GABRB2 in schizophrenia and bipolar disorder: disease association, gene expression and clinical correlations

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Abstract
The SCZ (schizophrenia)-associated GABA_A receptor (γ-aminobutyric acid type A receptor) β2 subunit gene GABRB2 was recently associated with BPD (bipolar disorder). Although weaker than its association with SCZ, significant association of GABRB2 with BPD was found in both German and Chinese, especially for the haplotypes rs1816071–rs187269 and rs1816072–rs187269 for which the M–M variants showed higher frequency in disease than the control. Significant genotype-dependent reduction in GABRB2 expression was shown for BPD, but to a lesser extent than that for SCZ. Temporal effects on GABRB2 expression were observed. Moreover, for the homozygous major genotypes of rs1816071, rs1816072 and rs187269, expression increased with time in CON but decreased in SCZ and BPD. The genotypes of these three SNPs (single nucleotide polymorphisms) were further correlated with antipsychotics dosage in SCZ cohorts. The findings highlight the importance of GABRB2 in neuropsychiatric disease aetiology, with respect to haplotype association, as well as reduction of and temporal effects on gene expression in both SCZ and BPD, but to a lesser extent in the latter, supporting the suggestion that functional psychosis can be conceptualized as a continuous spectrum of clinical phenotypes rather than as distinct categories.

Introduction
SCZ (schizophrenia) and BPD (bipolar disorder) are common multifactorial psychiatric disorders each with approx. 1% lifetime prevalence across world populations. SCZ is characterized by a constellation of symptoms, including hallucinations, delusions and negative symptoms, as well as cognition impairment [1], whereas BPD, also known as manic-depressive illness, is typified by episodes of dysphoria that are associated with somatic symptoms, possibly causing unusual disruption in a person’s mood, energy and ability to function. Twin and adoption studies have demonstrated considerable disease heritabilities [2,3], indicating a definite role of genetic factors in the aetiology of both diseases. Although genetic and clinical studies are consistent with the possible existence of features common to these two brain disorders [4–10], the most evident common clinical feature being psychosis, common genetic mechanisms underlying the comprehensive pathophysiology have proved highly complex and remain to be elucidated.

The recent discovery of a series of susceptibility genes has shed more light on the molecular mechanisms of SCZ and BPD, as well as possible overlap in their genetic susceptibilities. Such candidate genes include NRG1 [11], COMT [12], DAOA(G72) [13], DISCI [14], and the GABA_A receptor α1-subunit gene of GABRA1 [15,16]. The continuum model of psychosis has been proposed to account for such sharing of susceptible loci as well as the similarity in features between diseases within the category of functional psychosis, which includes unipolar disorder, BPD, schizoaffective illness and SCZ [17].

Involvement of GABA_A receptors in SCZ and BPD
The GABAergic system is the major inhibitory neurotransmission system in the central nervous system, and its dysfunction could be a factor in both SCZ and BPD [18–20]. Evidence supporting its involvement includes the altered expression of GABA_A receptor α1 and β2/3 subunits in the prefrontal cortex [21], the down-regulation of GABA-synthesis enzyme GAD67 (glutamic acid decarboxylase7) [20], and the decreased number of GABAergic neurons [22] in both SCZ and BPD. The BDNF (brain-derived neurotrophic factor), a regulator of GABA transporters, may play as well a role in both SCZ and BPD [23]. Moreover, the SCZ-linked risk locus chromosome 5q34 contains a cluster of GABA_A receptor genes (GABRB2, GABRA6, GABRA1 and GABRG2), and increasing evidence suggests...
that members of this cluster are associated with psychiatric disorders [16,24,25], consistent with pathological studies demonstrating GABAergic involvement.

For the GABA\(_{A}\) receptor \(\beta_2\) subunit \(GABRB2\) gene, highly significant association between SCZ and the intron 8–intron 9 region was first observed in the Chinese Han population [24] and subsequently cross-validated in Japanese and German samples [15,26,27] and additional Chinese samples [28]. Evidence for association of \(GABRB2\) with BPD was recently reported for the first time in U.S. Caucasian trios; both gene-based association tests and three-marker haplotype transmission tests were highly significant [29]. SNPs (single nucleotide polymorphisms) and haplotypes in the neighbourhood of exon 9 were also associated with BPD in Chinese and German cohorts (Figure 1). With the rs1816071–rs187269 (S3–S29) and rs1816072–rs187269 (S5–S29) haplotypes, cross-population evidence pointed to significantly higher frequencies for the major–major (M–M) variants in SCZ or BPD than in CON among Chinese and German cohorts (Figure 1). With the rs1816071–rs187269 (S3–S29) and rs1816072–rs187269 (S5–S29) haplotypes, cross-population evidence pointed to significantly higher frequencies for the major–major (M–M) variants in SCZ or BPD than in CON among Chinese and German cohorts (Figure 1). With the rs1816071–rs187269 (S3–S29) and rs1816072–rs187269 (S5–S29) haplotypes, cross-population evidence pointed to significantly higher frequencies for the major–major (M–M) variants in SCZ or BPD than in CON among Chinese and German cohorts (Figure 1). With the rs1816071–rs187269 (S3–S29) and rs1816072–rs187269 (S5–S29) haplotypes, cross-population evidence pointed to significantly higher frequencies for the major–major (M–M) variants in SCZ or BPD than in CON among Chinese and German cohorts (Figure 1). With the rs1816071–rs187269 (S3–S29) and rs1816072–rs187269 (S5–S29) haplotypes, cross-population evidence pointed to significantly higher frequencies for the major–major (M–M) variants in SCZ or BPD than in CON among Chinese and German cohorts (Figure 1). With the rs1816071–rs187269 (S3–S29) and rs1816072–rs187269 (S5–S29) haplotypes, cross-population evidence pointed to significantly higher frequencies for the major–major (M–M) variants in SCZ or BPD than in CON among Chinese and German cohorts (Figure 1). With the rs1816071–rs187269 (S3–S29) and rs1816072–rs187269 (S5–S29) haplotypes, cross-population evidence pointed to significantly higher frequencies for the major–major (M–M) variants in SCZ or BPD than in CON among Chinese and German cohorts (Figure 1). With the rs1816071–rs187269 (S3–S29) and rs1816072–rs187269 (S5–S29) haplotypes, cross-population evidence pointed to significantly higher frequencies for the major–major (M–M) variants in SCZ or BPD than in CON among Chinese and German cohorts (Figure 1).

