Homozygosity at the dopamine D3 receptor locus is not associated with schizophrenia

Recently, Crocq et al. found that schizophrenia correlates with homozygosity at the D3/Msicl locus. This locus is characterised by a point mutation causing the substitution of a Ser residue with a Gly residue in the extracellular N-terminal domain of D3.

We studied 76 unrelated schizophrenic patients (mean age 42 ± 12.3, 55 males and 21 females), including 17 familial cases and 86 unrelated controls (mean age 48 ± 8.3, 50 males and 36 females). Diagnosis was made according to DSM III criteria. The controls had no family history of the patients and were free from psychiatric disorders and somatic illness. All subjects were white and from Normandy, France.

Genomic DNA was amplified by PCR according to Lannfelt et al. Digestion with Msi1 yielded two bands of 111 and 47 bp in all subjects. Subjects with a 306 bp band were classified 1-1, those with 100 bp and 98 bp bands 2-2, and those with all five bands 1-2.

The allelic distributions in the patients and control groups were not significantly different. The data were analyzed by the method of Woolf. There was no significant difference between genotype frequencies among patients and controls (χ² = 0.17, p = 0.95). Hardy-Weinberg equilibrium was conserved in both groups (schizophrenic patients χ² = 0.045, p = 0.05, controls χ² = 0.18, p = 0.65).

The allele frequencies were consistent with those previously reported. Moreover, as in the study of Crocq et al., there was no allele association between those with a 1-1 karyotype and D3/Msicl polymorphism. However, in contrast to Crocq et al. we did not find an association between schizophrenia and homozygosity at the D3/Msicl locus.

Crocq et al. analysed British and Eastern French groups of schizophrenic patients and their matched controls. The inci- dend of homozygosity was high in both samples of patients. However, close examination of the French data shows that the departure from Hardy-Weinberg equilibrium was significant in the British schizophrenic patients but for the controls. Thus, differences in genotype frequencies between patients and controls in the French group were because of frequent heterogeneous homozygosity in the controls rather than frequent homozygosity among the patients. Indeed, the frequency of homozygosity among the French patients was not significantly higher than among the UK controls (χ² = 2.98, p = 0.009). This rather puzzling finding strongly suggests that only the UK patient group has a high frequency of homozygosity and that the French controls described by Crocq et al. were, by chance, not representative of the general population. There was no significant difference between the genotype distributions of our controls and the UK controls (χ² = 0.71, p = 0.427), the French controls described by Crocq et al. and our controls (χ² = 2.45, p = 0.122), our patients and the UK patients (χ² = 5.53, p = 0.018), or the French patients described by Crocq et al. and our patients (χ² = 1.05, p = 0.31).

When combining our data with those of Crocq et al., the genotype frequencies in controls and patients are still significantly different (χ² = 11.15, p = 0.004) with a significantly higher frequency of homozygosity in patients (χ² = 10.98, p = 0.001). If the French controls of Crocq et al. are excluded, the differences are no longer significant (χ² = 5.90, p = 0.052).

The high homozygosity in patients remains (χ² = 5.90, p = 0.018) although with a reduced statistical significance. Since the statistical significance of these results is entirely based on the groups reported by Crocq et al., further studies including more subjects are needed before any definitive conclusion can be drawn concerning the association between schizophrenia and homozygosity at the D3/Msicl locus.

We are grateful to Dr Guy Gorozhe for advice. This work received financial support from the Centre National de la Recherche Scientifique, the Association Française contre les Myopathies, and Rhône Poulenc Rorer. CL was supported by a grant from the Association Claude Bernard.


C LAURENT
S CAVOYE
D SABOULIN
R MELODI
J MALLET

Laboratoire de Génétique Moléculaire de la Neurotransmission et des Processus Neurogénétique, Bat 32, CNRS, avenue de la Terrasse, 91198 Gif-sur-Yvette, France

D CAMPION

M MARTINEZ

Unite de Génétique Épidémiologique, INSERM U 155, Château de Longchamp, 75015, Paris, France

T D'AMATO

SHU de Psychiatrie Adulte, Hôpital de l’Timatier, 69677 Lyon-Bron, France

C BASTARD

CTS, 76230 Boisgaufre, France

S DOLLUS

CHSR, 76300 Sotteville les Rouen, France

Clinical and molecular studies in fragile X patients with a Prader-Willi-like phenotype

We have read with great interest the recent paper by de Vries et al. who describe an extended phenotype in fragile X patients. They state that the typical fragile X phenotype, which is characterised by mental retardation, long face with large, everted ears, and megalocytoses, is seen in the majority of adult patients. The clinical spectrum in young children is broad and not well delineated.

The eight patients described by de Vries et al. have truncal obesity and mental retardation.

Distribution and frequencies of alleles and genotype counts for patients and controls

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