Letters to the Editor

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. Various non-specific features, such as asymptomatic adrenal neoplasia, thyroid nodules, carcinoid tumours, lipomas, and pheochromocytomas, have been reported at a much lower frequency. 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, four affected males were found to have metastatic thymic carcinoids but none of the patients was immediately related. One malignant and one benign case were reported in a kindred of German extraction and one case each in two kinships from Canada.

The gene responsible for MEN1 was first mapped to chromosome 11ql31 and subsequently predictive testing using RFLP markers was developed. The two commonest MEN1 lesions, parathyroid and endocrine pancreatic neoplasia and MEN1-related carcinoids, and their sporadic counterparts, have been shown to have loss of heterozygosity in the MEN1 region suggesting that the MEN1 gene is a tumour suppressor gene. 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. 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. 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 lipomata 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,II.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 (results submitted for publication) were hybridized to the DNA from cell lines and tumours which was extracted, digested to completion with appropriate restriction enzymes, electrophoresed, blotted onto nylon membranes, and hybridised to radiolabelled probes as previously described. Several DNA probes were mapped using the program LIPED with the criteria for scoring the disease state as described previously. Two malignant thymic carcinoids (II.1, II.5), five hyperplastic parathyroid glands (I.II.5, I.II.9, II.1, II.12), and one pancreatic tumour (III.2) were studied for loss of heterozygosity.

In linkage analysis, two markers, CL15 and CLG4W4, were uninformative in the pedigree. Meiotic recombinants were detected for markers telomeric of D11S427 (INT2 and D11S97), so negative lod scores (>-2.00 in both cases) were obtained for these markers. However, peak positive lod scores were obtained at a recombination fraction of 0.0 for each of the other markers, ranging from 0.21 (CD20) to 1.85 (D11S194 D11S427), 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 screenings, were "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 non-affected parent, that is, the putative wild type allele. The other four hyperplastic parathyroid glands and two malignant 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 failure to detect thymic carcinoids in MEN1 patients, suggests that the genetic trigger for their tumourigenesis 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 presymptomatic 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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Each year since 1970 a new volume of *Advances in Human Genetics* has appeared, edited every year by Harry Harris and Kurt Hirschhorn and every year containing five to seven review articles. It must be difficult picking topics which are interesting but not too fast moving for the inevitable slow book production process. Four of the five articles in this volume have suffered from this pedagogic handicap: advances coming too late to include. Moser's chapter on peroxosomal disorders missed the identification of the gene for X linked adreno-