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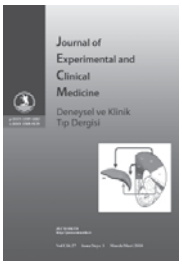

Review

Does serotonin 2A receptor gene polymorphism increase the vulnerability to panic attacks?

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ABSTRACT

Many studies have been conducted to show the genetic associations between the serotonin 2A receptor (HTR2A) gene polymorphisms and panic disorder (PD), but the overall results are inconsistent and replication proved difficult. Here, we provide a concise overview of recent findings on genetic association studies with PD, which are summarized in a table. It has been shown that the HTR2A receptor gene 102T-C polymorphism is associated with a pure phenotype, and with agoraphobia in PD patients, and with panic-flight behaviour in healthy volunteers. Furthermore, the polymorphism is quantitatively correlated with panic symptoms severity. Interestingly, a role for this HTR2A 102T-C polymorphism was not found in less well-delineated samples of PD patients, also suffering from co-morbid conditions, nor in PD patients without agoraphobic symptoms. However, the majority of the studies had low sample sizes, and therefore there is a need for a well-designed study with a sufficient statistical power. The genetic association of HTR2A 102T-C polymorphism with PD (related to agoraphobia or panic symptom severity) provides entry points for new studies on molecular mechanisms in PD.
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1. Introduction

Panic disorder (PD) is an anxiety disorder characterized by unexpected and repeated episodes of panic attacks with intense fear and psychosomatic symptoms (American Psychiatric Association, 1994). Regarding the genetic predisposition towards PD, a role has been proposed for the serotonin 2A receptor (HTR2A) 102T-C polymorphism on chromosome 13q14-q21 and its haplotype variants formed by linked single-nucleotide polymorphisms (SNPs) -1438A-G/T102C (Maron et al., 2005). The 102T-C gene polymorphism contains 3 polymorphic variants (TT, TC, and CC), as does the A-1438 gene polymorphism (AA, AG and GG). In a recent study by Perkins et al., carriers of the C allele of the 102T-C polymorphism (rs6313) within the HTR2A gene showed a significant increase of flight intensity as compared to non-carrier TT individuals, in a translational model of fear behaviour in humans (Perkins et al., 2009). This human behaviour was measured using a computerized translation of a rodent runway task that has previously been used for the mouse defense test battery, based on the principle of defensive reaction (Perkins et al., 2009). It is important to note that the latter study has demonstrated the first molecular genetic evidence of human defensive behaviour for a PD-flight link.

Many studies have been conducted to show the associations between the HTR2A gene polymorphisms and PD, but the overall results are inconsistent and replication proved difficult. Nevertheless, we hereby provide a concise overview of recent findings on genetic association studies with PD that are summarized in table 1. It is shown that the HTR2A receptor gene 102T-C polymorphism demonstrates a significant association in PD patients with a pure phenotype (Maron et al., 2005), with agoraphobia (Inada et al., 2003) as well as in the novel translational model of panic flight behaviour in healthy volunteers (Perkins et al., 2009). Furthermore, the polymorphism is quantitatively correlated with panic symptom severity (Unschuld et al., 2007; Yoon et al., 2008). Interestingly, the role of this HTR2A 102T-C polymorphism was not observed in less well-delineated samples of PD patients,

also suffering from co-morbid conditions, nor in PD patients without agoraphobic symptoms (Table 1) (Fehr et al., 2001; Rothe et al., 2004; Maron et al., 2005; Martinez-Barrondo et al., 2005). These findings are consistent with previous data in which PD with agoraphobia or with severe panic symptoms shows to be stronger genetically determined. All these studies suggest an impact of HTR2A 102T-C polymorphism on vulnerability to PD.

Neurobiological models of PD have suggested that a panic attack originates from loci in the brainstem that involve both serotonergic and non-serotonergic neurotransmission (Esquivel et al., 2009), particularly the dorsal periaqueductal gray (dPAG). Electrical stimulation of the dPAG has been shown to produce flight and freeze behaviours which mimic the response of a panic attack in humans (Lim et al., 2008). The neuroanatomical fear circuits of PAG-linked pathways include the prefrontal cortex (PFC), the insula, the thalamus, the amygdala, hypothalamus and other reciprocal connections (Graeff and Del-Ben, 2008). Notably, a recent study has demonstrated that greater mPFC HTR2A density was associated with a reduction of threat-related amygdala reactivity, indicating an important mechanism in the corticolimbic circuit function of emotional behaviour (Fisher et al., 2009). Moreover, it was shown that the differences of HTR2A density in mPFC are related with amygdala function, which may influence the functional genetic polymorphisms by affecting specific molecular signaling cascades.

It remains, however, difficult to draw final conclusions from the studies thus far, since the majority of the studies had low sample sizes. Therefore there is a need for a well-designed study with a sufficient statistical power. Nevertheless, the genetic association of HTR2A 102T-C polymorphism with PD (related to agoraphobia or panic symptom severity) provides a promising entry point for future investigation.

Table 1. Association studies of HTR2A gene polymorphism in PD. Abbreviation: PD, panic disorder; AP, agoraphobia; NS, non-specified; SNP, single nucleotide polymorphism.

Reference	HTR2A gene polymorphism	Subjects	Population	Co-morbidity	Condition	Polymorphism Association
Perkins et al., 2010	102T-C	Healthy (male, n=107; female, n=93).	Canadian	-	Human flight (panic) behaviour	Yes
Yoon et al., 2008	102T-C 1438A-G	PD patients (male, n=58; female=74) and healthy controls (male, n=87; female, n=74).	Korean	Excluded	PD	No
					Severity of panic symptom	Yes
Unschuld et al., 2007	SNP rs2296972	PD patients (n=154, 87.4% with AP; 12.6% without AP) and healthy controls (n=347).	German	Excluded	Severity of panic symptom	Yes
Martinez-Barrondo et al., 2005	102T-C 1438A-G	PD patients (n=92) and healthy controls (n=174).	Spanish	NS	PD	No
Maron et al., 2005	102T-C	PD patients (n=127; PD-comorbid, n=60; PD-pure, n=42) and healthy controls (n=146).	Estonian	Major depression and anxiety disorder	PD-all	No
					PD-comorbid	No
				Excluded	PD-pure	Yes
Rothe et al., 2004	102T-C	PD patients without AP (male, n=33; female=61), with AP (n=74) and matched healthy controls.	Canadian	Anxiety disorders or depression	PD with and without AP	No
		PD patients without AP (male, n=31; female=55), with AP (n=59) and matched healthy controls.	German			
Inada et al., 2003	102T-C	PD patients (n=33 with AP; n=30 without AP) and healthy controls (n=100).	Japanese	Excluded, except for secondary depression (≈ 17%)	PD with AP	Yes
					PD without AP	No
Fehr et al., 2001	102T-C	PD patients (male, n=14; female=21) and healthy controls (male, n=64; female, n=23).	German	NS	PD without AP	No

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