LETTERS TO THE EDITOR

Epidermal mosaicism and Blaschko’s lines

I read with great interest the recent publication by Moss et al on epidermal mosaicism and Blaschko’s lines.1 In their paper, the authors describe the cytogenetic studies that were carried out in their patients. It is noteworthy that in their patient 1, mosaicism was found in only a small proportion of the cells analysed: the abnormal karyotype 46.XX,1+ was observed in 1/71 cells from a fibroblast culture of the dark skin area and in 2/15 cells of the light skin area, and in four karyotypes from cultured keratinocytes of the light skin area. In patient 2, trisomy 7 was present in 96% of cultured keratinocytes from a light skin area. In patient 3, 4/8% of fibroblasts from the dark skin area had a missing Y chromosome. This is a micro deletion with a 46,XY karyotype; therefore the eponym “Turner’s syndrome” would not be appropriate.

The question remains whether very low levels of mosaicism are of significance in their possible association with Blaschko’s lines or if they may be the result of artefacts of cell culture. We reported in 1982 a patient with Blaschko’s lines and chromosomal mosaicism who presented with facial and body asymmetry and linear hypopigmented areas with precise limitation at the midline. In this patient, chromosome studies showed pure trisomy 18 in fibroblasts grown from skin biopsies taken from the lines of Blaschko, whereas in normal areas of the skin the karyotype was normal. The comprehensive review on pigmentary anomalies with chromosomal mosaicism by Thomas et al2 showed that the majority of chromosomal abnormalities were structural defects present in varying proportions both in lymphocytes and in skin fibroblasts from either dark or light skin areas. The most frequent finding was 1(1p). This is of particular interest since pigmentary skin changes are one of the characteristics of the Klinefelter’s syndrome, and it is known that all cases of pigmentary anomalies associated with chromosomal mosaicism are hypomelanosis of Ito.

The studies and the report of our patient seem to indicate that chromosomal structural anomalies or a non-disjunctional event in a euploid cell or chromatid loss in an aneuploid melanoblast may be associated with a mutational event at the level of melanoblast morpho- genetic or mesodermal regulation. Great care should be taken in choosing the site of the skin biopsy to minimise the risk of admixture of cell types, and it is also recommended that chromosomes from as large a number of cells as possible should be analysed.

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

Recently, Crocq et al3 found that schizophrenia correlates with homozygosity at the D3/Msc1 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 schizophrenia patients (mean age 42.2±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 psychotropic disorders and somatic illness. All subjects were white and from Normandy, France.

Genomic DNA was amplified by PCR according to Lannfelt et al.4 Digestion with Msc1 yielded two bands of 111 and 47 bp in all subjects. Subjects with a 304 bp band were classified 1-1, while those with 111 and 98 bp bands were 2-2, and those with all five bands were 1-2.

The allelic distributions in the patients and control groups were not significantly different. (x2=0.081, p>0.05). Data were analysed by the method of Woolf.3 There was no significant difference between genotype frequencies among patients and controls (x2=0.17, p=0.95). Hardy-Weinberg equilibrium was conserved in both groups (schizophrenic patients x2=0.045, p=0.05, controls x2=0.18, p<0.05).

The allele frequencies were consistent with those previously reported. Moreover, as in the study of Crocq et al, there was no allelic association between homozygosity at the D3/Msc1 and the risk for schizophrenia. However, in contrast to Crocq et al we did not find an association between schizophrenia and homozygosity at the D3/Msc1 locus.

Crocq et al5 analysed British and eastern French groups of schizophrenic patients and their matched controls. The incidence 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 group of schizophrenic patients but for the controls. Thus, differences in genotype frequencies between patients and controls in the French group were because of frequent heterozygosity 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 (x2=2.98, p=0.001). This rather puzzling finding strongly suggests that only the UK patient groups have 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 (x2=0.01, p=0.72), the French controls described by Crocq et al and our controls (x2=2.45, p=0.12), or our patients and the UK patients (x2=5.23, p=0.08), or the French patients described by Crocq et al and our patients (x2=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 (x2=11.15, p=0.004) with a statistically higher frequency of homozygosity in patients (x2=10.98, p<0.001). If the French controls of Crocq et al are excluded, the genotype frequencies are no longer significant (x2=5.90, p=0.052).

The high homozygosity in patients remains (x2=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/Msc1 locus.

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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 megalotestes, 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.