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Review Article

Is It Scientifically Possible To 'Cure" Reward Deficiency Syndrome (RDS) Via Transplice Molecular Genetic Technology?

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Abstract

In 1995, Kenneth Blum coined the term "Reward Deficiency Syndrome'(RDS) to provide the mental health field with an umbrella term expressing a dissatisfaction of everyday experiences due to a dysregulation of dopaminergic dysregulation especially the DRD2 Taq A1 polymorphism presenting with up to a 40% reduction of D2 receptors in brain tissue with two copies. While the concept of RDS as the actual real umbrella of all mental illness unlike the current DSM-V (the brain is not carved out as portrayed by this important psychiatric manual) awaits further intensive research. In fact, Steven Hyman (former director of NIMH) suggests otherwise and has urged for research related to etiological causes instead to help explain the failings of mental health. Certainly, the RDS Consortium agrees with this difficult but needed psychiatric challenge. It is noteworthy that as of 2-5-2025, there are 1615 articles listed PUBMED using the word term "Reward Deficiency" and 270 listed for RDS specifically. However, since the initial finding of the first gene discovered to associate with severe alcoholism being the DRD2A1 allele by Blum and Noble and their associates, at least 700 or more genes have been found to be involved in RDS behaviors. While this seems quite complex in a study submitted for publication elsewhere deep silico GWAS meta-meta-analysis and pharmacogenomics mining has filtered the actual gene network down to 29 as a predictive panel of RDS behaviors. However, only 15 of these genes are linked into a network and five of these genes include DRD2, DRD4, OPRMI, COMT and 5-HTTLR. Understanding the relevance of a shared genetic basis for mental illness the RDS consortium is developing novel technology to scientifically "cure" RDS via gene editing technology (e.g. Transplice molecular genetic technology). Certainly, the jury is not in as yet, but we are encouraged about the future following arduous research from the scientific community requiring "all hands on deck".

Keywords: Reward Deficiency Syndrome (RDS); Dopamine Dysregulation; Genetic Testing; Gene Editing, Trans -Splicing Molecular Genetic Testing and Messenger RNA (mRNA)

Introduction

The term trans-splicing refers to platform technologies that merge two RNA or protein molecules to create a chimeric product. This process reprograms endogenous messenger RNA (mRNA) or precursor mRNA (pre-mRNA), transforming them into a new, functional gene product. The versatility of trans-splicing depends on the inserted sequences and their specific targets. Compared to conventional gene therapy, trans-splicing RNA therapy offers notable advantages, including endogenous regulation of trans-spliced sequences, minimized ectopic expression, smaller constructs replacing only specific gene portions, and the ability to convert dominant-negative mutations into wild-type gene products (Figure 1).

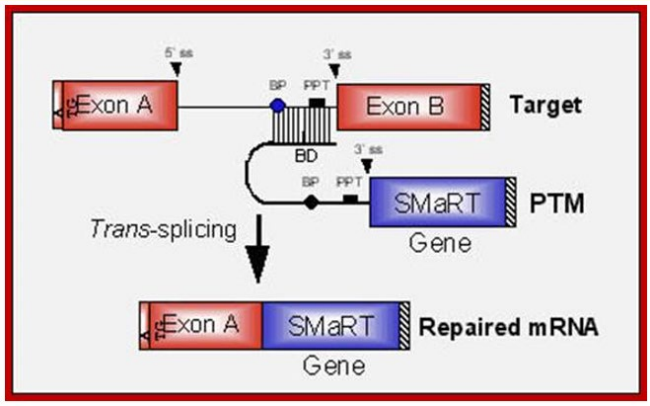

Figure 1: Schematic of Trans-splice molecular technology.

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To improve reader comprehension, we summarize key findings from the RDS Consortium's research. In a blinded study, we identified the first allelic association between the dopamine D2 receptor gene and alcoholism. Using 70 brain samples from alcoholics and nonalcoholics, DNA was digested with restriction endonucleases and analyzed with a probe containing the full 3' coding exon, the polyadenylation signal, and approximately 16.4

kilobases of noncoding 3' sequence of the human dopamine D2 receptor gene (lambda hD2G1). Within this dataset, the presence of the A1 allele correctly classified 77% of alcoholic subjects, while its absence classified 72% of nonalcoholics. These findings suggest that a genetic factor influencing susceptibility to certain types of alcoholism is located in the q22-q23 region of chromosome 11 [1].

