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 on the patient presented. It is not worthy 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 keratino-
cytes from a light skin area. In patient 3, 4/8% of fibroblasts from the dark skin area had a missing Y chromosome. Thus, this is a mosaicism 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 hyperpigmentation 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 skin the karyotype was normal. The comprehensive review on pigmentary anomalies with chromo-
somal mosaicism by Thomas et al.2 showed that the majority of chromosomal abnormalities were structural defects present in varying propor-
tions both in lymphocytes and in skin fibro-
blasts from either dark or light skin areas. The most common finding was i(12p). This is of particular interest since pigmentary skin changes are one of the characteristics of the Klinefelter’s, i(12p) syndrome, and it is known that not all cases of pigmentary abnor-
malities associated with chromosomal mosaicism are hypomelanosis of Ito.

These 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 mutatio-
nal event at the level of melanoblast morpho-
getic 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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Homozogosity at the dopamine D3 receptor locus is not associated with schizophrenia

Recently, Crocq et al.3 found that schizophrenia correlates with homozogosity at the D3/MscI 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 link with 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.4 Digestion with MscI yielded two bands of 111 and 47 bp in all subjects. Subjects with a 304 bp band were classified as either 71% and 47 bp and 98 bp bands 2-1, and those with all five bands 1-2.

The allelic distributions in the patients and control groups were not significantly different. (χ2 = 0.081, p > 0.95). Data were ana-
ysed by the method of Woolf. There was no significant difference between genotype frequ-
ces among patients and controls (χ2 = 0.17, p > 0.95). Hardy-Weinberg equi-
librium was conserved in both groups (schizo-
phrenic patients χ2 = 0.045, p > 0.95, controls χ2 = 0.18, p > 0.95).

The allele frequencies were consistent with those previously reported. Moreover, as in the study of Crocq et al., there was no allelic associ-
ation between those at the 71 and 47 bp bands of the D3 MscI polymorphism. However, in contrast to Crocq et al. we did not find an association between schizophrenia and homozogosity at the D3/MscI locus.

Crocq et al.3 analysed British and eastern French groups of schizophrenic patients and their matched controls. The incidence of homo-
zogosity was high in both samples of patients. However, close examination of the French data shows that the departure from Hardy-Weinberg equilibrium was significant only for 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 homoz-
ygosity among the French patients was not signi-
ficantly higher than among the UK controls (χ2 = 2.98, p > 0.091). This rather puzzling finding strongly suggests that only the UK patient group has a high frequency of homoz-
ygosity and that the French controls described by Crocq et al. were, by chance, not representative of the general population. There was no signi-
ficant difference between the genotype distribu-
tion of our controls and the UK controls (χ2 = 0.71, p = 0.72), the French controls de-
scribed by Crocq et al. and our controls (χ2 = 2.45, p = 0.05), our patients and the UK patients (χ2 = 5.23, p = 0.08), or the French patients described by Crocq et al. and our patients (χ2 = 1.05, p = 0.61).

When combining our data with those of Crocq et al.4, the genotype frequencies in con-

controls and patients are still significantly different (χ2 = 11.15, p = 0.004) with a highly

higher frequency of homozygosity in patients (χ2 = 10.98, p < 0.001). If the French controls of Crocq et al. are excluded, these differences are no longer significant (χ2 = 5.90, p = 0.05).

The high homozygosity in patients remains (χ2 = 5.90, p = 0.018) although with a reduced statistical significance. Since the statistical sig-
nificance 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 homozogosity at the D3/MscI locus.

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1 Crocq MA, Manti R, Asherson P, et al. Association between schizophrenia and homoz-
2 Lannfelt L, Sokoloff P, Martres MP, et al. Amniotic fluid acid phosphatase in the Dopamine D3 receptor as a useful polymorphism for investig-

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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 megalocornea, 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.

