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Multiple Endocrine Neoplasia Type 1 (MEN1)

J.T. Pang and R.V. Thakker

INTRODUCTION

MULTIPLE ENDOCRINE neoplasia type 1 (MEN1), which has also been referred to as Wermer's syndrome [1, 2], is characterised by the combined occurrence of tumours of the parathyroid glands, the pancreatic islet cells and the anterior pituitary gland [3–5]. In addition to these tumours which constitute the major components of MEN1, adrenal cortical, carcinoid and lipomatous tumours have also been described [3–10]. These MEN1 tumours may either be inherited in an autosomal dominant manner or they may occur sporadically, i.e. without a family history. However, this distinction between sporadic and familial cases may sometimes be difficult; in some sporadic cases, the family history may be absent because the parent with the disease may have died before developing symptoms. In addition, the combinations of the affected glands and their pathological features, e.g. hyperplasia or single or multiple adenomas of the parathyroid glands, have been reported to differ in members of

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Table 1. Characteristic tumours and associated biochemical abnormalities of MEN1

MEN1 tumours	Biochemical features
Parathyroids	Hypercalcaemia and ↑ PTH
Pancreatic islets	
Gastrinoma	↑ Gastrin and ↑ basal gastric acid output
Insulinoma	Hypoglycaemia and ↑ insulin
Glucagonoma	Glucose intolerance and ↑ glucagon
Vipoma	↑ VIP and WDHA
PPoma	↑ PP
Pituitary (anterior)	
Prolactinoma	Hyperprolactinaemia
GH-secreting	↑ GH
ACTH-secreting	Hypercortisolaemia and ↑ ACTH
Non-functioning	Nil
Associated tumours	
Adrenal cortical	Hypercortisolaemia or primary hyperaldosteronism
Carcinoid	↑ 5-HIAA
Lipoma	Nil

↑, increased; PTH, parathyroid hormone; VIP, vasoactive intestinal peptide; WDHA, watery diarrhoea, hypokalaemia and achlorhydria; PP, pancreatic polypeptide; GH, growth hormone; ACTH, adrenocorticotrophin; 5-HIAA, 5-hydroxyindoleacetic acid.

the same family [8, 10–12]. The manifestations of MEN1 [5, 13], which are related to the sites of the tumours and to their products of secretion, are summarised in Table 1, and the focus of this article will be to review the molecular genetics of MEN1.

TUMOUR DELETION MAPPING STUDIES IN MEN1

A two-stage genetic mutational model has been proposed for the development of tumours in MEN1 [14], and this is analogous to that reported for retinoblastoma [15]. A loss of alleles involving the whole of chromosome 11 is observed in the parathyroid tumour of a patient with familial MEN1 [16] (Figure 1). This loss of alleles in the tumour results from the loss of chromosomal regions containing the marker loci; the complete absence of alleles suggests that this abnormality has occurred within all the tumour cells studied and indicates a monoclonal origin of the tumour. In addition, combined pedigree and tumour studies have demonstrated that such tumour-related allelic deletions of chromosome 11 occur on the chromosome inherited from the normal parent and not the one from the affected parent [11, 17]. Thus, the second mutation involves the normal dominant allele, and these studies [11, 17] provided additional evidence for the proposed two stage recessive mutation model for the development of tumours in MEN1.

Studies of MEN1 and non-MEN1 parathyroid tumours [11, 18], insulinomas [17] and anterior pituitary tumours [19, 20] have revealed that allelic deletions on chromosome 11 are also involved in the monoclonal development of these tumours. A detailed examination of such tumours has revealed allele loss within tumours involving smaller regions of chromosome 11, and these studies have mapped the *MEN1* locus to the region within chromosome band 11q13 [18, 19, 21]. These results indicate that the *MEN1* gene is telomeric to the *PYGM* locus, which encodes human muscle glycogen phosphorylase, and centromeric to the locus D11S146. In addition, these studies have demonstrated that allelic deletions of chromosome 11 are involved in the development of sporadic non-MEN1 parathyroid tumours, gastrinomas, prolactinomas and somatotrophinomas [19–23], and thus, the region 11q13 appears to be involved in the development of non-MEN1 and MEN1 endocrine tumours.

