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Hypothesizing Dopaminergic Genetic Antecedents in Schizophrenia and Substance Seeking Behavior

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Abstract

The dopamine system has been implicated in both substance use disorder (SUD) and schizophrenia. A recent meta- analysis suggests that *A1* allele of the *DRD2* gene imposes genetic risk for SUD, especially alcoholism and has been implicated in Reward Deficiency Syndrome (RDS). We hypothesize that dopamine D2 receptor (*DRD2*) gene *Taq1 A2* allele is associated with a subtype of non- SUD schizophrenics and as such may act as a putative protective agent against the development of addiction to alcohol or other drugs of abuse. Schizophrenics with SUD may be

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carriers of the DRD2 *Taq1 A1* allele, and/or other RDS reward polymorphisms and have hypodopaminergic reward function. One plausible mechanism for alcohol seeking in schizophrenics with SUD, based on previous research, may be a deficiency of gamma type endorphins that has been linked to schizophrenic type psychosis.. We also propose that alcohol seeking behavior in schizophrenics, may serve as a physiological self-healing process linked to the increased function of the gamma endorphins, thereby reducing abnormal dopaminergic activity at the nucleus accumbens (NAc). These hypotheses warrant further investigation and cautious interpretation. We, therefore, encourage research involving neuroimaging, genome wide association studies (GWAS), and epigenetic investigation into the relationship between neurogenetics and systems biology to unravel the role of dopamine in psychiatric illness and SUD.

Keywords

schizophrenia; substance related disorders; dopaminergic; reward deficiency syndrome (RDS); gamma –endorphins

INTRODUCTION

This hypothesis was developed in consideration of the extensive comorbidity of substance use disorder (SUD) and schizophrenia. The involvement of dopaminergic neurotransmission in the genetic antecedents of schizophrenia, as well as genetic vulnerability to RDS, is discussed. This exploration establishes the circumstances for the hypothesis that a deficiency of gamma type endorphins may trigger self-healing SUD in schizophrenia and that the *DRD2* gene *Taq1 A2* allele may be protective agent against the development of SUD.

A brief synopsis of the genetic antecedents of schizophrenia

Multiple genes interacting with multiple environmental factors influence many psychiatric conditions (behavioral phenotypes). Evidence suggests that schizophrenia is a complex genetic disorder involving “polygenic” inheritance (1). For example, genetic studies have sought to identify subtypes or endophenotypes for schizophrenia in an effort to improve reliability of diagnosis. A number of chromosomal regions have been shown to have replicated linkage and/or association to schizophrenia susceptibility. Many of the genes that are associated with psychiatric conditions code for the proteins involved in synaptic transmission. Genetic studies are complicated by, fuzzy diagnostic boundaries and the presence of phenocopies, for example, the symptoms produced by schizophrenia that are similar to some symptoms produced by drugs of abuse (2).

Studies have identified a number of candidate genes for schizophrenia. These genes include those that are responsible for development of the messocortical-limbic system. In this regard, genes that control GABA, glutamate and dopamine have shown promising possibilities in animal models of schizophrenia. Moreover, GABA neurons that co-express the calcium binding protein paravalbumin are associated with both glutamatergic metabotropic receptors and dopamine D3 receptors. Other interesting genes include: the gene for catechol -0-methyltransferase (*COMT*); the gene for neuroregulation that affects the expression and activation of neurotransmitter receptors including glutamate receptors; the

