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Review Article

Polymorphisms in genes encoding dopamine signalling pathway and risk of alcohol dependence: a systematic review

Bhaskar LVKS, Arun Kumar S. Polymorphisms in genes encoding dopamine signalling pathway and risk of alcohol dependence: a systematic review

Background: Alcohol dependence (AD) is one of the major elements that significantly influence drinking pattern that provoke the alcohol-induced organ damage. The structural and neurophysiologic abnormalities in the frontal lobes of chronic alcoholics were revealed by magnetic resonance imaging scans. It is well known that candidate genes involved in dopaminergic pathway are of immense interest to the researchers engaged in a wide range of addictive disorders. Dopaminergic pathway gene polymorphisms are being extensively studied with respect to addictive and behavioral disorders.
Methods: From the broad literature available, the current review summarizes the specific polymorphisms of dopaminergic genes that play a role in alcohol dependence.
Results: No evidence indicating any strong association between AD and polymorphisms of dopamine pathway genes has emerged from the literature.
Discussion: Further studies are warranted, considering a range of alcohol-related traits to determine the genes that influence alcohol dependence.

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Summations

- Dopamine is a chemical produced by the brain that acts as a neurotransmitter.
- Alcohol consumption increases dopamine release in the nucleus accumbens from ventral tegmental neurons.
- Alcohol activates dopamine system and contributes to an individual's susceptibility to alcohol dependence by damaging the key components of the 'brain reward system'.

Considerations

- Alcohol dependence is a result of interaction between environmental and genetic factors altering multiple brain pathways.
- Several studies have also linked alcohol dependence to polymorphisms in certain genes that are exclusively involved in the dopamine pathway.

Introduction

Alcohol dependence is one of the major elements that significantly influence drinking pattern that provokes the alcohol-induced organ damage. Alcohol dependence is a complex and multi-factorial disorder arising from interactions between genetic and environmental risk factors (1). There are several independent lines of evidence for genetic contributions to vulnerability to alcohol dependence (2). Alcohol dependence leads to the development of an array of undesirable physical, mental, and social effects.

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Although the prevalence of alcohol dependence differs significantly between cultures, as well as between the two sexes within the same culture, the vulnerability to alcohol dependence corresponds partly to interindividual differences in pharmacokinetics and the pharmacodynamic response to alcohol (3). Our knowledge about alcohol's actions in the brain is very little. Unlike other drugs such as cocaine, marijuana, and heroin that interact with specific cellular proteins, alcohol is a relatively simple compound that has the potential to interact with many such proteins in the brain and show broad biological and pharmacological actions (4). The susceptibility to alcohol dependence among individuals is mainly attributed to the variations in genes that encode these proteins.

Evidence for genetic influences on alcohol dependence

Evidence from twin, adoption and family studies show that alcohol dependence is genetically influenced, with a heritability of 50–60% (5). Using standard alcohol dependence diagnostic criteria in both male and female twins, the Australian twin registry found a consistent heritability of 64% (6). By considering the intersection samples between the Swedish twin registry and Swedish temperance board registrations, the calculated prevalence was similar in monozygotic (MZ) and dizygotic (DZ) twins, but the concordance rate for such registration was significantly higher in MZ twins (5). As alcohol dependence co-occurs with other externalising disorders such as conduct disorder, antisocial personality disorder, and drug dependence, this common liability showed a heritability of 80% (7). Hence, alcohol dependence shares genetic vulnerability with nicotine dependence and the genes that influence risk for nicotine dependence may also increase risk for alcohol dependence and vice versa (8).