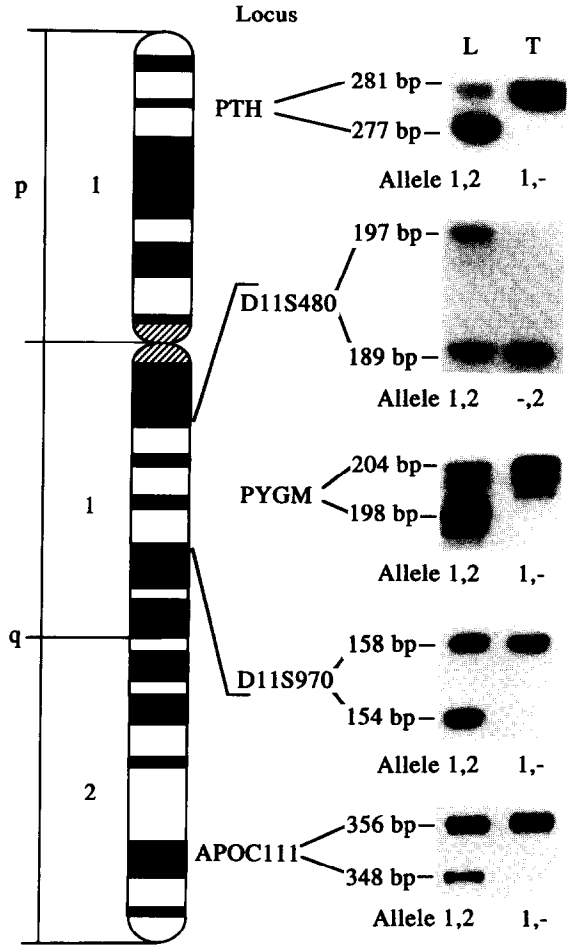

Figure 1. Loss of alleles on chromosome 11 in a parathyroid tumour from a patient with familial MEN1. The microsatellite polymorphisms obtained from the patient's leucocyte (L) and parathyroid tumour (T) DNA at the *PTH*, *D11S480*, *PYGM*, *D11S970* and *APOCIII* loci are shown. These microsatellite polymorphisms have been identified using specific primers or sequence tagged sites (STSs) for each of the loci which have been localised to chromosome 11, and are shown juxtaposed to their region of origin on the short (p) and long (q) arms of chromosome 11. The microsatellite polymorphisms are assigned alleles. For example, *D11S480* yielded a 197-bp product (allele 1) and a 189-bp product (allele 2) following PCR amplification of leucocyte DNA, but the tumour cells have lost the 197-bp product (allele 1) and are hemizygous (alleles −, 2). Similar losses of alleles are detected using the other DNA markers, and an extensive loss of alleles involving the whole of chromosome 11 is observed in the parathyroid tumour of this patient with MEN1. In addition, the complete absence of bands suggests that this abnormality has occurred within all the tumour cells studied, and indicates a monoclonal origin for this MEN1 parathyroid tumour.

FAMILY LINKAGE STUDIES IN MEN1

In order to localise the gene causing MEN1, family linkage studies were used as a parallel and complementary approach to the deletion mapping studies. This investigation of the tumour suppressor gene involved in the MEN1 syndrome was facilitated by the use of RFLPs (restriction fragment length polymorphisms) and microsatellite polymorphisms as genetic markers in studies of affected families. These polymorphisms

are inherited in a Mendelian manner, and their inheritance can be followed together with a disease in an affected family [24, 25]. The consistent inheritance of a polymorphic allele with the disease indicates that the two genetic loci are close together, i.e. linked. Genes that are far apart do not consistently cosegregate but show recombination because of the crossing-over during meiosis. By studying recombination events in family studies, the distance between two genes and the probability that they are linked can be ascertained [26–29]. The distance between two genes is expressed as the recombination fraction (θ), which is equal to the number of recombinants divided by the total number of offspring resulting from informative meioses within a family. The value of the recombination fraction (θ) can range from 0 to 0.5. A value of zero indicates that the genes are very closely linked, while a value of 0.5 indicates that the genes are far apart and not linked. The probability that the two loci are linked at these distances is expressed as a "LOD score", which is $\log_{10}$ of the odds ratio favouring linkage. The odds ratio favouring linkage is defined as the likelihood that two loci are linked at a specified recombination (θ) versus the likelihood that the two loci are not linked. A LOD score of +3, which indicates a probability in favour of linkage of 1000 to 1, establishes linkage between two loci, and a LOD score of −2, indicating a probability against linkage of 100 to 1, is taken to exclude linkage between two loci. LOD scores are usually evaluated over a range of recombination fractions (θ), thereby enabling the genetic distance and the maximum (or peak) probability favouring linkage between two loci to be ascertained [29]. This is illustrated in Figure 2 for family 16/91 which suffers from MEN1.