gene for dystrobrevin binding protein, with unknown function in the brain; a region of chromosome 13q14-q23 that contains the gene for the serotonin *5-HT-2A* receptor; a gene for the alpha 7 nicotinic cholinergic receptor subunit; a breakpoint in chromosome 1 affecting the genes *DISC1* and *DISC2* linked to both schizophrenia and affective disorders involved in neurite growth (3). The most promising gene regions include but are not limited: 22q12-q13, 8p22-p21, 6p24-p22, 13q14-q32, 5q22-q31, 10p15-p11, 6q21-q22, 15q13-q14, 9q34.3, 4q24-q32, 18 and 1q32-q41. While there is controversy concerning involvement of these gene regions there is emerging evidence of linkage to chromosome 11q and 14p (3). In this regard, the Cannabinoid CB1 receptor gene located at 6q14-q15 may be involved in gene expression during brain development. Hoenicka et al. has shown that the frequency of allele 4 of the cannabinoid receptor 1 (*CNR1*) gene microsatellite is significantly lower in schizophrenic patients when compared with healthy control individuals. Moreover, no differences have been found with respect to SUD in this schizophrenic population. These results suggest that independent of SUD differences in the cannabinoid system could impart vulnerability to schizophrenia (4).

Interestingly, schizophrenia is also associated with single nucleotide polymorphism of C957T *DRD2* gene (chromosome 11q). Specifically, in these patients the C homozygote genotype is overexpressed when compared with controls. It was therefore suggested that variation in the *DRD2* gene plays an important role in imparting vulnerability to schizophrenia (5). However, dopamine receptor involvement in hyper functioning of dopaminergic systems in schizophrenia remains controversial. While there are at least five ma in subtypes of dopamine receptors (D1 –D5), traditionally D2 receptors are considered most important. It was shown that clinical efficacy of antipsychotic drugs correlates with their ability to block D2 receptors (6). It was suggested that D2 receptor binding by antipsychotic agents may be “necessary and sufficient” for the anti-psychotic effect (7-16). Since there are few common polymorphisms with the coding region of the *DRD2* gene (15) we are not surprised that fewer studies of the *DRD2* and antipsychotic drug response have been conducted as compared to the 5-HT system. In recent years D3 and D4 receptors have also been implicated in development of schizophrenic symptoms (7-9).

Comorbidity of substance use disorder (SUD) and schizophrenia

Clinical and epidemiologic studies have found a high frequency of co-occurrence of SUD and psychiatric disorders. Psychiatric comorbidity in drug abusers is associated with greater severity of psychopathology, higher incidence of risky behaviors, higher psychosocial impairment and greater number of violent and criminal behaviors (17).

Since some psychotic symptoms caused by substances of abuse mimic schizophrenia it is difficult to identify phenotypes that are responsible for schizophrenia and not SUD (2,16). The prevalence of SUD is high in schizophrenia and the reason for this comorbidity is unclear. It was suggested that psychiatric patients use substances to cope up with anxiety and cognitive decline (18). Acute self-medication is pursued to ameliorate the symptoms associated with impaired processing of the mesocorticolimbic reward system defined as “Reward Deficiency Syndrome” (RDS) by Blum et al. (19).

Earlier work by van Ree and de Wied (20) provides an interesting hypothesis concerning the putative role of gamma-endorphin in schizophrenia and alternative pathways being involved both schizophrenia and SUD.

There is a high probability that genetic data supports the proposition that, overall schizophrenia vulnerability is distinct from SUD vulnerability. In fact, the truth may be that both co-exist with independent distinct polygenic polymorphisms. The dopamine system, however, has been implicated in both substance use disorder (SUD) and schizophrenia.

HYPOTHESIS

A deficiency of gamma type endorphins may be linked to a sustained increase in dopaminergic activity and consequently hallucinations as observed in Schizophrenia (20). We hypothesize that one plausible mechanism for alcohol seeking in schizophrenics with SUD, may be that it serves as a physiological self-healing process, linked to an increase in gamma endorphins known to reduced hallucination (20)[see figure 1].

We hypothesize that *DRD2* gene *Taq1 A2* allele is associated with a subtype of non- SUD schizophrenics and as such may serve as putative protective agent against the development of addiction to alcohol or other drugs of abuse (21). While schizophrenics with SUD may be carriers of the D2 receptor *Taq1 A1* allele, and/or other RDS reward polymorphisms and have hypodopaminergic reward function.

