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 hyponatremia, 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 parathyroids, anterior pituitary, and the endocrine pancreas.1 Genetic associations, such as asymptomatic adenomatous neoplasm, 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,3 four affected males were found to have metastatic thymic carcinoids but none of the patients was immediately related.4 One malignant and one benign case were reported in a kindred of German extraction5 and one case each in two kindships from Canada.6 The gene responsible for MEN1 was first mapped to chromosome 11q137 and subsequently predictive testing using RFLP markers was developed.8 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.9,10 To date, only one bronchial carcinoid from a MEN1 patient has been studied but no loss of heterozygosity was found in the MEN1 gene in this region.10 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.2 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 hypercalcemia. 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, I.I., II.9) and four children of the next generation (III.2, II.I., III.4, III.9, III.12) were all found to have hyperplastic parathyroid glands and an insulinoma was removed in addition from II.II.1. Lymphoblastoid cell lines were established from 24 family members.

Eleven DNA probes previously shown to be linked to the MEN1 locus, including 14% meiotic 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 Tentative assignment of the program LIPED with the criteria for scoring the disease state as described previously.10 Two malignant thymic carcinoids (II.I, II.II, II.II, II.III, III.12), and one pancreatic tumour (III.2) were studied for loss of heterozygosity.

In linkage analysis, two markers, CL15 and CLG4W, were uninformative in the pedigree. Meiotic recombinants were detected for markers telomeric of D11S427 (INT2 and D11S97), so negative lod scores (~2.6 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 (CD20) to 1.95 (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 screening, were "unknown" as were all 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 and 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 malignant thymic carcinoids did not show any loss of heterozygosity in the MEN1 region. Although somatic deletions or point mutations, undetectable by the current method, cannot be excluded, this finding, together with the lack of incidence 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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leucodystrophy. Jennifer Puck (X linked immunodeficiencies) writes that none of the genes, apart from that for chronic granulomatous disease, are X linked. Goddard and Solomon (Genetic aspects of cancer) discuss oncogenes and tumour suppressor genes but not microsatellite instability. Zannis, Kardas, and Zannat discuss oncogenes affecting lipoproteins, but only in connection with heart disease. The fifth chapter is by Grabowski on Gaucher disease. Each author, we are told, was given the opportunity at page proof time to write a short addendum containing the most up to date material, but only Moser took up the offer. The editorial hand was certainly not heavy. Chapters range from under 40 to almost 200 pages, and the style of references varies. Comparing Goddard and Solomon’s crisp 50 page summary of Genetic aspects of cancer with Moser’s 100 page review of peroxosomal disorders, both read well, but surely they are not aimed at the same audience? One audience wants an outline, the other wants details.

These books of major reviews, two to three years in gestation, are lucid and useful. It’s heartwarming that people of unquestionable authority are willing to put in so much time and effort for no material reward. The world must be the better for it and should at least have an editorial hand on it. It is a pleasant discovery that some of the world’s lesser known orphans have a sufficient number of them to survive, prosper, and even expe their parental alleles.

Now at last there is a book based on raw data discussed on a sound foundation of words, and aided but not dominated by suffi cient and necessary mathematics. Not only are all varieties of mutation discussed, largely around the authors’ expertise in blood and how it clots, but extensive appendices provide an anthology of all that is known to all our species and has been defined at the genomic level. Reading it imposes a pleasant if formid able task on the reviewer. Not only does it excel in clarity but many references, and their discussion, are remarkably recent.

In the treacherous fields of terminology and the word-number interface there are some minor problems worth comment. The diagrams, apparently based on astute use of a spreadsheet package, are very clear, numer ous, and well integrated with the text. How ever, the figures are referenced in the text by dimension in some does not assist clarity. The computer’s expression of chi squared to three places of decimals needs taming.

Harry Harris’s operational use of “polymorphism”, to cover frequencies exceeding ½, a reasonable use in the late sixties, is credited to Vogel and Motulsky 20 years later. Ford defined it unambiguously as “the occurrence together in the same locality of 2 or more discontinuous species of a species in such proportions that even the rarest of them cannot be maintained merely by mutation”. It is now used – or since the word is longer than the neutral term “variant” – misused – so extensively that Ford’s useful term, which dominated evolutionary theory for several decades, has died with him and it is too late to modify its well established misuse.

Linkage analysis, another casualty of widespread misunderstanding, features as a chapter, and benefits from Clayton’s advice. However, the pedigree shown does not indicate how a person’s family tree is used to calculate the probability of recombination between two genes. It would be helpful if the author had shown it, and explained it, on the same page as the last sentence. It is an important and fundamental concept with many applications.
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