In family 16/91, shown in Figure 2, the disease and *INT2* [32] loci are co-segregating in nine of the 10 children, but in one individual (III.6), assuming a 100% penetrance (see below) in early childhood, recombination is observed. Thus, *MEN1* and *INT2* are co-segregating in 9/10 of the meioses and not segregating in 1/10 meioses, and the likelihood that the two loci are linked at $\theta = 0.10$ is $(9/10)^9 \times (1/10)^1$. If the disease and the *INT2* loci were not linked, then the disease would be associated with allele 1 in one half (1/2) of the children and with allele 2 in the remaining half (1/2) of the children, and the likelihood that the two loci are not linked is $(1/2)^{10}$. Thus, the odds ratio in favour of linkage between the *MEN1* and *INT2* loci at $\theta = 0.10$, in this family, is therefore $(9/10)^9 \times (1/10)^1 \div (1/2)^{10} = 39.67 : 1$, and the LOD score = 1.60 (i.e. $\log_{10}$ 39.67). Additional studies from other families have also demonstrated positive LOD scores

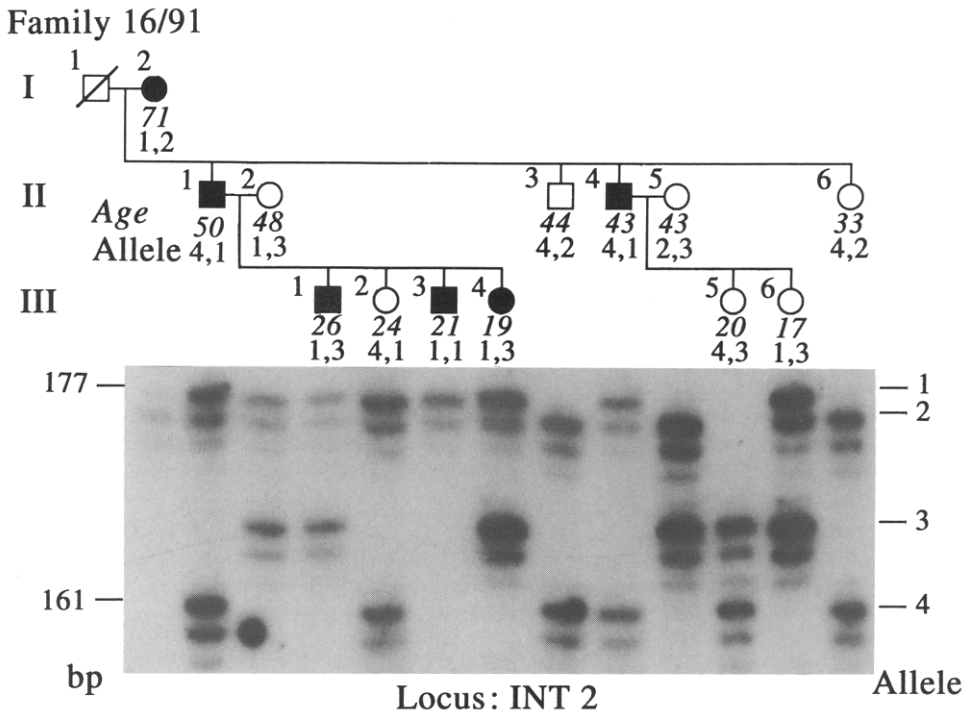

Figure 2. Segregation of *INT2* and *MEN1* in family 16/91. Genomic DNA from the family members (upper panel) was used with γ^{32} P triphosphate (ATP) for PCR amplification of the polymorphic repetitive element $(TG)_n$ at this locus. The PCR amplification products were detected by autoradiography on a polyacrylamide gel (lower panel). PCR products were detected from the DNA of each individual; these ranged in size from 161 to 177 bp. Alleles were designated for each PCR product and are indicated on the right. For example, individuals II.1 and II.4 reveal two pairs of bands on autoradiography. The upper pair of bands is designated allele 1 and the lower pair of bands is designated allele 4 and these two individuals are, therefore, heterozygous (alleles 1, 4). A pair of bands for each allele is frequently observed in the PCR detection of microsatellite repeats. The upper band in the pair is the "true" allele and the lower band in the pair is its associated "shadow" which results from slipped-strand mispairing during the PCR [30]. The segregation of these bands and their respective alleles together with the disease can be studied in the family members whose alleles and ages are shown. In some individuals, the inheritance of paternal and maternal alleles can be ascertained; the paternal allele is shown on the left. Individuals are represented as unaffected male (□), affected male (■), unaffected female (○) and affected female (●). The MEN1 phenotypes in this family were determined by biochemical screening and the age-related penetrance values derived from Figure 3 were used in linkage analysis, as described in the text. Individual II.1 is affected and heterozygous (alleles 4,1) and an examination of his affected children (III.1, III.3 and III.4) and his mother (I.2) and sibling (II.4) reveals inheritance of allele 1 with the disease. The unaffected individuals II.3, II.6, III.2 and III.5 have not inherited this allele 1. However, the daughter (III.6) of individual II.4 has inherited allele 1, but remains unaffected at the age of 17 years; this may either be a representation of age-related penetrance, or a recombination between the disease and *INT2* loci. (From Thakker RV, [31], with permission.)