Reward deficiency syndrome (RDS) and genetic vulnerability

In 1996, Blum's laboratory initially described RDS to define the symptoms associated with a common polymorphism of the DRD2 gene (22,23). These symptoms include impulsive, compulsive and addictive behaviors (19). The *DRD2* gene has been associated with pleasure, referred to as a 'reward gene' (24). *Taq1 A1* allele of the *DRD2* gene has been widely studied in neuropsychiatric disorders and SUD (25) and associations with antisocial personality disorder (25), high novelty seeking behavior (27), and related traits (28) have been found.

The dopaminergic mesocorticolimbic pathway is important in mediating reinforcement of addiction and may be a feature of addictions and various psychiatric disorders (29-32). Drug-seeking behavior (31-32) is a form of RDS that results when certain genetic variants cause mesocorticolimbic dopamine reward system dysfunctions (19). This breakdown of the reward cascade, (33-41) due to specific genetic and environmental influences, (42) that result in aberrant conduct, is referred to as RDS. It is well known that abuse of psychoactive drugs including; alcohol, (43) as well as most positive reinforcers like sex, food, gambling and aggression activate the release of neuronal dopamine (44-56) which can satisfy abnormal cravings (46) and increase positive feelings (57). A deficiency of D2 receptor then predisposes individuals to multiple addictive, impulsive, and compulsive behaviors (58-60). Although other neuromodulators and neurotransmitters like glutamate, GABA, (61) serotonin (62) and enkephalin, (63) have a role in determining the rewarding and stimulating effects of drugs of addiction, dopamine may be essential for initiating and reinstating drug use after protracted abstinence (63,64-67).

Following the initial findings of a positive association of the *Taq1 A1* of the *DRD2* gene and severe alcoholism (24) there have been a plethora of studies both positive (26,28,30,33,57,65,67-91) and negative (92-105) [see reviews (25, 58, 78, 95,105-125)]. A number of studies have found that the *Taq1 A1* allele is associated with low dopamine D2 density in alcoholics (72,79,125,127). There are conflicting results regarding dopamine transporter (DAT) densities (128-132) among alcoholics, but subtypes were not considered (84,85).

The concept of the dopamine D2 receptor gene as a specific target for alcohol, was appropriately dismissed by, Blum et al. (24), who initially suggested, that they have found a non-specific “reward” gene (133). Moreover, the *DRD2 TaqA1* allele is also associated with sensitivity to stress and anxiety (83, 134-135) both symptoms have been related to sensitivity of presynaptic D2 receptors (110). The sensitivity is elevated in high anxiety subjects compared with low anxiety subjects. Other RDS and related neurological and psychiatric disorders are also found to be associated with polymorphisms of the *DRD2* gene, and is the subject of another article. However, we do provide a list of PUBMED articles especially SUD (see table 1) a known subset related to a number of psychiatric problems also associated with dopamine gene polymorphisms such as *DRD2* gene including borderline personality (4 studies), anxiety (101studies), panic attacks (10 studies), depression (187), conduct disorder (24), anti-social personality (7 studies), obsessive – compulsive disorder (38) amongst others.

Table 1. The number of Pub Med listed papers that associate various Substance Related Disorders and the *DRD2* gene polymorphisms as of January 26th 2014.

