The dopamine D3 receptor gene: no association with bipolar affective disorder

S Shaikh, D Ball, N Craddock, D Castle, N Hunt, R Mant, M Owen, D Collier, M Gill

Abstract
Bipolar affective disorder and schizophrenia share many clinical and genetic characteristics, and are thought by some to be different expressions of the same underlying disorder. A recent study showed an excess of homozygosity at a Ball polymorphism in the dopamine D3 receptor gene in schizophrenic patients compared with controls, from two independent centres. We have found no evidence of such an excess in a comparable sample of patients with bipolar affective disorder compared with matched controls. If these findings are confirmed then at least one genetic distinction between these two disorders will have been ascertained and doubt cast upon theories of a common genetic aetiology.

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Bipolar affective disorder is one of the major psychoses characterised by intermittent episodes of depression or elation (the manic syndrome). It has a largely genetic aetiology but with an unknown mode of transmission and although nosologically separated from schizophrenia it shares many of that disorder's characteristics, such as delusions and hallucinations that respond to neuroleptic medication. A third condition, schizoaffective disorder, occupies the middle ground, and it has been suggested that the disorders occur at different positions on a continuum of psychoses.

Crocq et al have reported an excess of homozygotes at a Ball polymorphism at the dopamine D3 receptor gene in two independent samples of 68 and 73 unrelated schizophrenics compared to normal controls. When pooled data were analysed, the difference was highly significant (p = 0.0001) with a relative risk of schizophrenia in homozygotes of 2.61 (95% CI 1.60, 4.26). We have examined the same polymorphism in a sample of 75 bipolar affective disorder patients and controls. Genetic similarity, or otherwise, to schizophrenia may help in understanding the relationship between these two conditions.

Materials and methods
Seventy-five unrelated patients were diagnosed using the Schedule for Affective Disorders and Schizophrenia—Lifetime version (SADS-L) and met Research Diagnostic Criteria for bipolar affective disorder. Normal population controls were matched for age, sex, ethnic origin, and social class. All patients and controls were Caucasians of west European extraction.

A polymorphic site in the first exon of the dopamine D3 gene gives rise to a glycine to serine substitution in the N-terminal extracellular domain. This produces a Ball restriction site which was typed by restriction enzyme digest following amplification of genomic DNA. The presence of a 304 bp fragment denoted allele 1 and fragments of 206 bp and 98 bp allele 2. In addition, amplification produced constant fragments of 111 bp and 47 bp. Fragments were visualised by ethidium bromide staining after agarose gel electrophoresis.

Results
Allele frequencies and genotype counts are shown in the table. In contrast to the findings of Crocq et al the number of each genotype observed in the patients did not differ from values expected under Hardy-Weinberg equilibrium ( \( \chi^2 = 0.406, df = 1, p = 0.52 \)). No significant differences in allele frequency ( \( \chi^2 = 1.21, p = 0.27 \)) or homozygosity/heterozygosity counts ( \( \chi^2 = 1.50, p = 0.22 \)) were observed between the bipolar affective disorder group and the control sample.

Discussion
The excess of homozygotes at the Ball dopamine D3 receptor polymorphism reported by Crocq et al in schizophrenic patients has not been observed in a comparable sample of bipolar affective disorder patients. Nor are there any significant differences in allele frequency between bipolar patients and controls. We calculate that our study had a power of > 0.859 to detect a difference of the magnitude reported by Crocq et al. Thus this sequence variation, which alters the amino acid sequence of the D3 protein, is unlikely to confer susceptibility to bipolar affective disorder. Lack of an effect in bipolar illness has been noted in another study. If the findings for schizophrenia are confirmed then at least one genetic distinction between these two disorders will have been ascertained and doubt cast upon theories of a common genetic aetiology.

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