between *MEN1* and the *INT2* locus [11, 33]. LOD scores from individual families can be summated, and the peak LOD score between *MEN1* and the *INT2* locus has exceeded +3, thereby establishing linkage between *MEN1* and *INT2* loci [11, 33, 34].

This segregation analysis relies on an accurate assignment of the MEN1 phenotype (i.e. affected or unaffected). This depends on the methods used to detect MEN1 and the age of the individual (Figure 3). The age-related onset, which helps in the estimation of the penetrance of MEN1 [31], was used in the phenotypic assessment of individuals in MEN1 families. This assessment is difficult because the clinical and biochemical manifestations in members of any one family are not uniformly similar [10–12, 35, 36] and because the age-related penetrance (i.e. the proportion of gene carriers manifesting symptoms or signs of the disease by a given age) has not been established. The proportion of affected individuals who have been detected at a certain age by clinical symptoms or biochemical screening in different series [35–39] has ranged from 11 to 47% at 20 years of age, 52 to 94% at 35 years and 83 to 100% at 50 years; biochemical screening, which detects asymptomatic patients, increased the proportion of affected individuals at all ages. Thus, the likelihood of wrongly attributing an unaffected status to an individual with no manifestation of the disease at the age of 35 years may be as high as 1 in 2, or approaching 1 in 20 and depends on whether clinical symptoms alone or biochemical screening methods are used to detect the disease. To improve this situation, further biochemical screening and systematic family studies have been undertaken [10, 12, 16, 36, 39]. Results from two studies [12, 16], in which 87 patients with familial MEN1 were investigated, are shown in Figure 3. This reveals that the age-related onset for MEN1 detected by clinical manifestations (symptomatic group), at 20, 35 and 50 years of age is 9, 43 and 75%, respectively. The respective age-related onset for MEN1 detected by biochemical screening is markedly improved to 44, 74 and 91%. Using this information to assign the disease phenotype, linkage was established (i.e. LOD score greater than +3) between *MEN1* and the *11q13* loci, *PYGM* and *INT2* [11, 16, 17, 33, 34]. Recombinants between *INT2* and *MEN1* have been observed, and this indicates that the oncogene *INT2* is not the *MEN1* gene itself [33, 40]. No recombinants between

