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Influence of *DRD2* and *ANKK1* polymorphisms on the manifestation of withdrawal syndrome symptoms in alcohol addiction

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Abstract:
Background: We investigated the relationship between withdrawal syndrome symptoms and dopamine receptor 2 *DRD2* gene polymorphisms *-141 C I/D* (rs1799732) *exon 8 G/A* (rs6276) and *ANKK1* (Ankyrin Repeat and Kinase Domain Containing 1) gene polymorphism *Taq1A* (rs1800497).
Material: A total number of 213 patients who met the ICD 10 criteria for given phenotypes were enrolled in the study. Those phenotypes included: dissocial personality disorder, early onset, alcohol withdrawal syndrome with seizures, alcohol withdrawal syndrome with delirium tremens, and alcohol withdrawal syndrome with seizures and delirium tremens.
Results: Our results show statistically significant associations between SNP in *exon 8 A/G* in the *DRD2* gene and alcohol withdrawal syndrome with seizures, and between SNP in promoter *-141 C I/D* in the *DRD2* gene and early onset of alcohol dependence (AD). The *A/A* genotype in *exon 8 A/G* polymorphism seems to be a positive predictive factor for the presence or the lack of seizures in alcohol withdrawal syndrome. The *A/G* genotype is possibly a protective factor for this AD phenotype.
Conclusions: These results suggest that both investigated *DRD2* polymorphisms have an impact on the AD phenotype. The findings of the presented study reconfirm that dopamine receptor 2 gene polymorphisms are associated with alcohol addiction and alcohol withdrawal syndrome.

Key words:
DRD2, ANKK1, alcohol addiction, withdrawal syndrome

Introduction

Alcohol dependence (AD) is an etiologically complex disorder, whose development involves biochemical, metabolic and neurological factors [9]. Along with the progress in clinical genetics, it has been ascertained that many anomalies responsible for alcoholism are determined by genetics and can be inherited.

It is estimated that about 40–60% of predisposition to alcoholism is the genetic contribution [30]. To establish which genes are associated with this disorder, the candidate gene strategy was used. Its purpose was to identify genes involved in the etiology of alcohol addiction. Presupposition was that the knowledge of these genes would enable population screening tests and the identification of people with a higher risk of alcoholism. This, in turn, might result in the provision of accurate primary and secondary medical attention. The essence of the candidate gene strategy is to evaluate the relationship between being a carrier of a given gene polymorphism and the presence of a nosological entity. This approach helps to identify genes participating in biochemical processes, which may cause the addiction. They are mainly genes encoding enzymes that synthesize and metabolize catecholamines [1, 23]. So far, research has not shown that one of these genes is a universal marker of the enhanced predisposition to alcohol addiction [7, 46]. A multigenic etiology interferes with the identification of one specific gene that could be used in alcoholism predisposition screening tests. It seems that determination of a marker related to a phenotype is now a long-term trend in genetic research on AD [21]. The identification of allelic variants associated with the development of addiction may be useful while qualifying patients to different forms of therapy. It may also result in new treatment methods.

The dopaminergic system plays an essential role in the pathogenesis of addictions, including AD [24, 42]. Research shows that *ANKK1* (Ankyrin Repeat and Kinase Domain Containing 1) and *DRD2* genes might be genetic prognostic factors for an alcoholism phenotype [24]. The *DRD2* (11q 22-23) gene consists of 8 exons and 7 introns. Changes in the dopamine receptor 2 function are due to polymorphisms in the *DRD2* gene. The results that have been reported so far suggest that given polymorphic variants might be associated with an alcohol addiction-prone phenotype. These results are inconclusive, especially that the analyses were performed mainly on small groups. The *ANKK1* (11q23.2) gene [28], which has about 13 kb, consists of 8 exons and is expressed in the placenta, the spinal cord [13] and, according to the latest findings, also in astrocytes [18]. A peptide encoded by the *ANKK1* gene consists of 765 amino acids and is a member of a signal peptide family; it has 11 ankyrin repeats and a serine/threonine kinase domain (EC 2.7.10) [35]. There are at least 3 peptide isoforms of ANKK1 (containing RIP kinase and ankyrin repeats), the ANKK1-kinase, and the ANKK1-ankyrin [18]. One of the most commonly studied polymorphisms of this gene is *Taq1A* placed in 8 exon of the *ANKK1* gene [35].

Polymorphism *Taq 1A* in *ANKK1* gene

The *Taq1A* (E713K) polymorphism causes glutamine to lysine substitution in the 11th ankyrin repeat of ANKK1. The possibility that it affects peptide structure is very small, but it might change the substrate specificity. The electrostatic potential analysis of the ANKK1 crystal structure shows that some regions of protein surface are negatively charged [38]. The presence of negatively charged amino acids on the peptide surface and the combination of amino acids with particular charges are very conservative. Padmanabhan et al. [38] imply that a specific charge on the peptide surface is functionally significant for the peptide-peptide interaction. The change of amino acid sequence from negatively charged glutamine to positively charged lysine in the ANKK1 peptide at position 713 might alter its function. The presence of the *A1* allele (amino acid: K, nucleotide base: T) implies a lower density of D2 receptors in striatum. Furthermore, the *A1* allele affects glucose metabolism in brain regions with a high density of the D2 receptor [20, 27, 41, 47, 48].

The *-141* C Ins/Del polymorphism in the dopamine receptor *DRD2* gene

This polymorphism results in the insertion (ins, I) or the deletion (del, D) of cytosine (*C*) in the promoter region of the *DRD2* gene at position *-141*. The *-141 C* Ins allele demonstrates higher activity than del allele and is responsible for a higher density of D2 receptors in striatum. These findings were described by Jönsson et al. [20], but Pohjalainen et al. [41] did not confirm them. Thus, the functionality of this polymorphism is still under discussion. Lower levels of *DRD2* gene expression in striatum may be a consequence of the linkage between this particular polymorphism and another one in the same gene [20, 27, 39].

Polymorphism in *exon 8 A/G* in the *DRD2* gene

The next polymorphism in the *DRD2* gene is located in the exon 8 SNP and causes an adenine (*A*) to gua-