Addiction Severity Index Media Version (ASI-MV), to compare against Genetic Addiction Risk Severity (GARS) test results in a cohort from multiple chemical dependency programs. The study evaluated selected gene polymorphisms, their chromosomal locations, and risk variants associated with addiction. Blum's laboratory aimed to assess genetic risk for alcohol and drug use by investigating whether the cumulative effect of reward gene polymorphisms, which contribute to a hypodopaminergic trait, is associated with an increased risk of substance abuse linked to Reward Deficiency Syndrome (RDS). Among the participants who consented to provide a saliva sample for DNA genotyping, 273 individuals (derived from seven centers) also had accompanying ASI phenotypic information [94].

The patient population n=393, 17.6%, 80.7%, and 1. 5% of participants fell into the low, moderate, and high severity categories, respectively. The mean number of GARS alleles was 7.97 (SD = 2.34), with a range of 3 to 17 alleles. The analysis of the relationship between the GARS genotype panel and the Alcohol Risk Severity Score using Fisher's Exact Test indicated a significant predictive relationship ($X^2 = 8.84$, df = 1, p = 0.004, 2-tailed), which remained significant even after controlling for age ($p < 0.01$). A similar, albeit less robust, association was observed in chi-square analyses of the ASI Drug Severity Risk Score (p = 0.05, 2-tailed) Blum., *et al*. [95] provides a detailed explanation of the development of the Genetic Addiction Risk Score (GARSTM) and its predictive relationship with alcohol and drug severity risk scores derived from the ASI-MV [94].

The (GWAS) contribution

Since Blum., *et al*. first published in JAMA in 1990, the association between the DRD2 gene polymorphism and severe alcoholism has yielded mixed and controversial results in subsequent studies. More recently, a meta-analysis of 62 studies demonstrated a significant association between the DRD2 rs1800497 polymorphism and Alcohol Use Disorder (AUD). Other studies conducted at Yale University indicated that a haplotype block of the DRD2 gene A1 allele is associated with both Alcohol Use Disorder (AUD) and heroin dependence. GWAS studies of depression [96] and suicide [97] in 1.2 million veterans confirmed the initial findings of Blum., *et al.* regarding psychiatric candidate genes. In 1990, researchers found a significant association between the minor DRD2 allele, Taq A1 (rs1800497 C>T), and severe alcoholism. Furthermore, the DRD2 rs1800497 polymorphism is strongly associated with suicidal behaviors, with a significance level of p = 1.77 x 10^-7. The DNA polymorphic alleles associated with Substance Use Disorder (SUD) involving multiple substances were mapped through chromatin refolding, identifying the DRD2 gene and its associated polymorphism(s) as the primary gene signal (DRD2, p = 7.9 × 10^-12) [98].

In 2020, Blum's group published the biotechnical development of the GARS test, providing selective evidence for the relevance of polymorphic allelic risk in substance use disorder (SUD). The data collection procedures, instrumentation, and analytical methods employed to obtain the GARS, along with subsequent research objectives, were outlined (See figure 2). An estimation was provided based on the findings from previous literature. Although not representative of all association studies conducted to date, the sampling of case-control studies reveals significant associations between alcohol and drug risk. In fact, we presented a total of 110,241 cases and 122,525 controls based on the current literature [93].

Figure 2 illustrates the comprehensive pipeline for a meta-analysis of addiction-related genetic variations, including a genome-wide analysis of the molecular mechanisms underlying the implicated SNPs, as well as the pathways and gene interaction networks potentially involving these genetic factors. All data and insights contributed to an updated version of the Knowledgebase for Addiction-Related Genes (KARG) [99] modified.

Statistical validation of GARS

This initial statistical validation focused on reward-related genes and their associated polymorphisms, primarily known to contribute to diminished dopamine function within the mesolimbic brain reward circuitry. The risk alleles included in the GARS test for the early