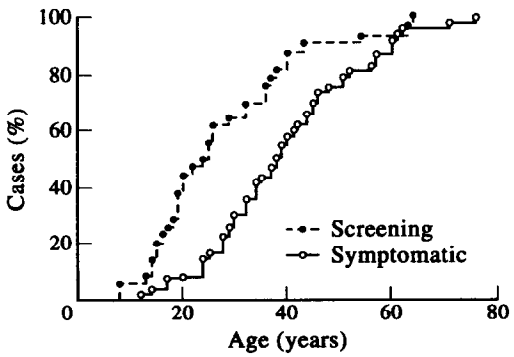

Figure 3. Age-related onset of familial MEN1. The ages for diagnosis in 87 patients with familial MEN1 were found to range from 8 to 76 years. The patients were subdivided into two groups, depending on the method used to detect MEN1. The symptomatic group consisted of 53 patients, and the age-related onset for MEN1 in these members at 20, 35 and 50 years of age was 9, 43 and 75%, respectively. In another 34 asymptomatic patients, MEN1 was detected by biochemical screening, and the respective age-related onset for MEN1 in these members increased to 44, 74 and 91%. Thus, biochemical screening detected an earlier onset of MEN1 in all age groups. (From Thakker RV, [24], with permission.)

Table 2. LOD scores for linkage of chromosome 11 markers and MEN1

Locus	Peak LOD score	Recombination fraction (θ)
D11S149	6.29	0.032
PGA	7.78	0.023
PYGM	13.71	0.047
D11S97	13.76	0.076
D11S146	8.27	0.000
INT2	7.04	0.059

Adapted from Thakker *et al.* [34], with permission.

MEN1 and *PYGM* have been observed in affected individuals from two large studies of six [41] and 27 [34] families with MEN1. The genetic map of this region (11q13) has been defined with polymorphic markers to be *11pter-D11S288-D11S149-11cen-PGA-PYGM-D11S97-D11S146-INT2-11qter* [42, 43] and linkage between *MEN1* and six of these markers has been established [34] (Table 2). In addition, the *MEN1* gene has been located by these studies to a region telomeric to *PGA* and centromeric to *D11S97* and in the vicinity of *PYGM* [34, 40]. The region containing the *MEN1* gene has been identified by genetic and physical mapping studies using pulsed field gel electrophoresis to be approximately 2–3 centiMorgans (cM) in size, which is equivalent to 2 to 3 million base pairs (Mbp) [24, 43]. The genetic markers defining this small region around the *MEN1* locus are proving useful in further studies of cloning the gene and in identifying individuals within a family who are at risk of developing the disorder.

INVESTIGATION OF CANDIDATE GENES FOR MEN1

The localisation of the *MEN1* gene to chromosome 11q13 and the elucidation of a 2–3 Mbp region which contains the *MEN1* gene has helped to reveal likely candidate genes from this region. A total of seven such genes (Table 3), referred to as *PRAD1*, *FAU*, *ZFM1*, *4F2HC*, *INT2*, *HSTF1* and *PP1α*, have been investigated as candidate genes for *MEN1*, on the basis of their functions and their localisations to chromosome 11q13, and this will be briefly reviewed.

PRAD1

The molecular basis of non-MEN1 parathyroid tumours has been investigated and a structural defect within the parathyroid hormone (*PTH*) gene itself identified. The human *PTH* gene has been localised to the short arm of chromosome 11 by using rodent–human hybrid cell lines [44, 45] and its nucleotide sequence determined [46]. Further analysis of the organisation of the pre-pro PTH gene revealed that it consists of three exons and two intervening sequences (introns). The first exon, at the 5′ end, encodes an untranslated regulatory domain, the second exon encodes the signal peptide and part of the "prohormone" sequence, and the third exon encodes the remainder of the "prohormone" sequence, together with the PTH peptide and the 3′ untranslated region [47]. Structural abnormalities within the organisation of the *PTH* gene have been identified in three non-MEN1 parathyroid adenomas [21, 48]. These abnormalities were associated with a separation of the first exon from the fragment containing the second and third exons together with a rearrangement in which the PTH regulatory elements became juxtaposed with "new" non-PTH DNA [49, 50], which was referred to as D11S287. Investigation of D11S287 localised it to

