

Candidate gene studies of dopaminergic and serotonergic polymorphisms

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The most researched candidate genes of psychiatric genetic association studies are the components of the monoamine neurotransmitter systems, out of which serotonin and dopamine transmitter systems gained particular attention due to their major role in regulating emotional functions and cognitive processes. The paper reviews association studies focusing on the polymorphisms of receptors, transporters and enzymes that belong to these two transmitter systems. Numerous studies demonstrated significant associations between serotonergic and dopaminergic polymorphisms and diagnostic categories, personality traits and cognitive functions, however, results of monoamine gene variants and psychological properties are often contradictory. The contradictions can partially be explained with relatively small sample sizes of earlier studies, heterogeneity of methods across the studies and our expanding knowledge of the function of polymorphisms. On the whole, however, it can be declared that psychogenetic research plays an important role in the development of personalized pharmacotherapy.

Keywords: polymorphism, serotonin, dopamine, association study, mental disorders, personality traits

Twin, adoption and family studies indicate that numerous psychological factors and psychiatric conditions are significantly heritable (Kendler, 2002; Cardno et al., 1999). In the recent two decades a growing number of studies aimed to identify the genetic background of these psychological processes. Although genome-wide association studies became increasingly more cost effective and therefore more widespread recently, candidate gene studies still represent the majority of psychiatric genetic research.

In case of candidate gene studies the most crucial point of the research process is selecting the genes assumed to contribute to psychological characteristics and behavior. Since the mentioned domains are primarily attached to neurological functions, targeted genes are the ones participating in the development and interaction of nerve cells. Some of these gene products are common through different neurons and pathways, such as membrane proteins, ion channels, proteins of synaptic vesicles, etc. On the other hand, enzymes, receptors and transporters are specific for certain neurotransmitter systems. This paper is limited to the review of association studies between psychiatric conditions and genetic polymorphisms of

a narrow range of neural components involved in neurotransmission, namely the dopamine and serotonin systems. Monoamines, mainly serotonin, dopamine and norepinephrine, are important regulators of a wide range of behavioral and physiological functions, such as sleep, nutrition, motor functions, sexual behavior, attention, memory, reward, punishment and mood. Hence mental diseases have been traditionally linked to the altered functioning of one or all of monoamine transmitter systems, most psychiatric diagnoses are somehow related to suboptimal serotonin and/or dopamine function, such as disorders of mood and personality, psychotic problems, anxiety, substance abuse etc. A further contributor to the unique attention to the dopaminergic and serotonergic systems is that they are the target of the vast majority of psychiatric drugs. Antidepressant medication mostly modifies serotonergic mechanisms, although some of the novel pharmaceuticals are considered to bind to dopaminergic and/or noradrenergic sites as well. The primary effect of antipsychotic medications is the decrease of the availability of certain dopamine receptors. Stimulants, such as nicotine, caffeine, cocaine or amphetamine, preferably influence

the dopamine and norepinephrine systems. Hallucinogens, like psilocybin or LSD, alter serotonergic transmission, while other substances have a marked effect on a great number of transmitters including both serotonin and dopamine.

DOPAMINERGIC COMPONENTS

The most obvious contributors of neurotransmission are receptors and transporters, as well as enzymes participating in the synthesis and catabolism of neurotransmitters. Receptors provide the surface on both pre- and postsynaptic neuron where the transmitter can bind and transmit stimuli, while transporters are responsible for the reuptake of transmitters to the presynaptic neurons. The availability of the transmitter molecules is regulated by the metabolic pathways of their synthesis and degradation. Vereczkei and colleagues provide a thorough review on dopaminergic candidate gene polymorphisms of receptors, transporters and degrading enzymes supporting their possible effect in heroin addiction (Vereczkei et al., 2009). A further Hungarian study focuses on the association between multiple dopaminergic polymorphisms and the development of borderline personality disorder (Nemoda et al., 2010). Tyrosine hydroxylase is the rate limiting step of dopamine synthesis, coded by the TH gene on chromosome 11p15. The TH gene has numerous mutations and polymorphisms. Mutations are connected to tyrosine hydroxylase deficiency, a disease which primarily effects movement. Polymorphisms have been studied to show association with suicidal behavior (for meta-analysis see Persson et al., 1997; Hattori et al., 2006; Giegling et al., 2008), bipolar disorder (Inayama et al., 1993; Souery et al., 1996; Oruc et al., 1997; Furlong et al., 1999), schizophrenia (Thibaut et al., 1997; Ishiguro et al., 1998; Kunugi et al., 1998; Kurumaji et al., 2001; Pae et al., 2003) and personality traits (Persson et al., 2000; Hibino et al., 2006; Tochigi et al., 2006; Giegling et al., 2009; Sadahiro et al., 2010; Tsuchimine et al., 2010). Results of tyrosine hydroxylase studies are contradictory, a possible explanation is that early studies worked with relatively small sample sizes and observed a wide range of polymorphisms.