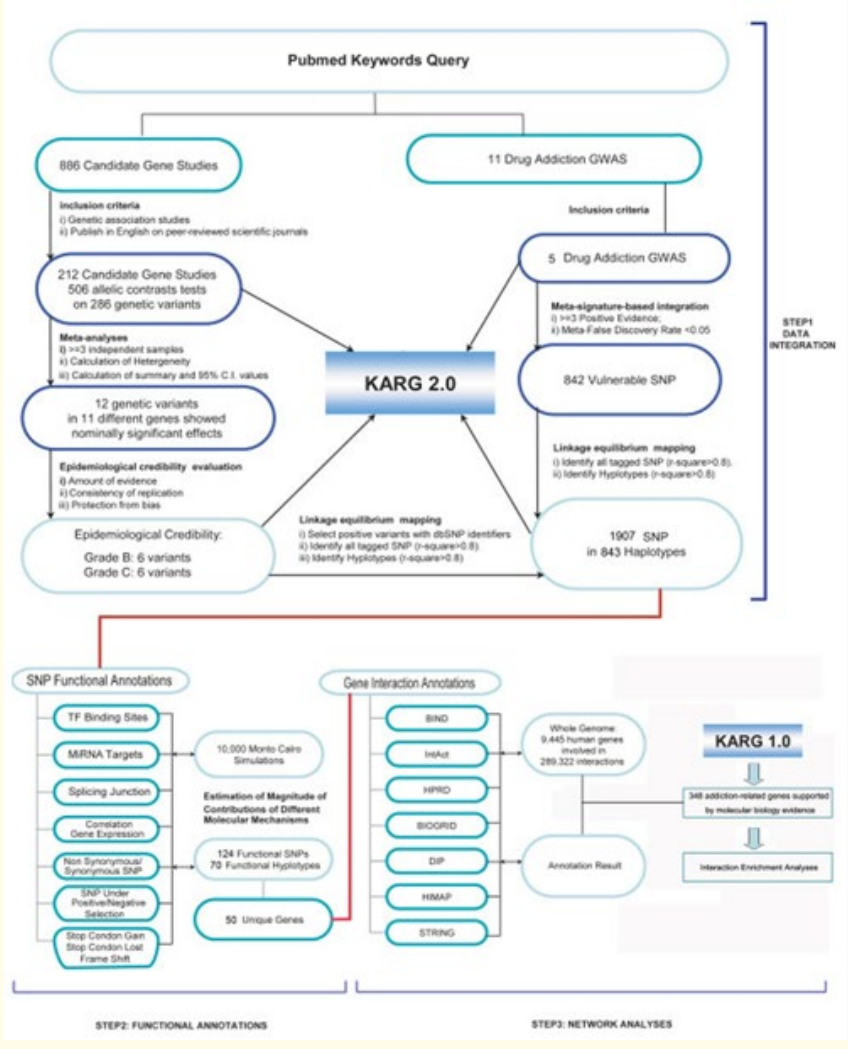

Figure 2: *Pipelines for conducting meta-analyses, functional SNP annotations, and interaction analyses were implemented (with permission) [99].*

detection of alcohol use disorder (AUD) were analyzed in a cohort of 74,566 case-control subjects [100]. The results of the statistical analysis indicated an odds ratio (OR) with 95% confidence intervals (CI), along with a projected population prevalence of alcoholism at 8% following risk assessment. The dopamine receptors DRD1, DRD2, DRD3, DRD4, along with DAT1, COMT, OPRM1, and 5HTT, all demonstrated significantly increased risk for Alcohol Use Disorder (AUD) in comparison to non-AUD controls, based on the odds ratios (OR) derived from this meta-analysis. The GABRB3 and MAOA variations were not significant due to insufficient sample sizes [100].

Currently, a study exploring the possibility that the true phenotype of preaddiction may be linked to dopaminergic dysregulation is pending publication. The study investigates the concept of "Pre-Addiction" in addiction biology through an extensive in silico analysis of 88,788,381 GWAS-based samples from 1,373 studies, identifying 18 significant genes (e.g., **APOE** with a p-value of 1.0E-126) associated with pathways related to opioids, pain, aging, and apoptosis. The goal is to correlate these genes with the GARS test. The most interconnected genes, identified using a STRING model, are **MAOA**, **COMT**, **APOE**, and **SLC4A6**. The analysis highlights notable interactions with the RNAs **hsa-miR-16-5p** and **hsa-miR-24-3p**, while the **SLC6A4** gene was found to be associated

with 27 unique genes. Pharmacogenomics (PGx) mining identified 1,173 variant annotations for these genes. Enrichment analysis and meta-analysis further supported these findings, demonstrating the crucial role of dopaminergic pathways in linking addictive behaviors with depressive symptoms. This analysis proposes Reward Deficiency Syndrome (RDS) as the core phenotype of preaddiction, with pain, opioid dependence, aging, and apoptosis identified as essential endophenotype.