Table 3. Oncogenes located in 11q13 representing candidate genes for MEN1

Gene symbol	Gene	Reference
PRAD1/BCL1/ CCND1	Parathyroid adenomatosis type 1/B-cell lymphoma type 1/cyclin D1	50,56,68
FAU	[FBR-MuSv]-associated ubiquitously expressed gene	74
ZFM1	Zinc finger gene in the MEN1 locus	76
4F2HC/MDU1	4F2 cell surface glycoprotein heavy chain/monoclonal Duke University antibody 1	77,78
INT2	Human homologue of murine mammary tumour virus integration site 2	83
HSTF1/HST1	Heparin secretory transforming factor type 1/human stomach cancer transforming factor 1	84
PP1α	Protein phosphatase type 1 catalytic subunit	89

the long arm of chromosome 11, band 11q13, a region which contains the *MEN1* gene [11, 17, 18]. Detailed analysis revealed that D11S287 contained a sequence that was highly conserved in different species and that was expressed in normal parathyroids and in parathyroid adenomas. This expressed sequence from D11S287 was designated *PRAD1* and further mapping studies revealed that the *PRAD1* gene was not itself the MEN1 gene [51]. However, the combination of the clonal rearrangement of one copy of the *PRAD1* gene and the altered gene expression indicated that *PRAD1* is a dominant oncogene whose activation is associated with the development of parathyroid tumours. Similar activation of cellular oncogenes through analogous rearrangements has been implicated in the pathogenesis of several tumours, for example, Burkitt's lymphoma [52, 53] and chronic myeloid leukaemia [54, 55]. The *PRAD1* complementary DNA (cDNA) was isolated from a human placental cDNA library, and an analysis revealed that this cDNA encoded a protein of 295 amino acids which had similarities to the cyclin family of proteins [56].

Cyclins were first identified in the dividing cells of clams and sea urchins [57] in which they were associated with a cell cycle-regulated proteolysis in the immediate period preceding the onset of anaphase. Cyclins have also been identified in man, in whom they also have an important role in regulating progress through the cell cycle (Figure 4) by activating cyclin-dependent kinases (cdks) [58]. There are five main types of mammalian cyclins, referred to as A, B, C,D and E, and the D cyclins are further subtyped as D1, D2 and D3. Cyclins A and B have been implicated in the G2–M transition in various species from yeast to man, and the synthesis of both of these cyclins can also be detected to S phase [59]. Cyclins A and B are distinguished by sequence motifs and the timing of their destruction in the cell cycle [60]. Thus, cyclin A can first be detected near the G1–S transition, after which it continues to accumulate during interphase, with its subsequent degradation occurring in the metaphase stage of mitosis (M). However, cyclin B, which is also first synthesised during S phase and accumulates during interphase, is found to persist longer than cyclin A and is degraded at the metaphase–anaphase transition of mitosis (M) [59]. Cyclins A and B thus regulate entry to and exit from mitosis [61], and cyclin A is also important for the onset of DNA replication [59]. The functional roles of both cyclins A and B in regulating progress through the S, G2 and M phases are similar and either cyclin can drive the embryonic cell cycle [62].

The progress of the cell through the G1–S phases of the cell cycle involves cyclins C, D and E. Cyclins C and E have been reported to have an important function in G1 and the G1–S transition phases of the human cell cycle [58]. Cyclin C expression, which is constant throughout the cell cycle, reaches a peak during early G1 [63], and in contrast, cyclin E expression, which is highly periodic throughout the cell cycle, reaches a peak in late G1 near the G1–S phase transition [64]. Thus, these findings suggest that cyclin C may activate events, e.g. kinases, at the G1 restriction point and that cyclin E then activates the subsequent events, by forming a complex with the cyclin-dependent kinase cdk2, at the G1–S transition and at the beginning of S phase [63]. The D type cyclins are similar to cyclin E in regulating G1 phase progression and S phase commitment. However, the D type cyclins differ from the other cyclins in not being integral components of the cell cycle but in being the end-points of mitogenic pathways which may be mediated by either growth factors, e.g. colony-stimulating factor 1 (CSF1) [65], or nuclear proteins, e.g. the retinoblastoma protein (pRb), or the Rb-related protein, p107 [66, 67]. The D