Dopamine receptors fall into two different subtypes; D1-like receptors including dopamine receptor D1 (DRD1) and D5 (DRD5), which mediate excitatory neurotransmission, and D2-like receptors involving D2 (DRD2), D3 (DRD3) and D4 (DRD4) mediating inhibitory neurotransmission. Dopamine transporter (DAT) is an integral membrane protein, its function

is to remove the dopamine from the synaptic cleft. DRD1 gene polymorphisms were mainly studied in relation to addictions, schizophrenia (Sander et al., 1995; Limosin et al., 2003; Kim et al., 2007) and in relation to bipolar affective disorder based on the dopamine hypothesis (Ni et al., 2002; Severino et al., 2005; Dmitrzak-Weglarz et al., 2006; Del Zompo et al., 2007). A substantial portion of addiction studies aimed to reveal association between alcohol abuse and DRD1 polymorphisms (Dmitrzak-Weglarz et al., 2006; Zhang et al., 2010; Novak et al., 2010). The most frequently studied polymorphism in the DRD1 gene is the -48A/G single nucleotide polymorphism (SNP) in the 5' untranslated (UTR) region of the gene, although in the above mentioned studies the function of this polymorphism is poorly discussed. DRD2 polymorphisms are repeatedly included in the association analyses along with DRD1 targets, however, DRD2 polymorphisms contributed to a substantially larger number of studies, most frequently in mood disorders and substance abuse. Zou et al. conducted a meta-analysis of DRD2 polymorphisms and mood disorders (Zou et al., 2010), involving 14 studies in their analyses (2157 cases and 3272 controls of both Caucasian and Asian population), and the -141C Ins/Del, the Ser311/Cys311 and Taq 1A polymorphisms of the DRD2 gene. According to their results only the DRD2 Taq 1A showed significant association with mood disorders: individuals with A1A1 genotype were more susceptible to mood disorders. Studies with substance abuse included a wide range of substances which are known to exert their rewarding effect through dopamine transmission (Tsai et al., 2002; Shahmoradgoli Najafabadi et al., 2005; Hou and Li, 2009). Both in mood disorder and substance abuse studies of DRD2 Taq 1A polymorphism appears to play an important role. A growing body of evidence indicates significantly reduced receptor density in A1 carriers (Jonsson et al., 1999; Ritchie and Noble, 2003). D3 dopamine receptor contains a thoroughly studied polymorphic site (rs6280), which encodes a Serine to Glycin amino acid change in the protein. This polymorphism has been widely examined among schizophrenic patients. DRD3 polymorphisms in general were studied to identify association with schizophrenia (for a meta-analysis see Nunokawa et al., 2010). DRD4 gene has been in the focus of psychiatric genetic research for its abundance of polymorphic sites. The most studied genetic variation of this gene is a 48-base pair VNTR in the third exon. Despite repeated attempts the molecular effect of this polymorphism is not fully understood. Asghari