Dopaminergic reward system

Mesolimbic dopamine has been shown to play a crucial role in mediating the reinforcing effects of alcohol. Dopaminergic neurons are present chiefly in the ventral tegmental area (VTA) of the midbrain and projected into the nucleus accumbens in the ventral striatum, and also innervate the amygdala, bed nucleus of stria terminalis (BNST), lateral septal area, and lateral hypothalamus. The VTA is in close proximity to the substantia nigra, another dopamine rich nucleus. VTA dopaminergic projections also influence the prefrontal cortex. In turn, the prefrontal cortex can provide feedback to the VTA either directly or through the nucleus accumbens. Magnetic resonance imaging scans revealed structural and neurophysiological abnormalities in the frontal lobes of chronic alcoholics (9). Alcohol may inhibit the action of enzyme monoamine oxidase, which is responsible for the breakdown of dopamine in the synaptic cleft (10). As the dopamine is not efficiently brokendown, its action persists on the post-synaptic neuron for a longer period than usual and exhibits increased pleasure. Individuals desire to continue to experience the pleasure caused by dopamine, and therefore continue to drink alcohol and finally become addicts. Furthermore, addiction to alcohol may alter the regular production of dopamine, and hence discontinuation of alcohol consumption after addiction may trigger withdrawal symptoms (11). As dopamine is considered as a pleasure molecule, any reduction in its levels leads to reward deficiency, which results in aberrant substance-seeking behaviour (12). It is well established that the synthesis, storage, and catabolism of dopamine is under the tight genetic control. These candidate genes involved in dopaminergic pathway are of immense interest to the researchers engaged in the study of a wide range of addictive disorders.

Dopaminergic system candidate genes

In brief, the dopaminergic pathway includes dopamine synthesis, release, receptor activation, re-uptake and catabolism. Various candidate genes involved in dopaminergic neurotransmission have been characterised and they have identified polymorphisms, including those for tyrosine hydroxylase (*TH*), dopamine transporter (*DAT1* or *SLC6A3*), dopamine receptors (*DRD1-DRD5*), dopamine β-hydroxylase (*DBH*), sulfotransferase 1A3 (*SULT1A3*) catechol-*O*-methyltransferase (*COMT*), and monoamine oxidase A and B (*MAOA* and *MAOB*) (Fig. 1). The simple molecule, dopamine, has been at the centre of interest for both the scientists and the clinicians alike for many years, as it is associated with a number of diseases such as Parkinson's disease, schizophrenia, psychoses, drug abuse, hyperprolactinemia, and reproductive disturbances. From the broad literature, this review summarises specific polymorphisms of dopaminergic genes that are involved in alcohol dependence.

Dopamine synthesis

The initial step involves hydroxylation of tyrosine to dihydroxyphenylalanine (DOPA), catalysed by the enzyme TH. Once formed, DOPA is rapidly decarboxylated to dopamine by aromatic L-amino-acid decarboxylase. Through the entire pathway,

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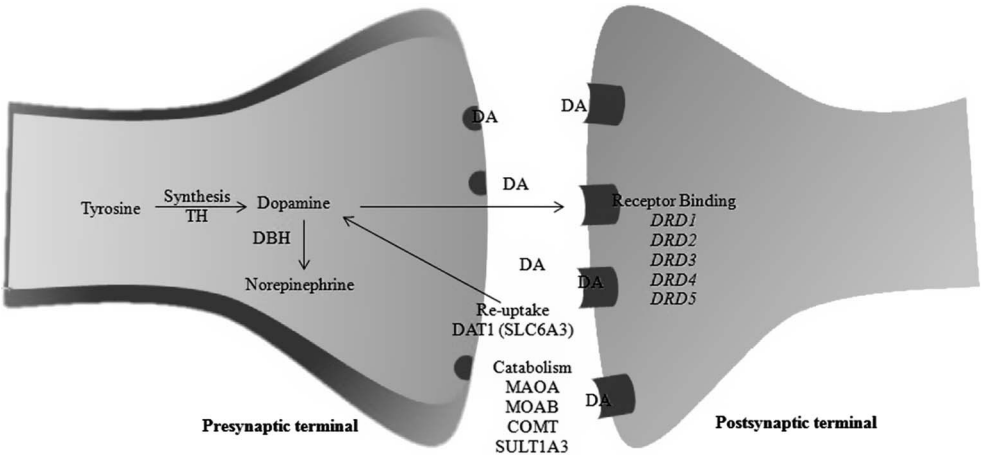


Fig. 1. Schematic representation of dopamine synthesis and breakdown pathways. DA, dopamine; TH, tyrosine hydroxylase; DBH, dopamine β-hydroxylase; DAT, dopamine transporter; MAOA, monoaminoxidase type A; MAOB, monoaminoxidase type B; COMT, catechol-*O*-methyltransferase; SULT1A3, sulfotransferase 1A3; DRD1–DRD5, dopamine receptor D1–D5.