Additionally, the relationship between the human D2 dopamine receptor gene and its binding properties was analyzed in 66 brains from alcoholic and nonalcoholic individuals. In a blinded study, DNA from the cerebral cortex was digested with the restriction enzyme Taq1 and hybridized with a 1.5-kilobase (kb) fragment of the human D2 dopamine receptor gene (lambda hD2G1). The receptor's binding characteristics, including Kd (binding affinity) and Bmax (number of binding sites), were measured in the caudate nucleus using tritiated spiperone as the ligand. Results showed that adjusted Kd values were significantly lower in alcoholics compared to nonalcoholics. The presence of the A1 allele, which was strongly associated with alcoholism, corresponded to a significantly reduced Bmax relative to individuals with the A2 allele. A progressive decrease in Bmax was observed across A2/A2, A1/A2, and A1/A1 genotypes, with A2/A2 carriers exhibiting the highest mean values and A1/A1 carriers the lowest. These findings suggest that variations in the D2 dopamine receptor gene and differences in receptor expression contribute to susceptibility for a specific subtype of severe alcoholism [2].

A subsequent study examined the role of the dopamine D2 receptor TaqA1 polymorphism in cocaine dependence. The objective was to assess the prevalence of D2 dopamine receptor (DRD2) alleles in male Caucasian (non-Hispanic) cocaine-dependent (CD) individuals and explore their relationship with family history and behavioral traits. Among CD subjects (n = 53), the A1 allele was present in 50.9%, a significantly higher frequency than in non-substance-abusing controls (16.0%, $P < 10^{-4}$) or general population controls (30.9%, $P < 10^{-2}$) that did not exclude substance abusers. Likewise, the B1 allele was more prevalent in CD individuals (38.5%) compared to non-substance-abusing controls (13.2%, $P < 10^{-2}$). Logistic regression analysis identified frequent cocaine use routes, early deviant behaviors, and parental alcoholism as significant risk factors linked to A1 allele presence. The cumulative impact of these three factors in CD subjects was positively correlated with A1 allele frequency ($P < 10^{-3}$). These findings strongly associate the minor alleles (A1 and B1) of DRD2 with cocaine dependence, suggesting a genetic susceptibility to this disorder on the q22-q23 region of chromosome 11 [3].

In 1995, one of us (KB) introduced the term "Reward Deficiency Syndrome" (RDS), first published in *Functional Neurology* [4]. The rationale for redefining addiction stemmed from the fragmented understanding of mental illness, which does not conform to the rigid classifications outlined in DSM-V. Instead of viewing psychiatric disorders as distinct entities, Blum proposed an overarching concept that encapsulates a spectrum of maladaptive behaviors linked to dysregulated reward processing. Initially, he debated whether the term should emphasize a deficiency or excess in reward function but ultimately chose "deficiency" due to its conceptual alignment with "Autoimmune Deficiency Syndrome (ADS)" [5].

Applying Bayesian theory, research indicated that individuals carrying the DRD2 A1 allele have a 74% probability of developing RDS-related behaviors in the future [5]. The dopamine D2 receptor plays a central role in the brain's reward system, and its dysfunction is associated with maladaptive substance-seeking behaviors, including alcohol, drug, tobacco, and food addiction, as well as conditions like pathological gambling, Tourette's syndrome, and ADHD. Given this evidence, we propose that genetic variants of the DRD2 dopamine receptor are key determinants of Reward Deficiency Syndrome and contribute to vulnerability across a broad spectrum of addictive and compulsive behaviors.

In 2014, Blum's team developed the Genetic Addiction Risk Severity (GARS) test, which holds both U.S. and international patents and was first published in *Molecular Neurobiology* [6]. Their extensive research on the neurogenetics of the brain's reward system has particularly focused on genes influencing dopaminergic function. They propose that early genetic testing could serve as a preventive measure to mitigate or even prevent maladaptive substance and behavioral addictions. By analyzing specific gene polymorphisms and their associated risks for Reward Deficiency Syndrome (RDS), Genome-Wide Association Studies (GWAS) suggest a convergence toward key reward-related candidate genes [7], reinforcing the potential for personalized interventions in addiction vulnerability.