et al. found reduced potency to inhibit forskolin-activated cAMP stimulation in the presence of the 7-repeat allele (1995). Recent studies indicate that the 7-repeat allele may decrease receptor expression due to its influence on RNA-stability (Schoots and Van Tol, 2003). Nevertheless, the DRD4 VNTR inspired a great variety of studies to search for possible association with psychological traits including persistence (Vereczkei et al., 2009), novelty seeking (Reist et al., 2007) and approach-related traits in general (for a meta-analysis see Munafo et al., 2008), ADHD (Bellgrove et al., 2005; Johnson et al., 2008) addictions (Stahl et al., 2004; Vandenbergh et al., 2000; for a review see Vereczkei et al., 2009) along with cognitive features such as reaction time (Vereczkei et al., 2009). DRD4 -521C/T (rs1800955) is a further extensively studied polymorphism associated with addiction (Sziglgyi et al., 2005) and ADHD (Bellgrove et al., 2005; Kereszturi et al., 2007). A relatively smaller number of studies examines the DRD5 candidate gene in psychiatric disorders despite its highly polymorphic nature (Feng et al., 1998), although its connection to ADHD was repetitively demonstrated (Newman-Tancredi et al., 1998; Manor et al., 2004; Johansson et al., 2008; Squassina et al., 2008).

Dopamine transporter retrieves the dopamine from the synaptic cleft terminating the dopamine signal. The DAT1 (SLC6A3) gene, coding for this transporter, is not particularly rich in polymorphisms, however it has a 40-bp VNTR in the 3' untranslated region which has been widely studied. According to a recent meta-analysis the 10-repeat allele has a significant role in the susceptibility of ADHD (Yang et al., 2007). Despite the determining role in the effect of substances like cocaine and amphetamines, associations between DAT1 polymorphisms and the mentioned stimulants are relatively understudied.

Catechol-O-methyl-transferase is the enzyme largely responsible for the breakdown of dopamine, particularly in the prefrontal cortex. This enzyme is encoded by the COMT gene, which contains a polymorphism of particular importance, an A/G SNP in the 158th codon resulting in a Valine to Methionine aminoacid change in the protein. The Methionine (A allele) shows 20-25% reduced activity compared to the Valine coding G allele (Lotta et al., 1995). The clarified, particular effect of this polymorphism initiated numerous association studies leading to an outstanding number of meta-analyses over the past 10 years demonstrating a significant association with obsessive compulsive disorder (Azzam and Mathews, 2003), ADHD (Cheuk and Wong, 2006), bipolar dis-

order (Zhang et al., 2009), cognitive effects (Barnett et al., 2008), suicidal behavior, personality traits (Calati et al., 2011). Further studies demonstrated association between COMT genotype and hypnosis (Vereczkei et al., 2009), opiate dependence (Demetrovics et al., 2010) and methylphenidate response in ADHD (Kereszturi et al., 2008).

SEROTONERGIC COMPONENTS

The rate-limiting enzyme of serotonin synthesis is tryptophan hydroxylase, which is responsible for the conversion of tryptophan to L-hydroxytryptophan. The two main isoforms of this enzyme is coded by the TPH1 and TPH2 genes. Most related research has focused on two SNPs of TPH1, located in intron 7, and designated as A218C (rs1800532) and A779C (rs1799913). These polymorphisms have been searched for association with major depression (Gizatullin et al., 2006), schizophrenia (meta-analysis: Watanabe et al., 2007), borderline personality disorder (Maurex et al., 2009; Wilson et al., 2009) and suicide (Koller et al., 2005; Baud et al., 2009; Galfalvy et al., 2009). Although the major part of related studies addressed the possible association of these SNPs and suicidal behavior, according to a recent meta-analysis it is connected to mental disorders in general with a secondary consequence of elevated risk for suicide (Saetre et al., 2010).