tyrosine hydroxylation is a rate limiting reaction and thus controls the rate of dopamine synthesis (13). Human *TH* cDNA encompasses 1921 bp coding for a protein of 528 amino acids and a molecular mass of 58.5 kDa. The human *TH* gene consists of 14 exons and various isoforms resulting from alternative splicing of pre-mRNA (14). *TH* is mainly expressed in brain and adrenal gland. A penta-allelic tetranucleotide $(TCAT)_n$ repeat polymorphism of the first intron and three other non-synonymous SNPs (Val81Met, Leu205Pro, and Val468Met) are known to alter the functional activity of TH protein (15). Tetranucleotide repeat polymorphism exhibits five different alleles known as K1, K2, K3, K4, and K5 with a size of 260, 256, 252, 248, and 244 bp, respectively (16). The presence of atleast one copy of the K1 allele had shown reduced homovanillic acid (HVA) levels in the cerebrospinal fluid of healthy individuals (13). Furthermore, allelic variations of the tetranucleotide repeats were found to be involved in quantitative and qualitative changes in the binding ZNF191, a zinc finger protein, and these repeats may regulate transcription (17).

Analysis of penta-allelic polymorphism at the *TH* gene in Scandinavian chronic alcoholics and control subjects did not show any significant association with alcohol dependence (18). Systematic screening of all the exons, the exon–intron boundaries, and the 5' promoter region of the *TH* gene in Japanese also failed to indicate a positive association between *TH* gene and alcohol dependence (19). In a small proportion of alcohol-dependent Germans subjects, the rare allele containing 10-repeats (A10) of a polymorphic tetranucleotide motif mediated the vulnerability to alcohol withdrawal delirium (20).

Dopamine receptors

In the central nervous system (CNS) of vertebrates, dopamine receptors are a class of metabotropic G protein-coupled receptors that play a key role in controlling motivation, learning, and fine motor movement. For dopamine receptors, the neurotransmitter dopamine is the primary endogenous ligand. Five subtypes of dopamine receptor have been so far identified and cloned. The D1 and D5 receptors are closely related; coupled with Gs alpha, they stimulate adenylyl cyclase activity. In contrast, the D2, D3, and D4 receptors couple with Gi alpha and inhibit the formation of cAMP. Impaired dopaminergic neurotransmission in CNS has been implicated in multiple neuropsychiatric disorders. Polymorphisms of each of the dopamine receptor genes (*DRD1*, *DRD2*, *DRD3*, *DRD4*, and *DRD5*) have been identified and examined in association studies of various conditions influenced by dopaminergic neurotransmission.

DRD1

The gene coding for DRD1 is located at chromosome 5q35.1 and contains two exons separated by a small intron in the 5'-untranslated region (UTR). Four polymorphic sites of *DRD1* were initially identified by single-strand conformational analysis (SSCA). The *Dde*I polymorphism is an A–G transition in the 5'-UTR (A-48G), one of the four polymorphisms initially identified by SSCA of *DRD1* (21). The other three are *Bst*N1 (G-94A) in the 5'-UTR, rare and synonymous *Pvu*I (G1263A) for codon 421, and *Bsp*1286I (T1403C; rs686) in the 3'-UTR. Although several other polymorphisms around *DRD1* were identified later, one resulted in a change of an

