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 polymeric 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 2.6 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 also observed a mild but not statistically significant trend towards an overrepresentation of homozygotes (table). 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 the Hardy-Weinberg equilibrium (X² = 0.07, p = 0.979) (table). Subgrouping of patients with regard to a family history of schizophrenia had 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 = 0.05, df = 1, p = 0.82, relative risk = 1.0) (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 the Hardy-Weinberg equilibrium (table). Our results suggest that if 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 is in addition to the excess of homozygotes in the patients, accounts for the observed relative risk. In the

SIGNIFICANT EXCESS IN HOMOZYGOSITY FOR POLYMORPHIC SITES IN THE FIRST EXON 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 the result of assortative mating; (2) that the excess of homozygotes among patients reflects heterozygote advantage. The authors favour the second explanation for reasons they discuss. However, we would like 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.

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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. They too have extended our initial observations by studying a further 66 patients with DSM IIIR schizophrenia and 98 healthy controls (table). Onset age was not different in both groups. Nothen et al. found 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 = 0.12, one tailed; patients v controls’ Hardy-Weinberg X² = 0.67, p = 0.42, 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 could be a characteristic of a particular subgroup of schizophrenic patients. Our preliminary unpublished observations suggest that the effect is consistently as strong 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