Serotonin receptors (5-hydroxytryptophan receptor (5HTR) type 1-7) are even more abundant and diverse than dopamine receptors, with at least 14 subtypes (Alex and Pehek, 2007). Here we present only the most frequently researched ones with their relevant polymorphisms. The type 1A receptor (HTR1A) is widely expressed throughout the brain both as a postsynaptic receptor and as a somatodendritic autoreceptor. Wasserman and colleagues examined a sample of 272 suicide attempters and found no association with 5HTR1A genotypes, but showed a strong trend in case of suicidal behavior with a history of stressful life events (2006). In a combined sample of 411 suicide attempters and suicide victims and 443 control subjects no association was found with 5HTR1A and 5HTR2C polymorphism (Serretti et al., 2007). Hettema did not find significant association between 5HTR1A, depression and anxiety related traits using a sample of 589 cases and 539 controls (2008). A meta-analysis in 2009 confirmed association between major depressive disorder (Kishi et al.) and 5HTR1A polymorphisms, moreover, the most recent meta-analysis also confirmed a significant association between polymorphic variations of 5HTR1A and

major depression, but not with schizophrenia (Kishi et al., 2011). Seemingly there is a consequent connection between 5HTR1A genotypes and mood disorders.

The serotonin receptor type 2A (5HTR2A) is another example of the extensively studied receptor genes. Polymorphic variants of 5HTR2A have been scrutinized to reveal association with schizophrenia and mood disorders. An early study of 100 schizophrenic patients and 103 control subjects did not find any association with 5HTR2A polymorphisms (Verga et al., 1997). A later family-based association study of a 5HT2RA polymorphism did not show significant effect with schizophrenia either (Spurlock et al., 1998). Chen and colleagues conducted a study on 471 schizophrenic patients and 523 controls with the lack of significant 5HTR2A association (2001). In support of the previously mentioned result a recent meta-analysis comprising 31 case-control studies confirmed this lack of association between 5HTR2A polymorphic variants and schizophrenia (Abdolmaleky et al., 2004). Nevertheless the question still remains open due to a novel study which demonstrated significant results with this gene and schizophrenia (Vaquero Lorenzo et al., 2006). A different line of studies attempted to find an association between 5HTR2A and mood disorders, also with contradictory results (Tsai et al., 1999; Oswald et al., 2003).

The rest of the serotonin (5HT) receptor genes are relatively understudied in connection with psychiatric disorders and personality traits, probably because their polymorphic structure is still poorly revealed. 5HTR1B is mainly linked to mood disorders similarly to the above mentioned serotonin receptor genes. Nishiguchi and coworkers failed to demonstrate a significant effect between the 5HTR1B polymorphism and suicide on a Japanese sample of 163 suicide victims and 163 control subjects (Nishiguchi et al., 2001). A significant association was found between 5HTR1B and the inattentive subtype of ADHD in a recent family based study (Smoller et al., 2006). A lack of association between 5HTR1B and alcohol dependence was reported on a sample of 322 alcohol dependent patients and 200 healthy controls (Lee et al., 2009). An early study of small sample size indicated the role of 5HTR2C Cys23Ser polymorphism in bipolar disorder in women (Gutierrez et al., 1996), the same polymorphism showed no association with schizophrenia in a family-based study (Murad et al., 2001).

The serotonin neurotransmitter is catabolized by monoamine oxydase A (MAO-A) and monoamine oxydase B (MAO-B) enzymes. Apparently the activity of MAO-A is higher (Shih and Chen, 1999). One of

the most outstanding findings of the past decade of MAO-A gene was its moderating effect of antisocial behavior of maltreated children (Caspi et al., 2002). MAO-A VNTR polymorphism has been identified as a possible risk factor for major depressive disorder in an early study of 146 MDD patients and 101 subjects without a history of depression (Schulze et al., 2000). A later study of MAO-A VNTR showed association with major depression along with sleep disturbances (Du et al., 2004). In an Italian family-based study the effect of a MAO-A SNP but not the VNTR showed association with bipolar disorder (Muller et al., 2007).

