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38. Order Primates Linnaeus 1758; suborder Anthropoidea Mivart 1864; infraorder Catarrhini Geoffroy, 1812; superfamily Hominoidea Gray 1825; family not assigned. Genus *Morotopithecus* gen. nov. **Generic diagnosis:** Large hominoid, male weight around 40 to 50 kg, most comparable in facial and dental morphology to *Proconsul* and *Afropithecus*. Differs from later Miocene and extant apes in having a longer midface and has less alveolar prognathism than extant large apes. Differs from *Afropithecus*, later Miocene hominoids, and extant apes in the greater degree of cingular development on cheek teeth, especially molars. Differs from *Afropithecus* and *Proconsul* in having a narrower interorbital region and larger premolars relative to M1; differs from *Proconsul* in a smaller M2 and M3 relative to M1. Differs from *Afropithecus* in possessing a shorter premaxilla, a higher face, a broader nasal aperture (*5*), a P^3 that is much broader buccally and in which the paracone is situated closer to the protocone, buccal wrinkling on the side of the molars, and a larger M^3. Judging from worn occusal surfaces, the enamel was intermediate thin as in *P. major* (*51*). Further, computed tomography scans on the skull of *Afropithecus* reveal a thick palate with a small incisive canal (*52*), an anatomical condition that is distinctly different from the large canal of the Moroto palate (*53*). The glenoid is rounder in shape and more like that of extant apes and atelines than can be inferred for Miocene hominoids other than *Oreopithecus* and possibly *Dryopithecus* (*42*). Lumbar morphology differs from that of *Proconsul* and resembles that of *Oreopithecus*, possibly *Dryopithecus*, and extant large apes and siamangs in transverse process position. Proximal femoral morphology resembles that of cercopithecines and primitive hominoids such as *Proconsul*, differing from that of extant apes. Distal femoral anatomy resembles that of *Proconsul*, *Kenyapithecus*, and extant apes in mediolateral breadth but differs from hylobatids, *Proconsul*, and *Kenyapithecus* in the buttressing of the intercondylar notch. In 1962, L. S. B. Leakey referred the Moroto palate to *Pseudogorilla* (*54*) but did so without any species diagnosis. *Pseudogorilla* was created by Elliot in 1912 for ape specimens from the "Upper Congo" (*55*), now referred to *Gorilla*. Regardless of the validity of *Pseudogorilla*, the Moroto fossil is clearly different from any extant ape. **Type species:** *Morotopithecus bishopi* sp. nov. **Etymology:** Moroto, after Moroto township in Karamoja District in Uganda, and *pithekos* from the Greek for ape; and after the late W. W. Bishop. **Type specimen:** UMP 62-11 (UMP, Ugandan Museum of Paleontology), a palatofacial specimen with all teeth. **Type locality:** Moroto II. **Distribution:** Early Miocene, Karamoja District, NE Uganda. **Hypodigm:** Type and UMP 62-10 and UMP 66-01, which are probably associated mandibular fragments; UMP 62-12, left upper canine; UMP 67-28, middle lumbar vertebra; UMP 68-05, middle lumbar vertebral body; UMP 68-06, a last thoracic vertebra; UMP 68-07, the lamina and base of a spine of a lumbar vertebra; MUZM 80, right and left femoral pieces (all from the Moroto II locality); and MUZM 60, scapular fragment with glenoid (Moroto I locality). **Specific diagnosis:** As for genus.
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56. We thank the many helpful individuals in Uganda, including the Office of the President, the National Research Council, and the staff at the Zoology Museum at Makerere University, as well as C. Chapman for the many efforts made on our behalf. We thank D. Aleper for assistance in the field; B. Masek for assistance in the laboratory; M. Mehrer and J. Flynn; and the American School of Prehistoric Research and the L. S. B. Leakey Foundation for contributing funding to this project.