Splice molecular technology [8-25] represents an advanced gene-editing approach that circumvents many of the challenges

associated with traditional gene therapy, DNA editing, and other RNA modification techniques for patient-specific therapeutics (Table 1). This method involves the optimization of RNA trans-splicing molecules (RTMs), which integrate into the natural splicing process of a targeted pre-messenger RNA (pre-mRNA). A single RTM can either correct or introduce therapeutic coding sequences into an edited mRNA by replacing specific exons or modifying a few to thousands of nucleotides. Since nearly all human genes require splicing for proper expression, this technique offers a broad potential for targeted gene editing. RTMs are typically delivered using viral vectors such as AAV or lentivirus for long-term gene correction but can also be used in transient editing applications to target and eliminate cancer or virally infected cells by interfering with the splicing of disease-associated genes (Table 1). For further insight into this groundbreaking technology, refer to figure 2.

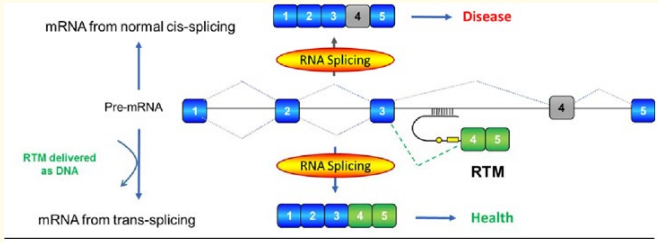

Figure 2: The trans-splicing technique.

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RNA Trans-splicing molecule (RTM) features

- **Delivery:** RTMs are usually delivered as DNA and expressed as RNA by any clinically relevant vector, including lentivirus or AAV for long-term therapeutic activity.
- **Mechanism of Action:** RTMs function at the RNA level. Each RTM contains a splice site that promotes an alternative splicing reaction in *trans*- with a partner splice site in the target pre-mRNA.
- **Specificity:** RTMs are activated upon base-pairing with a specific, complementary pre-mRNA target sequence. Determining the best sequence to target is critical for optimal specificity and efficiency.
- **Product:** The trans-spliced mRNA is reprogramed to express coding sequence carried by the RTM. Mutations in multiple exons can be corrected by a single RTM. Alternatively, one or more therapeutic genes can be inserted into cancer or viral transcript, or reporter genes can be specifically expressed for molecular or diagnostic imaging.

	RNA Trans-splicing	DNA Editors: CRISPR-Cas, etc		RNA Editors		
		Homology Directed Repair HDR	Non-Homologous End Joining NHEJ	CRISPR-Cas linked ADAR	Guide RNA linked ADAR	Activation of endogenous ADAR
Cell division required?	No	Yes	No	No	No	No
Small size of editor components?	Yes	No	No	No	No	Yes
Potential antigenicity of editing components?	No	Yes	Yes	Yes	No?	No
Number of different molecules needed for editing	1	3	2	2	1	1
Are off-target events permanent?	No	Yes	Yes	No	No	No

Convert disease-associated gene expression into a therapeutic?	Yes	Yes	No	No	No	No
Permanent gene correction. (*AAV or lentil-viral delivery)	Yes*	Yes	Yes	Yes*	No	No
Transient editing to image or kill cancer and viral infected cells?	Yes	No	No	No	No	No
# Of nucleotides efficiently edited.	> 4,000	< 2,000	Few	1	1	1
# Of products needed to correct all mutations in most genes.	2	2 or more	Can't correct most mutations	Many. Can't correct most mutations	Many. Can't correct most mutations	Many. Can't correct most mutations

Table 1: Advantages of RNA -Trans splicing Over other gene editing approaches.

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Conclusion

The presented evidence provides a plausible genetic framework that supports the development of targeted therapies aimed at enhancing recovery and preventing relapse on an individualized level. At the core of Reward Deficiency Syndrome (RDS) is a hypodopaminergic predisposition driven by both genetic factors and epigenetic modifications such as methylation and deacetylation affecting chromatin structure [26]. The field of addiction medicine has now evolved to incorporate neuroscience, recognizing RDS as a pathological disorder of the brain's reward circuitry that necessitates evidence-based interventions [27-29] and early genetic screening [29], requiring further extensive research.

The term "Reward Deficiency Syndrome" (RDS) was first introduced in 1995 to describe gene-linked behavioral traits associated with dopamine dysfunction**.** Since its inception, "Reward Deficiency" and "Reward Deficiency Syndrome" have been referenced in 1,615 and 270 scientific articles, respectively (as of March 1, 2025)**.** The concept of RDS has gained widespread recognition, appearing in numerous studies, medical dictionaries, book chapters, and scientific journals**.** Looking ahead, a fundamental question arises-can RDS, and perhaps all mental illnesses, be completely cured? While an ambitious goal, advancements in genetics and neuroscience suggest that this possibility may become reality before the end of the century.

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