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amino-acid residue. Systematic screening of the 5'-flanking regulatory region of *DRD1* gene did not reveal any polymorphism that influenced the transcriptional activity (22). By using an *in vitro* reporter assay, a recent study demonstrated that the allele variants of polymorphism rs686, located in 3'-UTR of DRD1, produced different expression levels of the chimeric luciferase gene, indicating rs686 to be a functional polymorphism that affected the expression of *DRD1* (23). A population-based association study failed to show any association between *Bsp*1286I RFLP of the *DRD1* gene and alcohol dependence (24). Alcoholics did not exhibit any significant difference in apomorphine-induced growth hormone release among different genotypes and treatment responses between different alleles of the *Bsp*1286I RFLP at the *DRD1* locus (25). In a relatively homogenous genetic population of male Finns, no association was found between alcohol dependence and the D1 receptor gene *Eco*RI restriction fragment length polymorphism alleles (26). The non-polymorphic structure of the *DRD1* gene among the Tourette's syndrome and the alcohol-dependent populations suggests that coding region mutations of the DRD1 gene are unlikely to contribute to the inheritance of these disorders (27). Analysis of *DRD1 Dde*I genotypes and the Zuckerman scores, exhibited a significant association only in men, indicating a male-limited association between the *DRD1* gene polymorphism and sensation-seeking score in alcohol-dependent subjects (28). The same polymorphism has not shown any significant association in both the male and the female subjects analysed (29). Furthermore, this polymorphism has shown a significant association with severity and temperament of alcohol dependence in Koreans (30). Analysis of *DRD1* gene rs686 and rs4532 polymorphisms revealed that the rs686T allele and rs686*T-rs4532*G haplotype was more precisely associated with alcohol dependence (31).

DRD2

Animal and human studies on addiction indicate the critical role played by the D2 dopamine receptor (DRD2) in the mechanism of reward and reinforcement behaviour. Any genetic polymorphism that affects the expression of D2 dopamine receptors may be a possible candidate for susceptibility to alcohol dependence (32). The *DRD2* gene is localised on human chromosome 11 at q22–q23, extends over 270 kb, and has eight exons (33). This transmembrane receptor is a member of the rhodopsin family. To date, the D2 dopamine receptor (*DRD2*) gene has been among the stronger candidate genes implicated in alcohol dependence and other substance-use disorders. A search for functional variants in the coding region (exons 2–8) of *DRD2* has identified three infrequent variants that altered the amino-acid sequence of the receptor (Ser311Cys, Val96Ala, and Pro310Ser) (34,35). Two polymorphisms were identified, one in the promoter region where the *DRD2* gene was further identified as deletion allele −141C Ins/Del, by *in vitro* functional assays (36). Furthermore, the intronic region of the *DRD2* contained three restriction-site polymorphisms (RSPs), *Taq*IA, *Taq*IB, and *Taq*ID, and two dinucleotide short tandem repeat polymorphisms (STRPs), CA, and CT repeats (37,38).

The bulk of research published to date has used the *Taq*1 allele system, Ser311Cys polymorphism, and −141C Ins/Del polymorphism. The 'A1' allele of *Taq*1A in *DRD2* gene has been associated with alcohol dependence (39). Since then, several studies have been published and an increase of 'A1' frequency in alcoholics has been reported in more severe forms of alcohol dependence (40). Eriksson et al. (41) reported that alcoholics with 'A1' allele have low-platelet monoamino oxidase-B activity than those with A2 allele. The 'A1' allele is associated with high-dopamine transporter density in detoxified alcoholics (42). Moreover, it should be noted that this variant of the *DRD2* gene has functional significance, as subjects carrying the *DRD2 Taq*1 'A1' allele had a significantly decreased dopamine D2 receptor B_{max} in the basal ganglia (43). Eriksson et al. (41) reported that alcoholics with the A allele have lower platelet monoamino oxidase-B activity than those with the 'A2' allele. The 'A1' allele is associated with high-dopamine transporter density in detoxified alcoholics (44). The association between *DRD2 Taq*IA allelic variation and the alcohol dependence remains controversial (8). In fact, *DRD2 Taq*IA polymorphism is not located in the *DRD2* gene, but rather within a protein-coding region, of the adjacent ANKK1 gene that is located downstream of *DRD2* gene (45).

DRD3

DRD3 is localised in limbic and cortical brain areas and probably affects locomotion as well as emotional and cognitive processes (46). The gene encoding *DRD3* was mapped to chromosome 3q13.3 and its polymorphic site in exon 1 with a serine 9 to glycine substitution has been postulated as a useful investigating tool in psychiatric disorder (47). Multiple studies have also been conducted to assess the role of the Ser9Gly polymorphism in alcohol dependence (24,48–52). This supported possible involvement of the *DRD3* gene polymorphism in the development of addiction to alcohol.