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Positional Cloning of the Gene for Multiple Endocrine Neoplasia–Type 1

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Multiple endocrine neoplasia–type 1 (MEN1) is an autosomal dominant familial cancer syndrome characterized by tumors in parathyroids, enteropancreatic endocrine tissues, and the anterior pituitary. DNA sequencing from a previously identified minimal interval on chromosome 11q13 identified several candidate genes, one of which contained 12 different frameshift, nonsense, missense, and in-frame deletion mutations in 14 probands from 15 families. The *MEN1* gene contains 10 exons and encodes a ubiquitously expressed 2.8-kilobase transcript. The predicted 610–amino acid protein product, termed menin, exhibits no apparent similarities to any previously known proteins. The identification of *MEN1* will enable improved understanding of the mechanism of endocrine tumorigenesis and should facilitate early diagnosis.

Familial cancer syndromes have attracted widespread interest over the past decade, in part because of their potential to shed light on the general mechanisms of carcinogenesis. Positional cloning methods have led to the precise identification of the responsible gene for more than a dozen such disorders (*1*). In keeping with the hypothesis originally articulated by Knudson for retinoblastoma (*2*), most of the responsible genes are of the tumor suppressor type. In such a circumstance, affected individuals have inherited one altered copy of the responsible gene from an affected parent, but the tumors have lost the remaining copy (the wild-type allele) as a somatic event. Thus, the inheritance pattern is dominant, but the mechanism of tumorigenesis is recessive. The importance of gene discovery often extends beyond affected pedigrees, as the same tumor suppressor gene is often found to play a role (by mutation of both alleles) in sporadic cases of the same neoplasm.

Multiple endocrine neoplasia–type 1 (MEN1) (OMIM *131100) appears to be a compelling example of this paradigm, with prevalence estimates ranging from 1 in 10,000 to 1 in 100,000 (*3*, *4*). Affected individuals develop varying combinations of tumors of parathyroids, pancreatic islets, duodenal endocrine cells, and the anterior pituitary, with 94% penetrance by age 50 (*4*). Less commonly associated tumors include foregut carcinoids, lipomas, angiofibromas, thyroid adenomas, adrenocortical adenomas, angiomyolipomas, and spinal cord ependymomas. Except for gastrinomas, most of the tumors are nonmetastasizing,

but many can create striking clinical effects because of the secretion of endocrine substances such as gastrin, insulin, parathyroid hormone, prolactin, growth hormone, glucagon, or adrenocorticotropic hormone.

Nine years ago *MEN1* was mapped (*5*) to chromosome 11q13 by linkage analysis (Fig. 1A). Subsequent investigation of a large number of pedigrees by many groups revealed no evidence of locus heterogeneity (*6*, *7*). The identification of critical recombinants recently led to the conclusion that the candidate interval is bounded by marker D11S1883 on the centromeric side and marker D11S449 on the telomeric side (*7*) (Fig. 1B).

In a concerted effort to identify *MEN1*, we developed 18 new polymorphic markers in the *MEN1* region of 11q13 (*8*) and constructed a fully overlapping 2.8-Mb contig map of yeast, bacteriae, and P1 artificial chromosome (YAC, BAC, and PAC) clones and P1 clones (*9*). We then carried out an intensive search for transcripts, which resulted in the identification of 33 candidate genes (*10*). To focus the search more precisely, we also took advantage of the observation that tumors arising in MEN1 patients are frequently found to have somatically lost the wild-type allele of markers in the vicinity of the gene (*5*, *11*). Interstitial deletions or mitotic crossing-over events of this sort provide information on candidate interval boundaries. We used tissue microdissection to separate tumor cells from stroma (*12*) in a large number of familial MEN1 tumors and sporadic gastrinomas, and we found an entirely consistent minimal interval (Fig. 1B) bounded centromerically by marker PYGM (*12–14*) and telomerically by marker D11S4936 (*14*).

We analyzed the sequence of two BACs (b137C7 and b79G17) covering most of this interval (Fig. 1C) (*15*), as well as publicly available sequence of a few cosmids just telomeric to b79G17 (*16*). A total of eight transcripts were identified by comparison with expressed sequence tag (EST) databases and computer analysis for the likely presence of exons. Each of these transcripts was considered a possible candidate for *MEN1*.