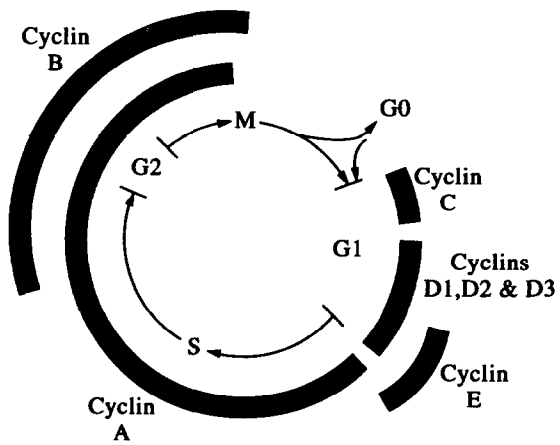

Figure 4. Schematic diagram of the cell cycle with the phases of mitosis (M), first gap (G1), DNA synthesis (S), second gap (G2) and the non-replicating stage of terminal differentiation (G0). The five main types of cyclins, referred to as A, B, C, D and E, which regulate in association with cyclin-dependent kinases, the progress of the cell through this cycle, are shown alongside their respective periods (solid bars) of expression. The expression of cyclin C is constant throughout the cell cycle and only the period of peak expression is shown.

type cyclins, unlike cyclins E or A, contain the motif Leu-X-Cys-X-Glu which is also found in the DNA viral oncoproteins SV40 T antigen, adenovirus E1A and human papilloma virus E7. The binding of these viral oncoproteins and the cyclin D-cdk4 complex directly to pRb and p107 is associated with phosphorylation and inactivation of these molecules, which in turn leads to an exit from the G1 phase and entry into the S phase. A comparison of the DNA sequences of cyclin D1 [68] and the *PRAD1* gene revealed them to be identical, and overexpression of the cyclin D1 (*PRAD1*) gene has been observed to occur in parathyroid tumours [50], breast carcinomas [69], squamous cell carcinomas of the head and neck [69], and oesophageal cancers [70]. In addition, chromosomal rearrangements involving the cyclin D1 (*PRAD1*) gene have been reported in B-cell lymphomas (BCL1) [71–73]. A further characterisation of the role of cyclin D1 in starting the cell cycle in these tumours will help to elucidate their respective aetiologies.

FAU

The *FAU* gene [Finkel-Biskis-Reilly murine sarcoma virus (FBR-MuSV) associated ubiquitously expressed gene] encodes a fusion protein of 133 amino acids that comprises the ribosomal protein S30 and a ubiquitin-like protein [74]. Investigation of the murine sarcoma viral genome (FBR-MuSV) revealed that it contains the mouse *c-fos* gene and the antisense sequence of the *fau* gene [74]. Thus, the interaction between the viral antisense sequence of the *fau* gene and the cellular *fau* gene would lead to a disruption of the normal constitutive expression of the *fau* gene, and this in turn was found to be associated with an increase in the transforming capacity of the virus and the occurrence of a sarcoma in the mouse. The association between the suppression of the *fau* gene and the occurrence of a tumour, suggested that the *fau* gene may be able to act as a tumour suppressor gene. The localisation of the *FAU* gene to human chromosome 11q13 raised the possibility that the *FAU* gene may be the gene causing MEN1. However, a further analysis using pulsed-field gel electrophoresis mapped the *FAU* gene 90 kb centromeric to *PYGM* [74]. In addition, detailed studies for germ-line mutations and somatic cell mutations in MEN1 patients and MEN1-associated tumours respectively, revealed no abnormalities of the *FAU* gene [75], and this combined with a more telomeric localisation of the *MEN1* gene [19] excluded the *FAU* gene as causing MEN1.

ZFM1

A novel gene, *ZFM1* (zinc finger gene in the *MEN1* locus) has recently been identified by the use of cosmids from 11q13 to screen cerebrum, cerebellum and fetal-liver cDNA libraries [76]. *ZFM1*, which is 20 kb in size, and consists of 14 exons, encodes a 623-amino-acid protein. The zfm1 protein contains a nuclear transport domain, a metal-binding motif and glutamine- and proline-rich regions. The gene is ubiquitously expressed, particularly in endocrine organs, e.g. the thyroid, pancreas, adrenal and ovary, and two mRNA transcripts of 3.3 and 2.7 kb have been detected. The role of *ZFM1* in the aetiology of MEN1 remains to be established.