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DRD4

The human D4 receptor gene has been localised to chromosome 11 (11q15.5). The third exon of *DRD4* contains an unusually polymorphical 48 bp variable number of tandem repeats (VNTR) (16 amino acids), and physiologic differences in ligand binding have been observed between the short (two to five repeats; four repeats is most common) and long (6–10 repeats; seven repeats is most common) forms of this repeat. The short alleles (two to five VNTR) frequencies showed significant differences between controls and alcoholics with delirium tremens (DT) or alcohol seizures. Furthermore, higher frequency of short alleles among individuals with an early age of onset of alcohol dependence was observed (53). A recent study has demonstrated the genotypes without the seven-repeat allele to be the risk factors for alcohol dependence in Mexican Americans (54). Other expressed polymorphisms in *DRD4* have also been known to occur, some of which have been examined in association studies, including a 12 bp duplication polymorphism and a 13 bp deletion, both located in exon 1 (55). Analysis of dopamine D4 receptor gene (*DRD4*) using six polymorphisms, both separately and as haplotypes in Taiwanese populations did not show any association with alcohol dependence (56).

DRD5

The human D5 receptor gene has been localised to chromosome 4 (4p15.1–p15.3). A common, silent polymorphism (Pro-326) has been reported (57). Five polymorphisms coding for amino acid changes have recently been identified for the D5 receptor; one of these, a rare nonsense change predicted to result in a 50% diminution of functional protein (58). A polymorphic dinucleotide repeat in the *DRD5* promoter has also been identified, but is not believed to be of functional significance (59). A few of *DRD5* gene polymorphisms were identified at Leu88Phe, Ala269Val, Pro330Gln, Asn351Asp, Ser453Cys, and Cys335Stop, which altered the protein configuration by amino-acid substitutions. The two amino-acid substitutions in the transmembrane domains had an effect on agonist binding to the human D5 dopamine receptor. Leu88Phe resulted in a small increase in dopamine-binding affinity. Asn351Asp resulted in an ~10-fold decrease in dopamine and threefold decrease in R(+)-SKF-38393 binding affinities (60). However, no study has been conducted to ensure the association of these polymorphisms with alcohol dependence.

Dopamine reuptake

Dopamine transporter (*DAT1*) mediates the active re-uptake of DA from the synapses and recycles DA back into the presynaptic terminal, thus terminating synaptic firing (61,62). The gene encoding *DAT1* (gene symbol SLC6A3) consists of 15 exons spanning 60 kb on chromosome 5p15.32 [MIM*126455] (63). A polymorphic 40 bp VNTR with repeats ranging from three to 13 copies was observed in the 3' untranslated region of the *DAT* gene (63). The functional effects of different *DAT* VNTR genotypes investigated intensely in experimental settings yielded conflicting results. Individuals with 10/10 genotype exhibited a 13% decrease in the efficiency of binding to the transporter (64). However, the *in vitro* and *in situ* studies showed that the nine-repeat sequence can enhance transcription (65). Furthermore, 10-repeat allele exhibited increased gene expression compared with the seven or nine-repeat alleles (66). In contrast, nine-repeat allele showed increased transcription relative to the 10-copy allele (67). Population differences in the *DAT1* allele frequency distribution patterns have been described (68).

DAT1 VNTR allele and genotype frequencies did not show significant differences between alcoholics and control subjects in five different ethnic groups of Taiwan (69). A population-based association study showed increased number of allele A of *DAT1* G2319A in homozygous carriers of the 10-repeat allele of *DAT1* with severe alcohol withdrawal symptoms (AWS) and DT in Germans (70). Several studies showed that an increased number of nine-repeat allele in alcoholics with either DT or AWS compared with healthy controls (71,72). Furthermore, nine-repeat allele is associated with sex-specific vulnerability to serious alcohol-related problems and its withdrawal complications in alcoholics (73,74). However, in western Europeans, the allele nine-repeat allele is strongly associated with alcohol dependence but not with withdrawal symptoms or daily alcohol intake (75). In contrast, no association between *DAT* VNTR and alcohol dependence was observed in a series of studies (76–79). The A9 allele of the *DAT1* VNTR was significantly associated with alcohol dependence in Badaga population but not in Kota population of India, which indicated that these associations are population specific (80).

