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+,mar 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. 7. This is a mosaic 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 hypopigmentation 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 al 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 consistent finding was Xp11p22. This is of particular interest since pigmentary skin changes are one of the characteristics of the Kitamura syndrome, and it is known that not all cases of pigmentary anomalies 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 mutational event at the level of melanoblast morphogenetic 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 chromosones 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 al2 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, 35 males and 21 females), plus 17 familial and 86 unrelated controls (mean age 48 ± 8, 35 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 al2. Digestion with MscI yielded two bands of 111 and 47 bp in all subjects. Subjects with a 304 bp band were classified as heterozygotes 96%, while 4 bp bands were 2-2, and those with all five bands 1-2.

The allelic distributions in the patients and control groups were not significantly different. (x2 = 0.08, p = 0.81). 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 = 0.68). Hardy-Weinberg equilibrium was conserved in both groups (schizophrenic patients: x2 = 0.045, p = 0.51, controls x2 = 0.18, p = 0.67).

The allele frequencies were consistent with those previously reported.4 Moreover, as in the study of Crocq et al1, there was no allelic association between those 17 familial and D3/MscI polymorphism. However, in contrast to Crocq et al2 we did not find an association between schizophrenia and homozogosity at the D3/MscI locus.

Crocq et al1 referred to other French and British groups of schizophrenic patients and the matched controls. The incidence of homozogosity 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 both the 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 homozogosity among the French patients was not significantly higher than among the UK controls (x2 = 2.98, p = 0.0011). This rather puzzling finding strongly suggests that only the UK patient group has a high frequency of homozogosity and that the French controls described by Crocq et al2 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 al2 and our controls (x2 = 2.45, p = 0.12), our patients and the UK patients (x2 = 5.23, p = 0.08), or the French patients described by Crocq et al2 and our patients (x2 = 1.05, p = 0.31).

We have found that the genotypes in controls and patients are not significantly different (x2 = 11.15, p = 0.004) with a significantly higher frequency of homozygosity in patients (x2 = 10.98, p = 0.0011). If the French controls of Crocq et al1 are excluded, the differences 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 al1, 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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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 megalocorneae, 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 trunical obesity and mental retardation.

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

| Distribution and frequencies of alleles and genotype counts for patients and controls |
|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|
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103 | 49 | 35 | 33 | 8 |
0.68 | 0.32 | 0.37 | 0.40 | 0.9 |

Genotypes
1-1 | 1-2 | 2-2

Schizophrenic patients (n=76)

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

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

1-1 | 1-2 | 2-2

Controls

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

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

1-1 | 1-2 | 2-2

Schizophrenic patients (n=76)

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Controls

Distribution and frequencies of alleles and genotype counts for patients and controls
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 neoplasms of the parathyroids, anterior pituitary, and the endocrine pancreas.1 Genetic reagents, such as asymptomatic adrenal neoplasia, thyroid nodules, carcinoid tumours, lipomas, and pheochromocytomas, have been reported at a much lower frequency.2 The age of presentation can range from early teens to late fifties. To date, only a few MEN1 related thymic carcinoids have been described. In the largest reported MEN1 family,1 four affected males were found to have metastatic thymic carcinoids but none of the patients was immediately related.1 One malignant and one benign case were reported in a kindred of German extraction3 and one case each in two kindships from Canada.9

The gene responsible for MEN1 was first mapped to chromosome 11q134 and subsequently predictive testing using RFLP markers was developed.6 The two commonest MEN1 lesions, parathyroid and endocrine pancreatic neoplasia and their sporadic counterparts, have been shown to have loss of heterozygosity in the MEN1 region suggesting that the putative MEN1 gene is a tumour suppressor gene.4,5,6,7,8 To date, only one bronchial carcinoid from a MEN1 patient has been studied but no loss of heterozygosity was found in the MEN1 genomic region.5 Thymic carcinoids, on the other hand, whether sporadic or familial, have never been studied at the molecular level.

We report here five affected sibs from a Tasmanian MEN1 family (Tasman family 2), of whom two were found to have malignant thymic carcinoids. Despite exhaustive genealogy study extending back to the first generation of this kindred in Tasmania, no consanguineous link can be established between this family and the largest reported MEN1 family in Tasmania.9 Furthermore, the mother of five affected sibs, who died of metastatic glucagonoma, was found to be the oldest member affected (figure).

The aims of this study were to determine the region of genetic linkage in Tasman family 2 and thus the feasibility of using MEN1 linked markers for predictive testing in this family, and to elucidate the genetic defects of MEN1 related thymic carcinoids.

Subject II.1 was admitted for surgery for primary hyperparathyroidism. Preoperative chest x-ray showed a shadow in the anterior mediastinum and CT scan identified a tumour mass arising in the thymus. An infiltrating mass of tumour and metastatic lymph node could not be dissected from the great vessels but were biopsied. Malignant thymic carcinoid was confirmed histologically. Patient II.5 had a history of insulinoma and multiple lipomatous and was found to have hypercalcaemia. CT scan showed a tumour in the anterior mediastinum arising from the thymus. Again a mass of tumour and lymph node extending around and infiltrating the great vessels was inoperable but was biopsied and malignant thymic carcinoid was confirmed. The other three sibs (II.3, II.7, II.9) and four children of the next generation (III.2, III.4, III.9, III.12) were all found to have hyperplastic parathyroid glands and an insulinoma was removed in addition from III.2. Lymphoblastoid cell lines were established from 24 family members.

Eleven DNA probes previously shown to be linked to the MEN1 locus using 14% metconic recombination, were used. DNA from the cell lines and tumours was extracted, digested to completion with appropriate restriction enzymes, electrophoresed, blotted onto nylon membranes, and hybridised to radiolabelled probes as previously described.9 DNA from the tumours and using the program LIPED with the criteria for scoring the disease state as described previously.10 Two malignant thymic carcinoids (II.1, II.5), five hyperplastic parathyroid glands (II.1, II.5, II.9, III.2, III.12), and one pancreatic tumour (III.2) were studied for loss of heterozygosity.