Review

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

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Key Words :

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. ????). 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, 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.
Maron et al., 2005; Martinez-Barrondo et al., 2005; Rothe et al., 2004). 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 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.

<table>
<thead>
<tr>
<th>Reference</th>
<th>HTR2A gene polymorphism</th>
<th>Subjects</th>
<th>Population</th>
<th>Co-morbidity</th>
<th>Condition</th>
<th>Polymorphism Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perkins et al., 2010</td>
<td>102T-C</td>
<td>Healthy (male, n=107; female, n=93).</td>
<td>Canadian</td>
<td>-</td>
<td>Human flight (panic) behaviour</td>
<td>Yes</td>
</tr>
<tr>
<td>Yoon et al., 2008</td>
<td>102T-C</td>
<td>PD patients (male, n=58; female, n=74)</td>
<td>Korean</td>
<td>Excluded</td>
<td>PD</td>
<td>No</td>
</tr>
<tr>
<td>Unschuld et al., 2007</td>
<td>1438A-G</td>
<td>PD patients (n=154, 87.4% with AP; 12.6% without AP) and healthy controls (n=347).</td>
<td>German</td>
<td>Excluded</td>
<td>Severity of panic symptom</td>
<td>Yes</td>
</tr>
<tr>
<td>Martinez-Barrondo et al., 2005</td>
<td>102T-C</td>
<td>PD patients (n=92) and healthy controls (n=174).</td>
<td>Spanish</td>
<td>NS</td>
<td>PD</td>
<td>No</td>
</tr>
<tr>
<td>Maron et al., 2005</td>
<td>102T-C</td>
<td>PD patients (n=129; PD-comorbid, n=60; PD-pure, n=42) and healthy controls (n=146).</td>
<td>Estonian</td>
<td>Major depression and anxiety disorder</td>
<td>PD-all</td>
<td>No</td>
</tr>
<tr>
<td>Rothe et al., 2004</td>
<td>102T-C</td>
<td>PD patients without AP (male, n=33; female=61), with AP (n=74) and matched healthy controls.</td>
<td>Canadian</td>
<td>Anxiety disorders or depression</td>
<td>PD with and without AP</td>
<td>No</td>
</tr>
<tr>
<td>Inada et al., 2003</td>
<td>102T-C</td>
<td>PD patients (n=33 with AP; n=30 without AP) and healthy controls (n=100).</td>
<td>Japanese</td>
<td>Excluded, except for secondary depression (≈ 17%)</td>
<td>PD with AP</td>
<td>Yes</td>
</tr>
<tr>
<td>Fehr et al., 2001</td>
<td>102T-C</td>
<td>PD patients (male, n=14; female=21) and healthy controls (male, n=64; female, n=23).</td>
<td>German</td>
<td>NS</td>
<td>PD without AP</td>
<td>No</td>
</tr>
</tbody>
</table>

REFERENCES
and functional coupling. Cerebral Cortex, 19, 2499-2507.