One of these eight candidates, originally designated *mu*, was first identified by PowerBLAST matches (*17*) between shotgun sequence assemblies derived from b137C7 and 44 different ESTs in the dbEST database. Twenty-six of these ESTs were human clones isolated from seven different tissues; the remaining 18 ESTs were derived from mouse or rat libraries. Interestingly, 20 of the human ESTs had previously been as-

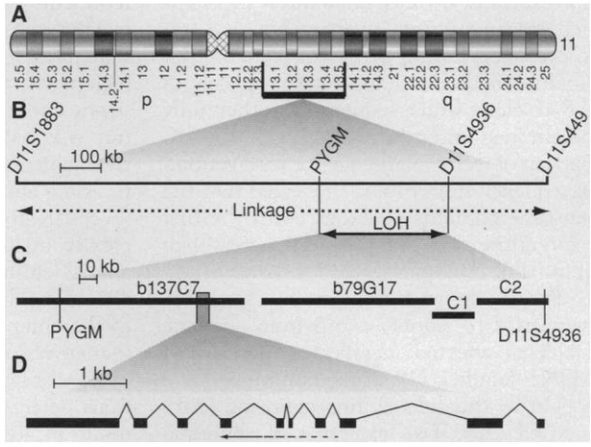

Fig. 1. Steps in the positional cloning of the *MEN1* gene. Initial linkage to chromosome 11q13 (**A**) led to finer mapping by meiotic recombination and tumor loss of heterozygosity (LOH) analysis (**B**). Nearly complete bacterial clone coverage of the most likely candidate interval (PYGM to D11S4936) was achieved with BACs b137C7 and b79G17 and cosmids cSRL116b6, 23c9, and 114g4 (*16*), which could be assembled into two sequence contigs, C1 and C2 (**C**). DNA sequencing revealed several candidate genes, one of which (**D**) was found to harbor mutations in 14 of 15 probands. The arrow indicates the direction of transcription.

Fig. 2. Predicted amino acid sequence of the protein encoded by the *MEN1* gene, as derived from an apparently full-length leukocyte cDNA clone. The first methionine is associated with an excellent Kozak (*26*) consensus sequence (GCCATGG), and no other in-frame ATG codons are found upstream. The GenBank accession numbers for the cDNA (2772 bp) and genomic (9181 bp) sequences are U93236 and U93237, respectively.

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MGLKAAQKTL FPLRSIDDVV RLFAAELGRE EPDLVLLSLV LGFVEHFLAV NRVIPTNVPE   60
LTFQPSPAPD PPGGLTYFPV ADLSIIAALY ARFTAQIRGA VDLSLYPREG GVSSRELVKK  120
VSDVIWNSLS RSYFKDRAHI QSLFSFITGT KLDSSGVAFA VVGACQALGL RDVHLALSED  180
HAWVVFGPNG EQTAEVTWHG KGNEDRRGQT VNAGVAERSW LYLKGSYMRC DRKMEVAFMV  240
CAINPSIDLH TDSLELLQLQ QKLLWLLYDL GHLERYPMAL GNLADLEELE PTPGRPDPLT  300
LYHKGIASAK TYYRDEHIYP YMYLAGYHCR NRNVREALQA WADTATVIQD YNYCREDEEI  360
YKEFFEVAND VIPNLLKEAA SLLEAGEERP GEQSQGTQSQ GSALQDPECF AHLLRFYDGI  420
CKWEEGSPTP VLHVGWATFL VQSLGRFEGQ VRQKVRIVSR EAEAAEAEEP WGEEAREGRR  480
RGPRRESKPE EPPPPKKPAL DKGLGTGQGA VSGPPRKPPG TVAGTARGPE GGSTAQVPAP  540
AASPPPEGPV LTFQSEKMKG MKELLVATKI NSSAIKLQLT AQSQVQMKKQ KVSTPSDYTL  600
SFLKRQRKGL                                                         610
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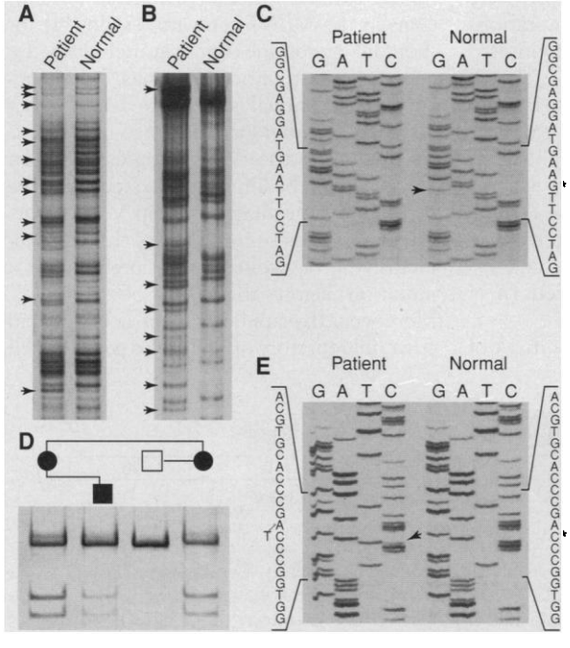

