Excess of homozygosity at the dopamine D3 receptor gene in schizophrenia not confirmed

We read with interest the paper by Crocq et al who reported an association between schizophrenia and homozygosity of a polymorphic site in the first exon of the dopamine D3 receptor gene. The polymorphic site which gives rise to a glycine to serine substitution in the N-terminal extracellular domain of the protein was investigated in two independent samples of patients and controls from France and the UK. After pooling the results of both studies the overall relative risk was 2.61 for schizophrenia in homozygotes.

As noted by the authors, we have studied this polymorphism in an independent series of schizophrenic patients (n = 60) of German origin and observed a marked but not statistically significant trend towards an overrepresentation of homozygotes (table).1 The finding by Crocq et al prompted us to study another 51 schizophrenic patients of German descent, including 25 index patients from highly loaded schizophrenic pedigrees collected for linkage studies, to see whether our initial trend remains stable in an extended sample. The results of the new patient group show a genotype distribution which is similar to the expected distribution according to Hardy-Weinberg equilibrium (X² = 0.07, df = 1, P = 0.79) (table). Subgrouping of patients with regard to a family history of schizophrenia who have no influence on the genotype distribution (results not shown). Our combined data on 111 schizophrenic patients do not provide evidence of a significant association between schizophrenia and homozygosity at the dopamine D3 receptor gene (X² = 0.54, df = 1, P = 0.45, relative risk = 1.19) (table). Moreover, our healthy German controls (n = 100), who were investigated as part of another study, showed a genotype distribution no different from the expected values according to Hardy-Weinberg equilibrium (table).2 Our results suggest that the excess of homozygotes in the French and English samples is indeed a real finding it cannot easily be applied to patients of German descent.

Finally, it should be noted that the genotype distribution in the French and the UK control samples showed an overrepresentation of heterozygotes which, in addition to the excess of homozygotes in the patients, accounts for the observed relative risk. In the French control group this deviation from Hardy-Weinberg equilibrium is significant (X² = 5.47, df = 1, P = 0.019). Although our controls did not show a similar deviation from Hardy-Weinberg equilibrium, the significant overrepresentation of heterozygotes in the healthy controls from France, and to a lesser extent also in the UK controls, is an interesting finding, which might reflect a heterozygote advantage.

In the view of (1) our failure to replicate the finding of an association between schizophrenia and homozygosity at the dopamine D3 receptor gene and (2) the finding of an overrepresentation of heterozygotes in the control groups studied by Crocq et al, it will be necessary to attempt replication in independent samples of patients as well as in well characterised controls deriving from the same ethnic populations where the initial positive findings were obtained.

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MARKUS M NÖTHEN
BERNARD J CICHON
PETER PROPPING
Institute of Human Genetics,
University of Bonn, Wilhelmsstrasse 31,
5300 Bonn 1, Germany.

ROLF FIMMERS
Institute for Medical Statistics,
University of Bonn, Germany.

SYBILLE G SCHWARZ
DIETER J WILDENAUER
Department of Neurochemistry,
Psychiatric Hospital,
University of Munich, Germany.


Association between schizophrenia and homozygosity at the dopamine D3 receptor gene

Recently, Crocq et al (J Med Genet 1992;29:858-60) reported a statistically significant excess in homozygosity for polyallelic variants in an intron of the dopamine D3 receptor gene. They offered two possible explanations for this observation: (1) that the deviation from Hardy-Weinberg equilibrium among the affected population is due to linkage disequilibrium; (2) that the excess of homozygotes among patients reflects heterozygote advantage. The authors favour the second explanation for reasons they discuss in their paper. It would be helpful to offer a third: (3) that there is an excess of persons hemizygous for the dopamine D3 receptor gene markers among the patient population surveyed. This possibility that the authors used relies on the ability to PCR amplify the first exon, and then resolve restriction fragments of the amplified DNA on an agarose gel. However, subjects who lack one or more of the PCR primer sites owing to a point mutation or deletion of one allele would be classified as homozygous for the other allele in this system. This phenomenon is known as allelic dropout and it is one of the pitfalls of PCR genotyping, especially when assaying candidate genes for mutant alleles. A similar situation was described by Fujimura et al when typing for allelic cassettes by PCR.

The hypothesis of allelic dropout has several advantages in explaining the observation of Crocq et al. It accounts for why there should be an excess of either of the homozygous alleles among the affected population. It also does not require that various unspecified mutant alleles be in linkage disequilibrium with two different polymorphisms at the locus, nor does it require that there be a functionally significant polymorphism among the dopamine D3 receptor gene products. I strongly encourage them to assay their patients for changes either in the primer sequences or in copy number at the dopamine D3 receptor locus.

ROBERT MORELL
Department of Zoology, Natural Science Building, Michigan State University, East Lansing, Michigan 48824, U.S.A.


These letters were shown to Dr Owen et al who reply as follows.

Nothen et al report that they are unable to replicate our finding of excess homozygosity at the dopamine D3 receptor gene in their extended sample of 111 patients. We too have extended our initial observations by studying a further 66 patients with DSM III-R schizophrenia and 98 healthy controls (75 persons, 23 jobs). Only then did we find excess homozygosity though the effect was not as strong as in our first study and did not achieve statistical significance on its own (patients v controls X² = 2.35, P = 0.06, one tailed; patients’ controls’ Hardy-Weinberg X² = 2.67, P = 0.05, one tailed). This led us to explore the possibility that there might be important differences between patients in our two studies and that excess homozygosity might be a characteristic of a particular subgroup of schizophrenic patients. Our preliminary unpublished observations suggest that the effect is consistently at its strongest in those patients who have a very high familial loading and in those who have a good response to neuroleptic treatment. We also observed that the proportion of good responders sampled...