Dopamine catabolism

In all primates the major end product of dopamine metabolism is HVA. Enzymes responsible for metabolism of dopamine to HVA are COMT, MAOA, and MAOB. An alternative metabolic pathway for dopamine leads to the formation of norepinephrine; the dopamine β-hydroxylase (DBH) enzyme catalyses this conversion. Furthermore, a supergene family of enzymes called sulfotransferases

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(SULTs) is involved in the catabolism of dopamine. Human SULT1A3 has been shown to be the major sulfotransferase that sulfonates dopamine.

COMT

COMT is one of the enzymes involved in the degradation of dopamine, norepinephrine, and epinephrine via a transmethylation reaction using *S*-adenosyl-methionine as coenzyme, and it exists in a soluble and membrane-bound form (81). The gene encoding COMT protein is located on chromosome 22q11.21–q11.23 (82). In humans, the *COMT* gene consists of six exons that encode 1.3 and 1.5 kb transcripts [membrane bound (MB) and soluble (S) *COMT*] (83). A common G–A transition in the fourth exon of the *COMT* gene (rs4680), results in a valine to methionine substitution at codon 158 of the MB form (Val108Met in the S form) (84). The allele encoding methionine is associated with low enzyme activity and thermolability compared with the valine allele (84), and exhibits tissue-specific expression (85). This polymorphism did not show any significant difference in the allelic distributions in Japanese alcoholics and controls indicating that the *COMT* gene is unlikely to play a significant role in alcohol dependence (86). Analysis of 5 *COMT* loci including Val158Met in community-ascertained American Indians showed that both male and female alcoholics were more likely to have at least one Val158 allele compared with non-alcoholics (87). High-activity COMT allele is associated with alcohol dependence in the Czech male but not in female population indicating the sex-specific differences in the influence of COMT Val158Met on alcohol dependence (88). Family-based and case–control study-based analysis using 100 Polish families with alcohol dependence and 196 ethnically and gender matched healthy controls failed to show statistically significant differences in allele transmission or association between *COMT* Val158met and alcohol dependence (89). Analysis of 18 SNPs in 219 multiplex alcohol-dependent families of European American descent from the Collaborative Study on the Genetics of Alcoholism did not support the association between alcohol dependence and variations in *COMT* (90). Analysis of *COMT* Val158Met in 122 alcoholics and 150 controls of polish origin did not show significant association with alcohol dependence when the whole group of alcoholics and the controls were compared. Similarly, there were no differences between either the Lesch type I or type II alcoholics and the control subjects (77). Gene polymorphisms in several genes that tested as predictors of relapse revealed that the met allele of the *COMT* Val158Met polymorphism is more likely to relapse than in patients without this allele (91). Screening of *COMT* Val158Met in 395 male alcoholics, and 326 healthy male controls of Russians showed that the frequency of Met allele was significantly higher in alcoholics with positive family history compared with the controls suggesting that the functional Val158Met *COMT* polymorphism is one of the significant markers of genetic predisposition to alcohol dependence (92).

MAOA and MAOB

Two different forms of monoamine oxidases, known as MAOA and MAOB, are found bound to the outer membrane of mitochondria in most cell types in the body. These two forms differ slightly in their localisation and their ability to metabolise dopamine and related biogenic amines. The genes encoding MAO-A and MAO-B are located side-by-side on the short arm of the X chromosome (Xp11.3). *MAOA* and *MAOB* genes span at least 60 kb, consist of 15 exons, and exhibit identical exon–intron organisation. Exon 12 codes for the covalent FAD-binding site, and it is the most conserved exon and has about 70% sequence similarity (93). Lower-platelet monoamine oxidase (MAO) activity has been associated with alcohol dependence (94,95). However, the finding of low-platelet MAO activity in alcoholics has not been consistently replicated (96,97). With regard to MAO-B activity changes during the withdrawal period, previous studies have yielded equivocal results. Some studies showed a transitory increase in platelet MAO activity during withdrawal (98,99), whereas others showed a decrease (100,101). However, platelet MAO activity in recovered alcoholics after long-term abstinence is not significantly different from that of the controls (102).