A major difficulty with associating the *DRD2 TaqA1* allele with alcoholism is that the *Taq1 A* polymorphism is located more than 10kb downstream from the coding region of the *DRD2* gene and a mutation at this site would not be expected to lead to any structural change in the dopamine receptor. The most likely explanation for an association is that the *Taq1 A* polymorphism is in linkage disequilibrium with an upstream regulatory element, or a 3′ flanking element, or another gene which confers susceptibility to RDS behaviors. Several linkage disequilibrium studies have found strong linkage disequilibrium between the *Taq1 A1* allele and the *Taq1 B* allele and the *SSCP 1* allele (53,70,88,134). As we have pointed out, the dopamine D2 receptor has been implicated extensively in relation to alcoholism, nicotine dependence, anxiety, memory, glucose control, pathological aggression, pathological gambling, and certain sexual behaviors -- all of these are RDS behaviors (24,135). The *Taq1 A* restriction fragment length polymorphism is the most frequently examined polymorphism linked to the *DRD2* gene and has been associated with a reduction in D2 receptor density. Neville and associates identified and named the “ankyrin repeat” gene, a kinase gene located in the 10kb downstream region of the *Taq1 A1* RFLP, and in a single serine/threonine kinase domain containing 1 (*ANKK1*), which is expressed at low levels in whole spinal cord RNA and placenta and is a protein one of the many involved in signal transduction pathways (136). *Taq1A* allele of the *DRD2* is a single nucleotide polymorphism (SNP) responsible for an amino acid substitution located within the 11th ankyrin repeat of *ANKK1* (p. Glu713lYs), which although it is unlikely to affect structural integrity, may effect substrate-binding specificity. If it does effect substrate-binding, then in

ANKK1 activity alterations may provide an alternative explanation for previously described (136) associations between the *DRD2* gene and RDS behaviors

Understanding the neural circuitry of rewards may provide a mechanism for understanding how positive reinforces motivate behavior (137). A positive reinforcer is operationally defined as an event that increases the probability of a subsequent response, and drugs of abuse are considered to be stronger positive reinforcers than natural reinforcers (e.g. food and sex) (138-140). The distinction between the primary or natural rewards like satisfaction of physiological drives like hunger and reproduction, and secondary or unnatural rewards is an important one. In fact, learned unnatural rewards like hedonic sensations (141) derived from alcohol and other drugs, as well as from gambling and other risk-taking behaviors are similarly important (138,142-143).

Specifically RDS refers to an insensitivity and inefficiency in the system that controls secondary (or unnatural) reward (19, 25, 58). The acquired need to escape or avoid negative affects created by repeated cycles of alcohol abuse (144) and dependence (145-151) is also encompassed by RDS and result in dopamine release. Dopamine is therefore associated with pleasure, and has been called anti-stress or pleasure molecule (31,32,83,152). The neural circuitry for positive reinforcement involves multiple brain regions and structures (201,153-158).includes the limbic system and the striatum (59). Functions of the limbic system include monitoring of internal homoeostasis, mediating emotional memory and learning, emotional processing (57,159) and processing of aspects of motivational behaviors including sexual behavior.

In disagreement with our initial hypothesis, a number of studies have found that the complex comorbidity of schizophrenia and SUD is also associated with high prevalence of *DRD2 A2* allele (17,158-161). If the dopamine receptor gene is not involved in this population of Schizophrenics with SUD then we propose that other multiple pathways that result in hypodopaminergic reward function must be considered as putative inducers of substance seeking behavior. These include polymorphisms in the dopamine D1 and D3 receptors, cannabinoid receptor, tryptophane hydroxylase, serotonin receptors, GABA receptors, opioid receptors, dopamine transporter, dopamine beta hydroxylase receptors, n-acetyltransferase, homer 2 genes, (3,162-175) that are associated with RDS.

Gamma type endorphins deficiency and increased dopaminergic activity

Processing pro-opiomelacortin (POMC) yields alpha, beta and gamma endorphins. Located predominantly in the pituitary, they are also found in neuronal pathways of the brain. Many studies have revealed that Gamma –endorphin has unique pharmacologic properties as compared to other endorphins (20). Certain effects of this compound are independent of the opioid peptide systems and receptors. In fact, removal of the N-terminal group of this substance eliminates opiate-like actions, and the resultant peptide (des-tyr)-gamma-endorphin (DTGE) resembles antipsychotic drugs in a number of tests. However, since this substance did not displace haloperidol from its binding site, it has been suggested that DTGE or a closely related peptide is an endogenous substance with anti-psychotic –like-action (176-177).