Fig. 3. Detection of frameshift and nonsense mutations. (**A**) Analysis of exon 2 in a MEN1 patient and a normal control, using ddF to reveal pattern differences (arrows) indicative of a possible mutation (*20*). (**B**) Abnormal ddF pattern in exon 9 from a different patient. (**C**) Identification of a single nucleotide deletion by sequencing of a cloned exon 2 PCR product from the patient whose ddF pattern is shown in (A). The sequence shown is of the antisense strand; the mutation is 512delC. (**D**) This frameshift mutation was confirmed by detecting the presence of a new AfI II site in PCR-amplified exon 2 from this patient and two affected relatives. (**E**) Direct sequencing of the exon 9 PCR product from (B), revealing the presence of a heterozygous C → T substitution. Again the sequence is of the antisense strand; the mutation creates a stop codon (TGG → TAG or W436X).

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sembled into a UniGene cluster and placed on the transcript map between markers D11S913 and D11S1314 (*18*).

These 26 human ESTs constituted a 1.9-kb cDNA contig. Northern (RNA) blotting (*10*) identified a transcript of 2.8 kb that was expressed in roughly equivalent amounts in all adult tissues tested, including pancreas, adrenal medulla, thyroid, adrenal cortex, testis, thymus, small intestine, stomach, spleen, prostate, ovary, colon, and leukocytes. Screening of a leukocyte cDNA library yielded an apparently full-length 2.8-kb clone whose sequence was then fully determined on both strands (Fig. 2). Comparison of the cDNA sequence with genomic sequence from b137C7 revealed that the *mu* gene contains 10 exons (with the first exon untranslated) and extends across 9 kb (Fig. 1D).

Primers designed from intronic sequence were used to amplify exons from genomic DNA of affected members of 15 typical MEN1 families (*19*), and mutations were sought by the dideoxy fingerprinting (ddF) method (*20*). Two examples of abnormal ddF patterns are shown in Fig. 3, A and B (exons 2 and 9). Sequencing of polymerase chain reaction (PCR)–amplified material (Fig. 3E), or in some instances cloned products (Fig. 3C), was used to identify the nature of the abnormality. For 10 different mutations for which other affected family members were available for study (all except E363del and W436X), we confirmed that the observed alteration was inherited concordantly with the MEN1 phenotype (Fig. 3D) (*21*).