**\(GABRB2\) genetic correlations with gene expression and antipsychotic dosage**

The \(\beta_2\) subunit, one of the principal components of most native GABA\(_{A}\) receptors, is found in two alternatively spliced isoforms, namely the short isoform \(\beta_2S\) and the long isoform \(\beta_2L\). The long isoform is more prone than the short isoform to current run-down induced by repetitive activation [30]. The SCZ-associated \(GABRB2\) genotypical variations have been correlated with \(\beta_2\)-subunit mRNA expressions and levels of alternative splicing in U.S. Caucasians and thus, in turn, with alteration in electrophysiological response of the receptor [30]. Similarly, in the case of BPD, the reduction was significant for \(\beta_{ST}\) (total \(GABRB2\) isoforms) expression. Moreover, when either DOI (duration of illness) or age was included as covariate in the quantitative trait analysis, significant genotype dependency in gene expression became observable, especially in the SCZ group compared with the CON or BPD group. Interestingly, the MM genotype favoured a negative correlation between \(\beta_{ST}\) expression and DOI in SCZ and BPD for S3, S5 and S29, but favoured a positive correlation between \(\beta_{ST}\) expression and time in CON, indicating that temporal changes in gene expression occur in both normal individuals and patients but these changes are altered both in direction and magnitude between the two cohorts.

GABAergic neurons are decreased in SCZ and BPD brains [19]. The negative correlation observed between genotype-dependent \(\beta_{ST}\) expression and time in the SCZ and BPD cohorts suggested that these SCZ- and BPD-linked GABAergic reductions are progressive over a period of decades. Such progressive reductions are consistent with GABAergic neuronal decreases being one of the consequences of disease and suggest that such decreases are genotype dependent.

On the basis of the antipsychotic drug dosages given to U.S. SCZ subjects, the MM genotypes of S3, S5 and possibly S29, indicated association with lower drug requirement. These significant correlations between \(GABRB2\) SNP genotype and antipsychotic dosage suggest that these genotypes are possibly correlated with the severity of psychotic symptoms in SCZ or with dose response to the drugs. Although there is so far little evidence for the GABA\(_{A}\) receptor being a determinant of the dose response to the antipsychotic drug(s), the observed correlations could nevertheless reflect higher drug efficiency in patients with the MM genotype at S3, S5 or S29. On the other hand, psychosis severity may also be considered as a possible factor for the observed genotype–antipsychotic dosage relationships, based on the assumed positive correlation between antipsychotic dosage and severity of psychosis.

**Implications for functional psychosis as a continuous spectrum**

Mental disorder co-morbidity ranges from 44 to 94%, depending on the disorder [31]. On the one hand, this co-morbidity reflects the phenotypic overlap of mental disorders, where the distinction between certain disorders,
whether categorized by either DSM or ICD, becomes unclear. On the other hand, the phenomenon may be in part due to pleiotropic genes that simultaneously affect different disorders; for example, variations in DISC1 (disrupted in schizophrenia 1) have been associated with SCZ, schizoaffective disorder, BPD, major depression as well as autism [14]. The finding that SNPs and haplotypes in GABRB2 were significantly associated with the two disorders SCZ and BPD is therefore consistent with evidence of overlap between the disorders. In itself, it highlights GABRB2 as a strong candidate gene for neuropsychiatric disorders, and it implies that GABRB2 may be pleiotropic, having a general role in functional psychosis rather than a specific role in any one of the subcategories. Moreover, the findings demonstrate a gradual difference in significance of both genotype-disease associations and genotype-expression correlations of GABRB2 on the different disorders, being more significant in SCZ than in BPD. This supports the suggestion that functional psychosis may be conceptualized as a continuous spectrum of clinical phenotypes or behavioural domains with susceptibility conferred by overlapping sets of genes, and also that less emphasis should be placed on the artificial phenotype boundaries that are currently used to define the disorders [7,9,32,33].

In conclusion, the GABRB2 gene is associated with both SCZ and BPD, which share between them underlying genetic elements. The SNPs and haplotypes within the 3879 bp segment of GABRB2, located from 2041 bp upstream to 1265 bp downstream of exon 9, play a key role in determining not only susceptibility to these diseases, but also temporal changes in the diseased brains and, at least in the case of SCZ, antipsychotic drug requirement.

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