Research of the serotonin transporter is of unique importance since it is the common target of the second generation of antidepressant medications. Its most widely studied polymorphism, the 5HTTLPR (5-hydroxytryptophan transporter linked polymorphic region) repeat variation is located in the promoter region of the gene. 5HTTLPR has two common forms, the 14 repeat or short form (S) and the 16 repeat long form (L), the short form of which can be described with smaller transcriptional activity compared to the long one, but there are conflicting findings, indicating a lack of difference in mRNA levels in human pons tissues (Lim et al., 2006). The gene contains an A/G SNP within the VNTR polymorphism, the transcriptional activity of the Lg allele was found similar to the S allele. A 2003 study demonstrated a significant association between 5HTTLPR variants and violent suicide attempts in schizophrenia (Bayle et al., 2003) in search of the role of intermediate phenotypes such as aggression and impulsivity. A recent study provided further support for the role of 5HTTLPR genotypes in suicide (Gonda et al., 2010). Further support of the association of aggression and 5HTTLPR genotype was provided by a family-based association study conducted in a sample of healthy children (Haberstick et al., 2006). Bellivier and colleagues studied two polymorphisms in the serotonin transporter gene and their influence on the age of onset in patients with bipolar disorder (Bellivier et al., 2002). A further family-based study examined these polymorphisms in the background of bipolar disorder without finding any significant association (Mansour et al., 2005). The presence of the 5HTTLPR short allele was found to be associated with major depression in subjects with a history a stressful life events (Caspi et al., 2003), a finding recently confirmed by new evidence (Lazary et al., 2008; Lazary, 2010).

The aim of this review was an overview of the most commonly studied gene polymorphisms of the dopaminergic and serotonergic systems in order to

provide an overall picture of their relation to psychiatric disorders and psychological traits. Although gene polymorphisms of the monoaminergic systems are present in numerous association studies of mood disorders, schizophrenia and ADHD, results of these candidate gene studies are still contradictory. There are multiple reasons for the conflicting results. The early studies operated with moderate sample sizes therefore they are statistically weak. Small sample sizes also carry the problem of the underrepresentation of rare genotypes, therefore results provided by them are consequently overruled by later researches. Another important contributor of contradictory results is the lack of functional description of observed polymorphisms. A further explanation of opposing findings is the choice of different polymorphism of the same gene across various studies. Finally, it is possible – as recent research trends point out – that employing diagnostic categories in search for genetic association might be misleading due to their highly complex nature, therefore the study of intermediate phenotypes, such as personality traits or cognitive performance might be more beneficial. Despite the contradictions and difficulties in psychiatric genetic research, detailed study of dopaminergic and serotonergic gene polymorphisms are considered to have a promising application in the field of personalized medicine (Lazary et al., 2011).

Acknowledgement: This work was supported by the National Fund OTKA K81466.

Abbreviations: Attention deficit hyperactivity disorder ADHD, tyrosine hydroxylase TH, Dopamine transporter DAT, single nucleotide polymorphism SNP, variable number of tandem repeats VNTR, serotonin 5HT, 5-hydroxytryptophan transporter linked polymorphic region 5HTTLPR.

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Dopaminerg és szerotonerg polimorfizmusok kandidáns génvizsgálatai

A pszichiátriai genetikai asszociáció vizsgálatok legtöbbet vizsgált kandidáns génjei a monoamin neurotranszmitter rendszerek komponensei, melyek közül a szerotonin és dopamin transzmitterek komponensei kiemelkedő figyelmet kaptak hangulati és kognitív folyamatok szabályozásában betöltött szerepük miatt. A jelen összefoglalóban a szerotonin és dopamin rendszer receptorainak, transzportereinek és bontóenzimeinek leggyakrabban vizsgált génváltozataira vonatkozó fontosabb eredményeket tekintjük át. Számos esetben mutattak ki szignifikáns asszociációt szerotonerg és dopaminerg polimorfizmusok és diagnosztikai kategóriák, személyiségvonások, kognitív funkciók között. A monoamin génváltozatok kapcsolata diagnosztikai kategóriákkal és pszichológiai jellemzőkkel ugyanakkor gyakran ellentmondásos. Ezek az ellentmondások részben magyarázhatóak a korai vizsgálatok alacsony elemszámaival, a módszertani heterogenitással és a polimorfizmusok funkciót érintő ismeretek fokozatos bővülésével. Összességében azonban elmondható, hogy a pszichogenetikai kutatások fontos szerepet töltenek be az egyénre szabott gyógyszerterápia kialakításában.

Kulcsszavak: polimorfizmus, szerotonin, dopamin, asszociációs vizsgálat, mentális zavarok, személyiségvonások