Several lines of evidence suggest that the MAO enzyme activity is under genetic control of a single major locus (103). The *MAOA* gene presents a 30-bp VNTR in the promoter region with different repeat sizes (3, 3.5, 4, or 5 copies) and is in linkage disequilibrium with other *MAOA* and *MAOB* polymorphisms. This polymorphism selectively influences the protein transcription and alters the enzymatic activity (104). Alleles with 3.5 or 4 copies of the repeat sequence are transcribed 2–10 times more efficiently (*MAOA* high) than those with three or five copies of the repeat (*MAOA* low), suggesting an optimal length for the regulatory region (105). A dinucleotide repeat polymorphism in intron 2 (MAO-A CA repeat) is in linkage disequilibrium with a regulatory VNTR (106). There are two groups of CA repeats in the *MAOA* gene (short with one to three repeats; long with four to eight repeats) (107).

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Association of the *MAOA* dinucleotide repeat length polymorphism with alcohol dependence has now been demonstrated in Euro-Americans (108,109) and Han Chinese (110). In Caucasians the low-activity three-repeat alleles of the VNTR polymorphism were significantly high in antisocial alcoholics compared with control subjects (111). In Brazilians, the functional VNTR polymorphism is associated with female subjects but not the male subjects; the genotype containing at least one three-repeat allele was significantly more frequent among alcoholics than controls (112). Among the Swedish students, girls with long *MAOA* u-VNTR variant showed a higher risk of alcohol consumption. On the contrary boys with short allele were related to higher alcohol consumption suggesting sex difference in the G × E interaction (113).

The *MAOB* gene harbours a polymorphic repeat region in the intron 13, and includes a transition (A–G) polymorphism, but it is not associated with the MAO-B enzyme activity in platelets (114). Individuals with A-allele in intron 13 showed lower MAO-B enzyme activity in blood (115). Conversely, the G allele is linked to lower enzyme activity in postmortem human brains (116). *MAOB* dinucleotide repeat length polymorphism did not show any significant association with alcohol dependence in five different ethnic groups in Taiwan (110). In Americans, a *MAOB* haplotype has shown significant association with alcohol dependence independently from antisocial personality disorder (117). In contrast, the Monoamine oxidase-B polymorphism (*MAOB*-A/G) failed to reveal any association with alcohol dependence in Croatians (118).

DBH

Dopamine β-hydroxylase is present in the synaptic vesicles of postganglionic sympathetic neurons and catalyses the oxidative hydroxylation of dopamine to norepinephrine (119). DBH is a 290 kDa copper-containing oxygenase consisting of four identical subunits, and its activity requires ascorbate as a cofactor (120). The gene coding for DBH is localised to 9q34. The DBH gene, ~23 kb in length, is composed of 12 exons (121). Several mutations in the *DBH* gene have been found to reduce dopamine β-hydroxylase activity. A 'C' to 'T' polymorphism at nucleotide −1021 in the five-prime region of the *DBH* gene was related to dopamine β-hydroxylase activity levels in plasma accounting for 35–52% of the variation in plasma DBH activity in several ethnically different populations (122,123). The IVS1 + 2T > C is a T-to-C transition in the donor splice site of exon 1 of the *DBH* gene and is found to be in linkage disequilibrium with −1021C-T polymorphism thereby interfering with the normal processing of dopamine β-hydroxylase (119). Analysis of unrelated adults of African American, European American, and German origin and African American mothers and infants revealed the frequency of the IVS1 + 2T > C (124). This splice site mutation was also observed as a compound heterozygote along with two coding mutations such as Val87Met and Asp100Glu (119).

