Identification of susceptibility genes for bipolar affective disorder and schizophrenia on chromosome 22

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ABSTRACT

Linkage analyses suggest that chromosome 22q12-13 may harbor one or more shared susceptibility loci for bipolar affective disorder (BPD) and schizophrenia (SZ). In a study of distantly related cases and control individuals from the Faeroe Islands our group has previously reported that chromosome 22q13 may harbor two shared susceptibility loci for BPD and SZ.

The aim of the PhD project was to identify and characterize susceptibility genes for BPD and SZ located in these two loci on 22q13, primarily by association analyses of selected positional candidate genes in a number of population samples (total of 1751 individuals), and by bioinformatic and expression analyses of a subset of disease associated genes and gene variants.

In total 67 single nucleotide polymorphisms (SNPs) located in 18 positional candidate genes, and four microsatellite markers were investigated, using a Scottish case-control sample (162 BPD subjects, 103 SZ subjects, 200 controls), an extension of the previously analyzed Faeroese sample (17 BPD subjects, 11 SZ subjects, 44 controls) and two replication samples, one from the UK (300 BPD subjects, 265 SZ subjects, 314 controls) and one from Denmark (124 BPD subjects, 115 SZ subjects, 96 controls).

We found association with BPD and SZ for single-marker and multi-marker haplotypes in all samples analyzed in the proximal as well as in the distal locus. The most significant findings regarded the gene *GPR24*, the gene *BRD1*, and a region slightly distal to GPR24 containing a number of genes (*EP300*, *PIPPIN*, *NHP2L1* and *SERHL*). The bioinformatic analyses showed a possible impact of several of the disease associated SNPs on gene expression. Expression analysis of BRD1 mRNA and protein in brain regions of human and other mammals showed widespread neuronal expression. Quantitative mRNA analysis in fetal pig brain revealed a spatiotemporal differential profile with high expression at early embryonic stages.

The results obtained suggest *GPR24* and *BRD1* as novel, shared susceptibility genes in BPD and SZ, and provide evidence that *BRD1* may play a key role in orchestrating important aspects of brain development. Furthermore, the results indicated that an additional potential susceptibility gene might reside within the region slightly distal to *GPR24*, containing the genes *EP300*, *PIPPIN*, *NHP2L1*, and *SERHL*.