The endorphin (DTGE) and other gamma type endorphins function as antagonists of D2 and/or D3 receptors, which are present in the NAc, a terminal area of the mesolimbic dopaminergic pathway (178-179). It has been proposed that endogenous gamma type endorphins exert control over the dopamine system and that a chronic deficiency of these peptides, an RDS phenomenon, may lead to a sustained increase in dopaminergic activity as observed in Schizophrenia (179). Most interestingly, the postulate that, psychosis of the schizophrenic type may result from a deficiency of gamma-type endorphins (180) stimulated research on antipsychotic effects of these peptides (181-182).

Self-healing using alcohol in schizophrenics with SUD

It was reported that alcohol increases these peptides in the brain and may be in part a physiological reason to abuse alcohol by the schizophrenic patients to reduce psychosis. In animal studies Jackson et al. reported an attenuation of behavioral effects of ethanol by desenkephalin –gamma- endorphin (183-184). Alcohol abuse in a subtype of schizophrenics may be explained by this finding.

DRD2 gene *taq1 A2* allele may be protective against the development of SUD (alcohol) in schizophrenia

It is plausible that certain sub-populations of schizophrenics carry the *DRD2 A2* allele, and this might confer a protection against SUD since the DRD2 A1 allele, and not the *DRD2 A2* allele, has been associated with SUD and other addictive behaviors (18,185-193) Possibly, during embryonic development normal regulatory controls of dopaminergic activity are deficient (i.e. lack of DTGE) leading to an increased release of dopamine. Thus, we hypothesize that, there is an overexpression of the *DRD2 A2* allele. Noble et al. (72) pointed out that the number of D2 receptors is determined by the DRD2 genotype: A1/A1 = lowest number of D2 receptors; A1/A2 = moderate reduction of D2 receptors (one-third normal) and A2/A2 = highest number of D2 receptors. The overexpression of the *DRD2 A2* allele may be an adaptive mechanism necessary to balance hyperactivity of the dopamine system.

There are other examples of genomic adaptations that protect against alcoholism like. the inactive aldehyde dehydrogenase -2 gene (*ALDH2*), Individuals with at least one *ALDH2*2* allele have little to no ALDH2 activity (194-195). Owing to a high level of blood acetaldehyde after the ingestion of even small doses of alcohol, they exhibit the flushing response (196). This response is unpleasant enough to prevent people with the inactive *ALDH2*2* allele form from becoming alcoholic. Although this polymorphic *ALDH2*2* allele is found in ~50% of Chinese and Japanese, only 10% of Chinese and Japanese alcoholics possess this allele (197).

It is noteworthy that comparing DRD2 Taq1 A1 allele frequencies; Matsushita et al. (198) found the A1 allele more often in all subjects with *ALDH2*2* than in those without it, regardless of whether subjects were alcoholics or healthy controls. Moreover, because alcoholics with inactive *ALDH2*2* have overcome severe adverse reactions to develop alcoholism may be due to a genetic drive toward alcoholism. One such genetic trait may be the possession of the *DRD2 A1* allele.

Huang et al. (199) examined the relationship between *DRD2* gene and alcohol-metabolizing genes, alcohol (*ADH1B*) and aldehyde (*ALDH2*) dehydrogenase genes, in a specific subtype of alcoholics. Not only have these genes and associated polymorphisms been considered protective against alcoholism they are both involved in dopamine metabolism (200-201). As expected, the *DRD2 A1* allele was associated with anxious –depressive alcoholics (ANX/DEP ALC). Furthermore, the association between the *DRD2 A1* allele and ANX/DEP ALC was shown to be under control of both the *ADH1B* and *ALDH2* genotypes.