After hospitalisation, mean serum DBH levels in alcoholics were not statistically significant when compared with control groups, indicating that serum DBH activity is not an important parameter to screen alcohol susceptibility (125). The plasma DBH activity levels among nonalcoholic young men with or without family history demonstrated a 20% lower level of DBH in men with positive family history; however, a statistical difference could not be seen (126). Although the plasma DBH activities in chronic non-abstinent alcoholics and controls were not significantly different, the uncontrolled alcoholics showed a significant reduction of DBH activity when compared with the controlled alcoholic subgroup (127). Further, functional studies using *in vitro* and *in vivo* models demonsrated a fivefold to sixfold increase in *DBH* mRNA levels in response to ethanol, thus confirming *DBH* as a major ethanol-responsive gene (128). In German alcoholics, the plasma *DBH* activity was significantly lower than the controls, but this reduction is independent of *DBH*-1021C > T genotype (123). This is supported by a study in Brazilians, where the distribution of *DBH*-1021C > T allele and genotype frequencies are not statistically significant between alcoholics and controls (129). The *DBH**444G/A polymorphism of the dopamine-β-hydroxylase gene is associated with alcohol dependence but not with alcohol withdrawal seizures and DT (130).

SULT1A3

SULT1A3 catalyses the sulphate conjugation of dopamine and structurally related drugs. Two copies of the gene coding for cytosolic sulfotransferase *SULT1A3* is located on chromosome 16 and both genes are known to produce mRNA transcripts. The *SULT1A3* gene is 8.4 kb in length and consists of 10 exons, the first three of which are untranslated (131). Several known and novel SNPs were identified, and studies on functional genomics showed that some of these SNPs resulted in decreased SULT1A3 activity (132,133). So far no study has been conducted reliably to evaluate the association between *SULT1A3* gene polymorphisms and alcohol dependence.

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Ethnicity and alcohol

Alcohol consumption is governed by socio-cultural practices that are imparted through an individual's cultural and ethnic contextual experiences. In addition, differences in drinking patterns and consequences of alcohol use may exist among various ethnic and cultural groups. Overlooking these influences can lead to false views on appropriateness and inappropriateness of alcohol consumption and concomitant behaviours (134). Further genetic difference between ethnic groups occurs among other enzymes involved in metabolising alcohol in the liver. According to the HapMap SNP database, gene polymorphisms are seen in highly varying percentages in different populations worldwide. The genetic demographic studies demonstrate variation in the frequency of DAT1 nine-repeat allele in worldwide populations (68). DRD4 exon III VNTR seven-repeat allele also showed striking variations among world populations in their frequency ranging from 0% to 2% of South Asians to 78% of native South Americans (135).

Gene–environment (G × E) interactions and alcohol dependence

Alcohol dependence and related diseases are the result of gene to gene and gene to environment interactions. Although, several genetic factors that are associated with alcohol-related diseases have been identified, the environmental factors involved in modifying the risk of alcohol-related diseases remain undefined. The possible environment factors that modulate alcohol abuse or alcohol dependence include the exposure to ethanol and other drugs, cultural factors, and life stage events. With reference to alcohol dependence, the most studied environments include various kinds of physical and social stressors, or early drug exposures (136,137). Initial gene–environment interaction studies demonstrated that the genetic influences on alcohol use can be moderated by marriage (138), religion (139), parental monitoring (140) and friends (141). Hence, studies on gene–environment interactions will help in understanding how genes influence alcohol abuse and alcohol dependence behaviours.

Conclusions

From the current literature review, no evidence emerged to indicate a strong association between alcohol dependence and polymorphisms of dopamine pathway genes. Ethnic differences, variations in socio-cultural practices, genetic difference among populations, gene–gene interactions, gene–environment interactions, and different linkages to the polymorphisms might have influenced heterogeneity of alcohol dependence risk.

Future directions

Only a fraction of the genetic risk is yet accounted for by known loci, but a growing number of replicable loci are encouraging. Similarly encouraging are the facts that these loci coincide with protein products that could be related to alcohol-dependence risk and that they were identified by the application of standard methods. Admittedly, though, the proof for a specific variant to be related to a disease risk on the basis of studies that take into account the function of allelic variants, statistical evidence from linkage, and association studies is not sufficient. Despite the advances, there is a long way to go to fully characterise the genetic basis for alcohol dependence, and while it is likely that linkage and candidate gene or targeted association analysis will not take us the rest of the way, it is also now the case that these methods are rapidly being augmented by newer methodologies. Identifying various environmental conditions that alter the epigenetic status of neurotransmitters and their receptor genes may help us to understand the role of environmental factors that are critical in the development of alcohol-related diseases.

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Conflicts of Interest

There are no conflicts of interest.

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