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 I.1 and I.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.11

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,1 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.

GABRIELE GILLESSEN-KAASCH
BERNHARD HORSTMHEK
Universitätsklinikum Essen,
Hoflandstrasse 55,
D-43122 Essen, Germany.


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 features, 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,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 extraction4 and one case each in two kindships from Canada.5

The gene responsible for MEN1 was first mapped to chromosome 11q136 and subsequently predictive testing using RFLP markers was developed.7 The two commonest MEN1 lesions, parathyroid adenomas and pancreatic neoplasia and their sporadic counterparts, have been shown to have loss of heterozygocity in the MEN1 region suggesting that the presumptive MEN1 gene is a tumour suppressor gene.8–10

To date, only one bronchial carcinoid from a MEN1 patient has been studied but no loss of heterozygocity was found in the MEN1 genetic region.11 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.12 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 I.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 I.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.1, II.7, II.9) and four children of the next generation (III.2, II.1, II.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 (locus 1 using 14% mitotic 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.5,6 DNA was extracted using the programme LIFED with the criteria for scoring the disease state as described previously.5 Two malignant thymic carcinoids (II.1, II.5, II.12), five hyperplastic parathyroid glands (II.1, II.5, II.9, III.12, III.12) and one pancreatic tumour (III.2) were studied for loss of heterozygocity.

In linkage analysis, two markers, CL15 and CLG44, were uninformative in the pedigree. Meiotic recombinants were detected for markers telomeric of D11S427 (INT2 and D11S97), so negative lod scores (~2.60 in both cases) were obtained for these markers. However, positive lod scores were obtained at a recombination fraction of 0 for each of the other markers, ranging from 0.21 (C2D20 to 1.85 (D11S121 and D11S821), 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, Ms 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 repeat follow up to detect early signs of disease.

The insulinomas (II.2) and one hyperplastic parathyroid gland (II.9) showed loss of heterozygocity 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 malignant thymic carcinoids did not show any loss of heterozygocity in the MEN1 region. Although minute somatic deletions or point mutations, undetectable by the current method, cannot be excluded, this finding, together with the higher incidence of thymic carcinoids in MEN1 patients, suggests that the genetic trigger for their tumorigenesis might be different from that for the common MEN1 related tumours. Further studies in delineating specific genetic mutations in thymic tumours are required.

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BIN T TEH* NICHOLAS K HAYWARD MARILYN K WALTERS Queensland Cancer Fund Research Unit, Joint Experimental Oncology Program, Queensland Institute of Medical Research, Herston 4029, Australia.
JOSEPH J SHEPHERD CATHARINA LARSSON Department of Clinical Genetics, S-10401 Stockholm, Sweden.

*Present address: Department of Diabetes and Endocrinology, Princess Alexandra Hospital, Woolloongabba 4102, Queensland, Australia.


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, II.12, III.12, and III.9.

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leucodystrophy. Jennifer Puck (X linked immunodeficiencies) writes that none of the genes, apart from that for chronic granuloma-tous disease, is ready for closure. Goddard and Solomon (Genetic aspects of cancer) discuss oncogenes and tumour suppressor genes but not microsatellite instability. Zannis, Kardas-sis, and Zann discuss mutations affecting lipoproteins, but only in connection with heart disease. The fifth chapter is by Grazowsk-i 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 peroxisomal 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 a major undertaking. It is heartwarming to see 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 I hope that the readers will keep themselves informed? I’m reluctant to recommend them to students writing dissertations because most of the benefit to the student is in locating and digesting primary publications. They are good for orienting new postgraduates, with supplemental reading to bring them up to date. They would be good for summarising a field which has reached a milestone: next year would be just right for a major review of Huntington’s disease (but this series had one in 1991). Do working scientists read them? Personally I find them too long and too detailed. The much shorter articles in Annual Reviews of Genetics are about my limit for general interest topics. Trends in Genetics, Nature News and Views commentaries, and Cell minireviews are my main sources for filling in my own knowledge. Should you buy Advances in Human Genetics? Yes, if it contains a review you particularly want. No, if you just want to keep an adequate reference desk on shelf. Looking through the contents of past volumes, if you had them all on your shelf you would not have a summary of the milestone developments in human genetics over the period. For example, you would have nothing on physical mapping, on mitochondrial diseases, on microdeletions, on imprinting, on trinucleotide repeats, or, until this year, on retinoblastoma or onco-genes. Advances in Genetics does not possess a better job of covering a wide field at a consistent level. But if you happen to want an encyclopedic review of lipoproteins – and now that they are the centre of their efforts. But it is disease as well as heart disease, who doesn’t? – then this volume is just the ticket.

BOOK REVIEWS

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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 or more reviews. 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 the padding added to reviews coming too late to include. Moser’s chapter on peroxisomal disorders missed the identification of the gene for X linked adreno-