FUTURE PERSPECTIVES

In the future, we will begin to see many more genetic studies utilizing GWAS, EWAS and neuroimaging experiments that will shed light on the "true" relationship between SUD and other psychiatric conditions. Most interestingly, while there is a significant history of the role of opioid peptides (202) in specific neurons distributed throughout the nervous system (tel-di-mes – rhombencephalon and the spinal cord) little is known about the possible interaction of Gamma – endorphins and SUD. The last study we found on Gamma – endorphin and Schizophrenia was published in 2002 (203). We found a total of 812 articles listed in Pubmed on Gamma – endorphin (9-3-13). As far back as 1982, the neuropeptide des-1-tyrosine-gamma-endorphin (DTGE) was found to have similar behavioral effects in rodents as known drugs acting upon the CNS and it was hypothesized that this effect was due to the accelerating influence of DTGE on tyrosine hydroxylation in the striatal synaptosomes. It was suggested that the effect of DTGE on the brain dopamine biosynthesis might be involved in the development of antipsychotic effects (204). It is noteworthy that Des-tyrosine-gamma-endorphin [beta-endorphin-(2-17); DTG E] lacks direct in-vitro activity at dopaminergic receptors, but does inhibit in vivo [3H] spiperone binding in various rat brain areas an effect similar to beta-endorphin-(6-17) which is now considered a major metabolite of DTGE (205). Additionally, local administration of [Des-Tyr1]-gamma-endorphin (LPH62-77) but not alpha-endorphin (LPH61-76) in either the NAc or the neostriatum mimics the effect of anti-psychotics potentially through ACTH and dopaminergic mechanisms (206).

It is well known that schizophrenic patients are behaviorally supersensitive to dopamine-like drugs (amphetamine, methylphenidate). Accordingly, there is evidence for increased release of dopamine; a slight increase in dopamine D2 receptors and an increase of dopamine D2High receptors in these patients (207) which may explain this supersensitivity. Most interestingly, Seeman (207) pointed out that the elevation in apparent D2High receptors in schizophrenia matches the elevation in D2High receptors, in many animal models of psychosis. This could be due to a number of factors: the rate of phosphorylation and desensitization of D2 receptors by kinases; the attachment of arrestin to D2 receptors; internalization of D2 receptors; rate of receptor de-phosphorylation; formation of D2 receptor dimers; GTP regulation by various GTPases. Importantly and clinically relevant, haloperidol reduces the number of D2high receptors induced by psychostimulants. In terms of SUD, Blum et al. proposed a neurobiological and neurogenetic mechanism involving supersensitivity of *DRD2* (208).

The potential role of dopaminergic polymorphisms and psychiatric disease and SUD have been the subject of intense investigation (209-223) since the initial findings of Blum et al. on the *DRD2* gene and severe alcoholism (24). We have entered the new genomic era and as such true understanding of the role of gene polymorphisms in SUD and Schizophrenia will be unraveled, as researchers continue to investigate the effect of antipsychotics on brain function (224). One area that has not been evaluated concerning the role of gamma endorphin and vulnerability to schizophrenia is the brain genetics of this important neuropeptide. We are encouraging the scientific community to heretofore initiate genotyping of associated polymorphisms of gamma-endorphin regulatory genes (synthesis, synaptic release; catabolism etc.) to determine schizophrenia susceptibility in large case control studies.

SUMMARY

Both SUD and schizophrenia are complex “polygenic” disorders involving the dopamine system. It was shown that A1 allele of *DRD2* gene is a genetic risk for SUD (especially alcoholism) but not for carriers of the *DRD2 A2* allele. We hypothesize that a plausible mechanism for alcohol seeking behavior in schizophrenics, carriers of the Taq1 A1 allele, could be a deficiency of gamma type endorphins. This deficiency could be the mechanism of aberrant hyperdopaminergic activity. We further propose that alcohol consumption in schizophrenics, may serve as a physiological self–healing process linked to the increase function of the gamma–type endorphins that consequently, reduced dopaminergic activity at the NAc. We suggested that there may be an overexpression of the *DRD2 Taq1 A2* allele, an adaptive mechanism necessary to balance hyperactivity of the dopamine system, due to a lack of DTGE during embryonic development. Further, we hypothesize that in carriers of the *DRD2* gene *Taq1 A2* allele is associated with a subtype of non-SUD schizophrenics and as such this allele may serve as putative protective agent against the development of addiction to alcohol or other substances. These hypotheses support the proposition that within the dopamine system vulnerability to SUD and schizophrenia may result from two distinct sets of genetic associations that may be studied in sub-populations of schizophrenics and warrant further investigation and cautious interpretation.