A total of five frameshift mutations, three nonsense mutations, two in-frame deletions, and two missense alterations were identified (Fig. 4). Two mutations (416delC and 512delC) were encountered twice in families not known to be related. None of these mutations were observed in an analysis of 71 normal DNA samples. Four relatively common polymorphisms—R171Q (CGG/CAG), L432L (CTG/CTA), D418D (GAC/GAT), and A541T (GCA/ACA)—were also encountered and were observed in 1.4%, 0.7%, 42%, and 4% of normal chromosomes, respectively (n = 142).

The identification of mutations in 14 of 15 unrelated affected individuals leaves little doubt that the *MEN1* gene has been identified. We propose the name menin for the 610–amino acid predicted protein product. Sequence analysis provides few clues to its normal function. There is no signal peptide, and, although there are four moderately hydrophobic regions in the NH_2-terminal half of the protein, these are not likely to represent transmembrane domains. Three leucine-rich regions match the PROSITE signature for leucine zippers (*22*), but these regions are not amphipathic and have no strong coiled-coil potential, and this signature is known to generate many false positive matches. Nuclear localization signatures are absent. The protein sequence has several regions of low compositional complexity, including a very hydrophilic mixed-charge cluster between residues 446 and 491 (*23*). There is no detectable homology to the complete genomic sequence of *Saccharomyces cerevisiae*.

The observation that many of the mutations detected (Fig. 4) would most likely result in loss of function of the protein product is consistent with a tumor suppressor mechanism. Such a mechanism distinguishes MEN1 from the related disorder multiple endocrine neoplasia–type 2, where activating mutations of the *RET* oncogene are responsible (*24*). Although, in the absence of examples of complete gene deletion, we cannot rule out the possibility of a dominant negative effect of the truncated menin protein product, the observation of mutations in which as few as 82 amino acids would be left intact (357del4, Fig. 4) makes this mechanism unlikely. It will be of great interest to determine whether, as predicted by the Knudson model (*2*), somatic mutations in the *MEN1* gene are responsible for sporadic endocrine tumors, including the common parathyroid adenomas, which occur at an annual incidence of 154 per 100,000 in individuals over age 60 (*25*).

Now that the *MEN1* gene has been cloned, it will be important to study the role of *MEN1* gene diagnostics in younger at-risk individuals so as to assess the value of identifying or excluding the presence of a mutation before the onset of symptoms. Moreover, the application of a broad and powerful repertory of molecular genetic, cell biological, and animal model approaches can now be initiated to pursue an understanding of the molecular basis of this disorder, with the eventual goal of developing better therapeutic strategies.

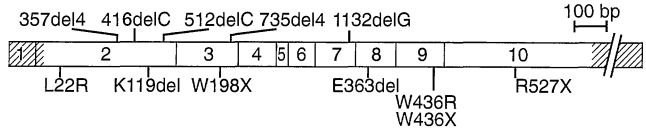

Fig. 4. Summary of mutations identified in 15 unrelated MEN1 patients. The locations of the five frameshift mutations are shown above a diagram of the *MEN1* gene, with the exons numbered; cross-hatched areas are untranslated. Two in-frame deletions of a single amino acid, three nonsense mutations, and two missense mutations are shown below the gene diagram. The 416delC and 512delC mutations were each encountered twice. Mutation abbreviations follow standard nomenclature (*27*).