Discussion of practical applications of the GARS test

Three applications are of current interest. These encompass pharmacogenetics (mainly assessing metabolizing enzymes for high and low metabolizers, such as with opiates), the Genetic Addiction Risk Score to evaluate vulnerability to various Reward Deficiency Syndrome (RDS) behaviors through a panel of reward gene polymorphisms, including pain tolerance, and pharmacogenomics for personalized addiction medicine, which involves genotyping individuals to target specific gene loci.

Pharmacogenetics

Genotypes refer to specific gene variants. An individual possesses multiple genotypes rather than being limited to just one. To effectively implement DNA-customized formulations, it is essential to understand the various genotypes of an individual across multiple biological and metabolic pathways. For instance, alcohol impacts Asians and Native Americans differently than it does Caucasians, and the polymorphism in the alcohol dehydrogenase gene holds predictive value in alcohol addiction. Pharmacogenetic medical monitoring can lead to improved clinical outcomes. For example, the A1 allele of the **DRD2** gene decreases binding to delta receptors in the brain, which diminishes the clinical effectiveness of Naltrexone.

Genomic testing through the Genetic Addiction Risk Score (GARS) can enhance clinical interactions and inform decision-making

- Alleviation of guilt and denial.
- Confirmation of family genograms.
- Decisions regarding appropriate therapies, including pain medications, based on risk severity and addiction liability.
- Determination of the appropriate level of care placement (e.g., inpatient, outpatient, intensive outpatient, residential).
- Duration of treatment stay.
- Relapse and recovery liability and vulnerability based on genetic severity.
- Medical necessity for insurance evaluation.

DNA customization of KB220 formulations

The application of this natural dopaminergic-stimulating DNA customization method over time is expected to enhance neuronal dopamine (DA) discharge in the nucleus accumbens (NAc), resulting in an increase in D2 receptor abundance, improved resting state functional connectivity, and anti-craving effects. These outcomes have been observed in various peer-reviewed clinical trials that employed randomized, double-blind, placebo-controlled designs [79].

Futuristic Perspective

The comprehensive schematic (Figure 3) represents the culmination of this research, which encapsulates the genomic foundations supporting Reward Deficiency Syndrome (RDS) as the primary pre-addiction phenotype. Additionally, it illustrates the critical role of Genetic Addiction Risk Score (GARS) testing in identifying other endophenotypes, underscoring the importance of genetic markers in understanding and addressing addiction. This body of work reinforces the genetic basis of addiction, opening new avenues for treatment and intervention in the future of addiction psychiatry and medicine.

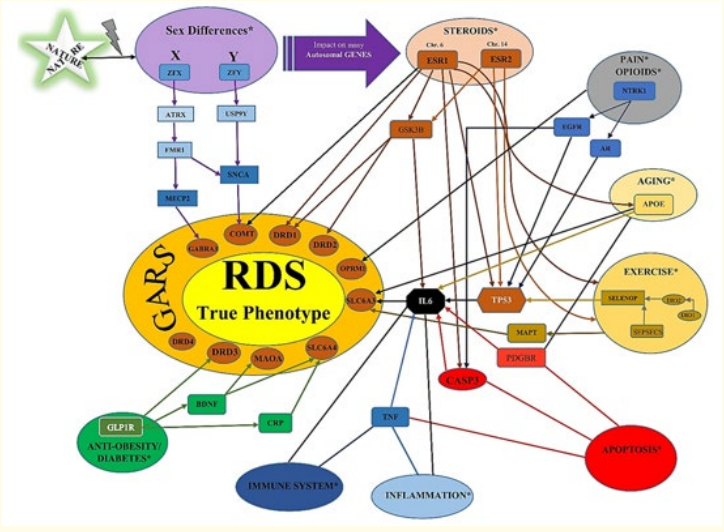

Figure 3: *The concept of sub-genomic intelligence (SuGIN).*

Conclusion

We are proposing that based on our high level Pharmacogenomic and GWAS studies the GARS test may provide an accurate early identification of RDS (true phenotype for pre-addiction) and dopamine dysregulation seems to be the etiological root cause of not only addiction but putatively shared psychiatric disorders. It is further proposed that following GARS testing early and if positive for DNA dysregulation of the genes (resulting proteins) the utilization of the pro-dopamine regulator KB220 variant should be utilized to induce dopamine homeostasis. Original Blum and open access

Author Contribution and Acknowledgements

MAM AND KB developed the first draft which was approved and edited by each co-author.

Conflict of Interest

KB is the owner through his companies (Synaptamine Inc. and TranspliceGen Holdings Inc.) domestic and foreign patents related to GARS and KKB220.

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