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

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These are non-specific features and are present in the Prader-Willi syndrome (PWS) and many other conditions. The authors themselves state that their patients lack the typical features of PWS, which are low birth weight, neonatal hypotonia, narrow bifrontal diameter, hypogonadism, short stature, and feeding problems during the first year of life followed by hyperphagia and obesity in early childhood. In contrast, patients 1 and 2 developed severe obesity between the ages of 5 and 10 years without a change in diet. None of the patients fulfills the diagnostic criteria described by Holm et al. Although we agree that obese and mentally retarded boys should be tested for the fragile X syndrome, we feel that this phenotype should not be described as "Prader-Willi-like." This description is misleading and confusing, because all of the typical features of PWS are absent in the patients described by de Vries et al. Careful use of the terms "Prader-Willi syndrome" and "Prader-Willi-like" is important, because the syndrome is overdiagnosed by geneticists and paediatricians who are not familiar with the specific features of PWS. Although PWS can be rapidly tested for at the DNA level, careful clinical distinction of this syndrome from other conditions is necessary.

In conclusion, we suggest that obesity should be included as an important feature in the fragile X syndrome and the term "Prader-Willi-like" should be avoided.

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Genetic studies of thymic carcinoids in multiple endocrine neoplasia type 1

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disease characterised by hyperplasia or neoplasia of the parathyroid, anterior pituitary, and the endocrine pancreas.1 Genetic carriers are usually asymptomatic, but may present with related associated features, such as asymptomatic adrenal neoplasia, thyroid nodules, carcinoid tumours, lipomas, and pheochromocytomas, and have been labelled as a "malignant" or familial endocrine syndrome.2 The genetic basis for MEN1 is due to heterozygous mutations of the MEN1 gene. Most MEN1 cases have a de novo mutation, but familial cases with an autosomal dominant trait have been reported.3 The MEN1 gene spans over 250 kilobases, contains 12 exons, and is located on chromosome 11q13.4,5 These mutations include monogenic deletions, chromosome rearrangements, point mutations, and changes in the size of the gene.6,7

In linkage analysis, two markers, CL15 and CLGW4, were uninformative in the pedigrees. Meiotic recombinants were detected for markers telomeric of D11S197 (INT2 and D11S97), so negative lod scores (≥ 2.0) in both cases were obtained for these markers. However, peak positive lod scores were obtained at a recombination fraction of 0 for each of the other markers, ranging from 0.21 (D21S20) to 1.85 (D11S191 and D11S98), thus supporting linkage of this family to the MEN1 locus at 11q13 (results not shown). Genotypes of the family members are shown in the figure. In the youngest generation, four are evidently affected but the other 11, despite negative findings in biochemical and radiological screening, are "unknown" as all were below 35 years of age. One of these "unknown" cases (III.6) was found to have inherited the mutant (hatched) chromosome and thus requires repeated follow up to detect early signs of disease.

The insulinomas (III.2) and one hyperplastic parathyroid gland (II.9) showed loss of heterozygosity for all informative markers from D11S288/D11S149 to INT2 (results not shown). In all cases the loss involved the allele derived from the unaffected parent, that is, the putative wild type allele. The other four hyperplastic parathyroid glands and two megacystic thymic carcinoids did not show any loss of heterozygosity in the MEN1 region. Although minute somatic deletions or point mutations, undetectable by the current method, cannot be excluded, this finding, together with the lack of evidence of thymic carcinoids in MEN1 patients, suggests that the genetic trigger for their tumorigenesis might be different from that of common MEN1 related tumours. Further studies in delineating specific genetic mutations in thymic tumours are required.

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Pedigree of Tasman family 2 showing segregation of chromosome haplotypes for the marker systems which are listed on the left. The chromosome carrying the mutant allele (hatched line) has been inherited by subject III.6, illustrating the usefulness of linkage studies in preymomatic testing for MEN1. Meiotic crossovers, indicated by thin lines extending from the hatched lines, occurred in II.5, II.7, III.6, and III.9.
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