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15. BAC clones were from the Research Genetics library (Huntsville, AL). BAC DNA was purified by means of a cleared-lysate diatomaceous earth method [H. Q. Pan *et al.*, *Genet. Anal. Tech. Appl.* **11**, 181 (1994)]. Sequencing was undertaken using the double-stranded, shotgun-based approach [A. Bodenteich, S. Chissoe, Y. F. Wang, B. A. Roe, in *Automated DNA Sequencing and Analysis Techniques*, M. D. Adams, C. Fields, J. C. Venter, Eds. (Academic Press, London, 1994), pp. 42–50]. The resulting sequences were screened to eliminate vector, assembled into contiguous fragments, and proofread using the Phred/Phrap/Consed system developed by P. Green (http://chimera.biotech.washington.edu/uwgc/). Contigs larger than 1 kb were deposited before publication in the "unfinished" division of the high-throughput genome sequencing (HTGS) GenBank database with no restriction on public access. Accession numbers are AC000134 and AC000159 for BACs b13767 and b79G17, respectively. Completion of the BAC sequences is still in progress.
16. These cosmid sequences are available at http://mcdermott.swmed.edu.
17. All assembled contigs larger than 1000 bases were analyzed with the program PowerBLAST (J. Zhang and T. Madden, *Genome Res.*, in press; ftp://ncbi.nlm.nih.gov/pub/sim2/PowerBlast/), which masks low-complexity sequences and repetitive elements and then performs simultaneous BLASTN and BLASTX searches, reporting the results in graphical form. Both the nr and est databases at http://ncbi.nlm.nih.gov/were searched. Contigs were also analyzed with the program GRAIL (http://avalon.epm.ornl.gov/) and the programs FEXH and HEXON (http://dot.imgen.bcm.tmc.edu:9331/gene-finder/gf.html).
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19. The diagnosis of MEN1 was based on the presence of tumors in two of the three principal systems (parathyroid, enteropancreatic endocrine tissue, or anterior pituitary). Diagnosis of familial MEN1 required at least one first-degree relative with a tumor of one or more of these systems. There were 1 to 47 living affected members in each kindred, with a median of 5. All participating family members gave full informed consent in a protocol approved by the NIDDK Institutional Review Board.
20. Genomic DNA was isolated from blood samples with the Qiagen Kit (Chatsworth, CA). Exons 2 through 10

Endosomal Targeting by the Cytoplasmic Tail of Membrane Immunoglobulin

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Membrane-bound immunoglobulin (mIg) of the IgG, IgA, and IgE classes have conserved cytoplasmic tails. To investigate the function of these tails, a B cell line was transfected with truncated or mutated γ2a heavy chains. Transport to the endosomal compartment of antigen bound by the B cell antigen receptor did not occur in the absence of the cytoplasmic tail; and one or two mutations, respectively, in the Tyr-X-X-Met motif of the tail partially or completely interrupted the process. Experiments with chimeric antigen receptors confirmed these findings. Thus, a role for the cytoplasmic tail of mIg heavy chains in endosomal targeting of antigen is revealed.

The B cell antigen receptor (BCR) is a multiprotein complex that includes the membrane-bound immunoglobulin molecule (mIg) and the Ig-α,Ig-β heterodimer (*1*). The latter molecules function as the signaling subunit of the BCR. They are also required for the intracellular transport of IgM-BCR to the endosomal compartment, where the bound antigen is proteolytically degraded (*2*). All classes of mIg are associated with the Ig-α,Ig-β heterodimer (*3*), but the heavy chains differ in the length of their cytoplasmic tails: there are 3 amino acids for μm and δm tails and 28 amino acids for γm and εm tails. No function has so far been attributed to the conserved cytoplasmic sequence of mIgG molecules that are expressed on memory B cells.

To analyze the function of the 28–amino acid cytoplasmic tail of the γ2am heavy chain, we truncated or mutated the sequence (*4*) coding for this tail in the expression vector pSV2neoγ2am (*5*). The chain lacking all cytoplasmic amino acids except for the three KVK (*6*) residues (which are identical to the COOH-terminus of the μm chain) we called γ2amtl. Point mutations were introduced to change the YXXM motif in the γ2am cytoplasmic sequence to either LXXM (γ2amY20L) or LXXL (γ2amY20L,M23L). Expression vectors for these heavy chains were transfected into K46λ12 B lymphoma cells expressing a λ1 light chain. The expressed wild-type and mutated γ2am chains associate with the λ1 light chain to form 5-iodo-4-hydroxy-3-nitrophenyl-acetyl (NIP)–specific mIgG2a molecules.

