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, hypergonadism, 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. 4

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. 4 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, 5 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 Other associated 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 extraction 4 and one case each in two kindships from Canada. 5

The gene responsible for MEN1 was first mapped to chromosome 11q13 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. 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 gene region. 9 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 genealogic 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. 3 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.I. 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 lipomatosa 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.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 10-14 were used. DNA from the cell lines and tumours was extracted, digested to completion with appropriate restriction enzymes, blotted onto nitrocellulose membranes, and hybridised to radio-labelled probes as previously described. 15-17 Again using the program LIPED with the criteria for scoring the disease state as described previously, 15 Two malignant thymic carcinoids (III.5, II.2) and five hyperplastic parathyroid glands (II.1, II.5, II.9, III.12, and one pancreatic tumour (III.2) were studied for loss of heterozygosity.

In linkage analysis, two markers, CL15 and CLG64, were uninformative in the pedigree. Meiotic recombinations 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, peak positive lod scores were obtained at a recombination fraction of 0 for each of the other markers, ranging from 0.21 (CD20) to 1.85 (D11S140) (D11S97), 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, have been termed "unknown" as all were below 35 years of age. 3 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 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 lack of incidence of thymic carcinoids in MEN1 patients, suggests that the genetic trigger for their tumorigenesis might be different to the factor linked to the 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.
leucodystrophy. Jennifer Puck (X linked immunodeficiencies) writes that none of the genes, apart from that for chronic granulomata
tissue disease, have been found. Goddard and Solomon (Genetic aspects of cancer) discuss oncogenes and tumour suppressor genes but 
not microsatellite instability. Zannis, Kardas-
sis, and Zanni discuss situations affecting lipoproteins, but only in connection with 
heart disease. The fifth chapter is by Gra-
bowski on Gaucher disease. Each author,
we are told, was given the opportunity at page 
proof time to write a short addendum contain-
ing 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 re-
view of peroxisomal disorders, both read well,
but surely they are not aimed at the same audience? One audience wants an outline, the
others wants details.

These books of major reviews, two to three 
years in gestation are useful beasts. 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 the health of
those doing it also be improved. Harry
wonder just how much better it is? How many
people on the one hand are ready to spend a
two or day digesting the detail but, on
the other, aren't part of the personal
networks by which people active in the field
keep themselves informed? I'm reluctant
to recommend them to students writing disserta-
tions because most of the benefit to the stu-
dent 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 for occasional gaps in my reading.
Should you buy Advances in Human Gen-
etics? Yes, if it contains a review you particu-
larly want. No, if you just want to keep an
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had them all on your shelf you would not
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encyclopedia review of lipoproteins - and
now that the term is in disuse - or in Alzheimer's
disease as well as heart disease, who doesn't?
then this volume is just the ticket.

ANDREW P READ


Mutation remains both the major intellectual problem in its decipherment and interpre-
tation: it presents the major practical problem of the detection of mutations and the protec-
tion of our future.

It was assumed that loci were few and
alleles few or absent, and that mutation rates
difficult at all and from all alleles, and
equal in man, mouse, and fly, the basis for
the one in two chance of survival and death
life expectancy, were defined by Haldane,
Fisher, Wright, and Muller. These firm
theoretical foundations are now known to
have a somewhat tenuous relation to reality.
The theological concept of the purpose of human life is often built around the idea of homologous ideal, based on God's image, 
continued to permeate concept formation. When variation occurred it was assumed that
selection, rather than chance, dominated sur-

ival, and Fisher's term linkage disequilibrium (now often termed linkage disequilibrium)
and E B Ford's term polymorphism were
defined in 1930 and 1940 to cover allelic association and common allelic variation
respectively.

The realities of blood transfusion and the
display of extreme variation by the starch gel test have led to a somewhat more realistic
view that reality was often much more
tenuous, which abolished both the problem
and the possibility of having evolved to
discuss it, introduced a fertile mathematical di-

ROB HARRIS, University of Manchester, Manchester, UK

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Each year since 1970 a new volume of Adv-
cances in Human Genetics has appeared, edited
every year by Harry Harris and Kurt Hirsh-
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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 pedagogical important ad-

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