4F2HC

The cell-surface glycoprotein 4F2 is a 120-kDa heterodimer that consists of a large 85–93 kDa glycosylated heavy chain (4F2HC) and a smaller 41 kDa non-glycosylated light chain (4F2LC) [77, 78]. The expression of the 4F2 glycoprotein, which is increased in actively proliferating cells, occurs rapidly and within 4 h after stimulation with a mitogen. These findings suggested that the expression of 4F2 may be associated with the G0–G1 transition of the cell cycle [79] (Figure 4). In addition, the monoclonal antibody to 4F2 was found to reduce calcium-stimulated PTH secretion from adenomatous parathyroid cells, thereby indicating a possible role for the 4F2 glycoprotein in the calcium-sensing receptor signal transduction pathway [80]. The gene encoding 4F2HC, which has also been referred to as MDU1 (Monoclonal Duke University Antibody 1), is 8 kb in size, consists of nine exons and is located on chromosome 11 [78]. A further sub-chromosomal localisation of this gene was revealed by comparative mapping studies of loci between the homologous regions on mouse chromosome 19 and human chromosome 11 and these indicated that the *4F2HC* (*MDU1*) gene was located on chromosome 11q13 in man [81]. Thus, this localisation to 11q13 and the likely functions of *4F2HC* indicated a role for this gene in the aetiology of MEN1. However, further localisation studies mapped the gene encoding 4F2HC to the interval between *PGA* and *PYGM* [82] and thus to a region that is centromeric to *MEN1*. These results indicate that the *4F2HC* gene is unlikely to be the *MEN1* gene.

INT2 and *HSTF1*

The proto-oncogenes *INT2* (human homologue of the murine mammary tumour virus integration site 2) [83] and *HSTF1* (heparin secretory transforming factor type 1) [84], formerly referred to as *HST1* (human stomach cancer transforming factor 1), are within 100 kb of each other, and are both located in 11q13 [84–86]. *INT2* and *HSTF1* encode basic fibroblast growth factor (bFGF)-related proteins and a role for bFGF as a circulating mitogenic factor for parathyroid cells has been defined by identifying a mitogenic stimulus, for bovine parathyroid endothelial cells, from the plasma of patients with MEN1 [87, 88]. However, genetic linkage studies which have demonstrated recombinants between *MEN1* and *INT2* [33, 34, 40] revealed that the distance between these two loci was in the region of 6cM, equivalent to 6Mbp, and thus, both *INT2* and *HSTF1* have been excluded as the *MEN1* gene.

PP1α

A cDNA encoding the catalytic subunit of protein phosphatase 1, referred to as *PP1α*, has been localised to 11q13 by somatic cell hybrid mapping and *in situ* hybridisation studies [89]. Protein phosphatases and protein kinases, respectively, dephosphorylate and phosphorylate serine and threonine residues, and by their opposing actions help to regulate cellular functions and cell division. For example, a lack of *PP1α* in *Drosophila* mutants inhibits the progression of the cell cycle in the late stage of mitosis (M, Figure 4) [89], and in mammals the conversion and maintenance of the retinoblastoma protein (pRb) in its active form involves PP1α-mediated dephosphorylation [90, 91] and PP1α binding to the hypophosphorylated retinoblastoma protein [92], respectively. Thus, PP1α plays an important role in cell proliferation, and the localisation of the *PP1α* gene to the interval between PYGM and D11S97 on chromosome 11q13 [43, 93] indicates that the *PP1α* gene may be a candidate for the *MEN1* gene. The role of this interesting gene in the aetiology of MEN1 remains to be elucidated.

CONCLUSIONS

Molecular genetic studies have localised the gene causing MEN1 to a 2–3 cM region within 11q13 and have revealed the

MEN1 gene to be a tumour suppressor gene. The establishment of genetic markers flanking the disease locus have helped in further studies aimed at cloning this gene, and also in identifying those family members who are at a high risk of developing the disease. In the future, a greater understanding of the pathogenesis of endocrine tumours will result from the cloning and characterisation of the gene causing MEN1.

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