We encourage research involving neuroimaging, genome wide association studies (GWAS), and epigenetic investigation into the relationship between neurogenetics and systems biology to unravel the role of dopamine in psychiatric illness and SUD.

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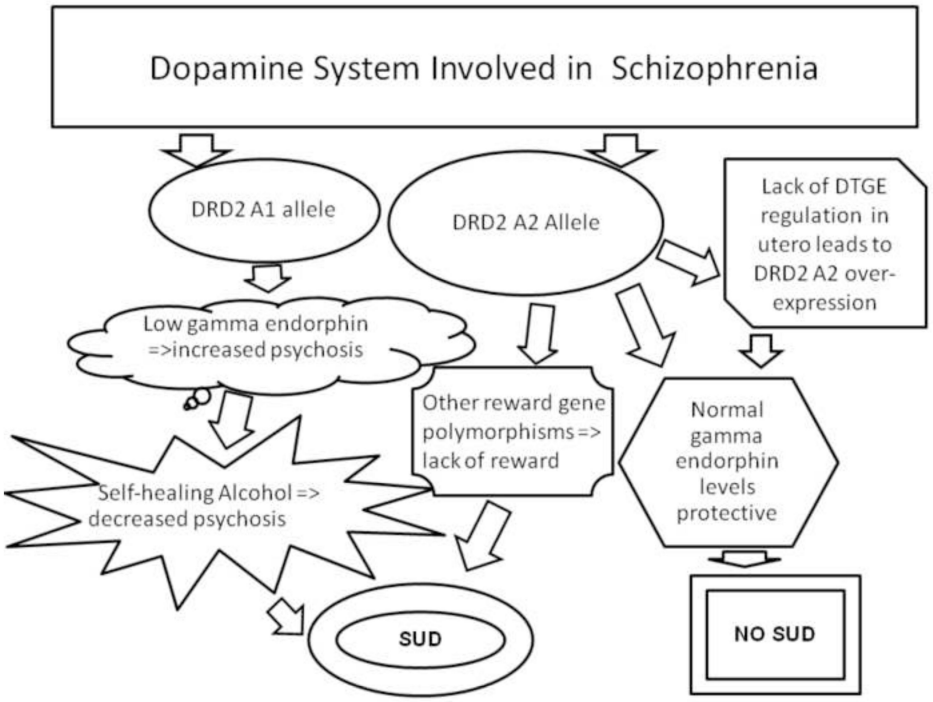

Figure 1. Dopamine and opioid peptide interaction in Schizophrenia and alcoholism

Left side: Carrying the *DRD2 A1* increases the "wanting" of alcohol and in carriers with a low gamma endorphin (DTGE) would augment the risk for psychosis leading them to increased self medication by using alcohol. Right side: Carrying the *DRD2 A2* may be protective against alcohol drinking in Schizophrenics. Lack of Gamma Endorphin (DTGE) in utero leads to an over-expression of *DRD2 A2*. Center: However, some Schizophrenics with the *DRD2 A2* allele along with unknown reward gene polymorphisms may use substances due to lack of reward.

Table 1

The number of Pub Med listed papers that associate various Substance Related Disorders and the DRD2 gene polymorphisms (1-26-14)

Substances	Pub Med Listed
Alcohol	346
Caffeine	20
Hallucinogens	13
Inhalants	0
Opioids	51
Sedatives/Hypnotics	16
Stimulants	177
Tobacco/Nicotine	131
Glucose	35