Genome Medicine

MINIREVIEW

Serotonin transporter polymorphisms and panic disorder

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Abstract

Panic disorder (PD) is the most common anxiety disorder. Although PD seems to occur unprovoked and the underlying etiology is not well understood, studies have consistently shown that genetic factors explain approximately 48% of the variance. Moreover, family and twin studies support the view that the majority of PD cases have a complex genetic basis. Promising findings have most recently implicated the polymorphisms at the 3' end of the serotonin transporter gene *SLC6A4* as PD risk variants. If independent studies can replicate the observed association with the *SLC6A4* variants and their functional effects on gene expression, this would have a great impact on our understanding of the disease pathophysiology and would provide opportunities to investigate genotype-phenotype correlations.

The genetics of panic disorder

Panic disorder (PD) has a population prevalence of 3.4 to 4.7% and is the most common anxiety disorder [1,2]. According to the American Psychiatric Association, PD is defined as an episode of abrupt, intense fear accompanied by additional physiological or cognitive symptoms. Other anxiety disorders and also mood and substance-use disorders are frequently observed as co-morbidities [3,4]. Family and twin studies have consistently shown that genetic factors explain approximately 48% of the variance in the disease [5], and segregation analyses support the view that the majority of PD cases have a complex genetic basis. This is also highlighted by several animal breeding experiments, which reveal that anxiety or emotional activity analogous to panic and anxiety is controlled by multiple genes, possibly in varying combinations [6]. However, the genetic architecture underlying PD is heterogeneous and differs between cases. For example, the degree of genetic complexity and the pattern of genes involved might be different in familial versus non-familial, early- versus late-onset cases or when different co-morbid conditions, gender and potential intermediate or sub-phenotypes are considered.

On the molecular genetic level, linkage and candidate gene studies have been used for the genetic analysis of PD, and several potential linkage loci and tentative associations with candidate genes have been found [7]. For several reasons, serotonergic neurotransmission, and especially the serotonin transporter gene *SLC6A4,* has attracted attention in the PD research field. Selective serotonin reuptake inhibitors (SSRIs) that target *SLC6A4* are commonly used and effective treatments for PD [8]. In addition, mouse experiments have shown that *SLC6A4* underexpression leads to anxiety-like behavior [9], which would be in accordance with human studies that have found decreased *SLC6A4* expression in brains of PD patients [10].

On the genomic level, *SLC6A4* is located on chromosome 17q11 and consists of 15 exons. A large amount of genetic variation has been observed in *SLC6A4.* An insertion-deletion polymorphism in the promoter region of *SLC6A4*, called 5-HTTLPR, has attracted particular attention because it has been shown that this polymorphism alters gene and protein expression and the low-expressing short variant has been associated with anxiety [11]. Moreover, an association has been found, in healthy individuals as well as in patients with major depression, between 5-HTTLPR and increased amygdala activation in response to fearful stimuli [12-14]. However, most PD genetic association studies have failed to find an association between 5-HTTLPR variants or amygdala activation and panic disorder [15-17].

The role of a 3' *SLC6A4* polymorphism in PD

A recently published study by Gyawali *et al.* [18] reports evidence that *SLC6A4* might contribute to the development of PD by a mutation other than 5-HTTLPR. Their study [18] followed findings [19] of an association between PD and polymorphisms located in the 3' untranslated

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region (UTR) of *SLC6A4*. None of these 3' UTR-associated variants showed linkage disequilibrium to 5-HTTLPR, suggesting an independent *SLC6A4* locus at the 3' end of the gene. It is known that the *SLC6A4* 3' UTR is expressed in two alternative forms that differ by the presence or absence of a 123-bp element [20] and the more 3' (distal) form contains an additional polyadenylation signal. Gyawali *et al.* [18] hypothesized that one particular SNP - rs3813034 - located within this signal would alter the usage of this form relative to the more 5' (proximal) form. To test this hypothesis, the authors [18] analyzed 65 post mortem human brain samples and found that in brains expressing one of the rs3813034 alleles - coding for G - the relative expression of the distal to the proximal *SLC6A4* form was significantly lower than that of brain samples carrying the alternative (T) allele. The same effect was seen in 71 human lymphoblast cultures. The authors [18] also found evidence that gender-specific effects contributed to the observed allele-specific expression differences. The distal form of *SLC6A4* was less expressed in brain samples from females than in those from males. To ensure that the gender-specific association is a true positive finding, the authors [18] analyzed both expressed *SLC6A4* isoforms in brains of male and female mice. In this dataset they also observed gender differences similar to those seen in humans, with a lower expression of the distal *SLC6A4* isoform in female mouse brains.

Gyawali *et al.* [18] also examined whether rs3813034 is itself the variant causing the observed *SLC6A4*-expression differences. Using a functional approach, they cloned both forms of the 3' *SLC6A4* UTR into plasmids; one construct encoded allele G and the other one allele T of rs3813034, and the remaining sequence was identical. The relative expression of the two polyadenylation forms was then quantified and the authors [18] observed that the G allele of rs3813034 caused significantly lower usage of the distal polyadenylation form than allele T.

Finally, rs3813034 was tested for PD association in a large case-control study (n = 307 PD patients and 544 controls) [18]. The G allele - associated with lower expression of the distal *SLC6A4* isoform - was significantly more frequent in patients (51%) than in controls (44%; P = 0.002) and thereby found to be the PD risk allele. This effect became stronger when the participants were stratified by gender. The risk allele was significantly more frequent in female PD patients (51%) than female controls (42%) (P = 0.003), whereas no G-allele association was observed in males (P = 0.233) [18]. The finding was in accordance with the expression experiments, in which lower expression levels of the distal *SLC6A4* form were observed in female brain samples from both humans and mice.

Conclusions and perspectives

These results are encouraging and are shedding new light on the role of *SLC6A4* variation in panic disorder. Nevertheless, some questions remain. In particular, it has yet to be shown how a lower expression level of the distal *SLC6A4* isoform affects protein function quantitatively and qualitatively, for example in a gender- and/or cell-type-specific manner. This is especially important because the short 5-HTTLPR, with an obvious lower protein expression, has consistently been shown not to be associated with panic disorder. Given that *SLC6A4* has never been tested systematically for association and the gene might harbor several potential risk variants, possible explanations for the discrepant findings may be that the interaction between different polymorphisms has not been controlled for in previous studies or that it has gender- or cell- type-specific consequences. Studies on large PD datasets with sufficient marker coverage for extensive haplotype analyses and additional functional studies are now required.

Although these two recent reports [18,19] are evidence that candidate-gene studies can still provide some surprises, this approach has obvious limitations. In contrast, as with other disorders, modern genome-wide association studies of sufficiently large sample size will most probably lead to the identification of novel PD risk genes in the coming years and will contribute to our understanding of the underlying neurobiology of anxiety-related disorders and behaviors [21,22]. This will increase our understanding of anxiety disorders and aid the development of better prevention strategies.

Abbreviations

PD, panic disorder; SSRI, selective serotonin reuptake inhibitor; UTR, untranslated region.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

The authors contributed equally to this work.

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