After surface biotinylation of K46λγ2am and K46λγ2amtl cells, the wild-type and tailless IgG2a-BCR complexes were affinity-purified over NIP-Sepharose (*7*) and analyzed by protein immunoblotting (Fig. 1). This analysis confirmed that the γ2amtl chain has a lower molecular weight than the wild-type γ2am chain (Fig. 1, lanes 4 and 2) and showed that both mIgG2a molecules are associated with the Ig-α,Ig-β heterodimer to the same extent. Yet unidentified surface proteins of 41 and 42 kD were copurified together with the wild-type but not truncated IgG2a-BCR complex. These molecules may thus require the γ2am tail for efficient binding. A fluorescence-activated cell sorter analysis confirmed that similar amounts of mIgG2atl and wild-type mIgG2a were expressed on K46 cells, whereas the two point-mutated mIgG2a molecules were expressed in amounts that were reduced by a factor of 3 to 5.

The endosomal transport of antigen bound to wild-type or mutated IgG2a-BCR was tested in an ovalbumin (OVA) peptide presentation assay (*8*). The different γ2am transfectants of K46λ12 cells were cocultured with the T helper cell line 3DO54.8, which is specific for the OVA 323-339 peptide in the presence of NIP-OVA or OVA alone (Fig. 2). The K46λγ2am cells, which express wild-type IgG2a-BCR, were able to present the antigenic peptide to the T cells when exposed to low amounts of NIP-OVA, whereas exposure to the same amount of OVA did not result in antigen presentation (Fig. 2B; $P < 0.001$). K46λγ2amtl cells, which express the tailless IgG2atl-BCR complex, did not present the OVA peptide even when cultured with large amounts of the specific antigen (Fig. 2C). The same defect was found in two independent γ2am transfectants of K46λ12 that expressed an IgG2a-BCR with a double (Y → L, M → L) (*6*) mutation of the YXXM motif. These are referred to as K46λγ2amY20L,M23L (Fig. 2, E and F). K46λγ2amY20L cells, expressing an IgG2a-BCR with a single Y → L mutation of the YXXM motif, had a modest but not statistically significant capacity to present antigen (Fig. 2D; $P < 0.3$). The

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were amplified individually or in groups from genomic DNA by means of primers designed from intron sequences (supplementary PCR primer and ddF primer sequences can be found at www.sciencemag.org or www.nhgri.nih.gov). PCR was performed in 25-μl reactions containing 100 ng of DNA and 0.5 U of AmpliTaq Gold (Perkin-Elmer) according to the manufacturer's protocol. Dimethyl sulfoxide (final concentration 5%) was included for exons 2, 9, and 10. The primary PCR products were subjected to a dideoxy chain termination reaction with 200 μM dideoxyguanosine triphosphate (Boehringer Mannheim) and AmpliTaq Gold, as described [G. H. Sarkar, H. J. Yoon, S. S. Sommer, *Genomics* **13**, 441 (1992)], with modified gel running conditions. The ddF reactions were diluted 1:4 in buffer containing 7 M urea, 50% formamide, bromophenol blue, and xylene cyanol. Reactions were heated at 94°C for 5 min and chilled on ice, and a 5-μl sample was loaded on a nondenaturing gel [0.75× Mutation Detection Enhancement (MDE) (FMC Bioproducts, Rockland, ME) in 0.5× tris-borate EDTA (TBE)] on a sequencing apparatus. The gel was electrophoresed at a constant power of 8 W at room temperature in a buffer system (consisting of 0.5× TBE in the top reservoir and 0.8× TBE with 0.5 M sodium acetate in the bottom reservoir) until the bromophenol blue reached the bottom of the gel. The gel was removed on Whatman paper, dried for 30 min in a sequencing gel drier, and autoradiographed overnight. One ddF primer could screen about 250 bp; if the region to be screened in the primary PCR product was larger, additional primers were used for ddF. Samples showing changes in band patterns were subjected to cycle sequencing with the same primary PCR product and the same end-labeled primer as was used in the ddF reaction. For insertion or deletion type changes in which the actual bases involved could not be ascertained from the sequence of the heterozygous patient sample, the primary PCR product was cloned in the TA cloning vector pCRII (Invitrogen) and then sequenced.

21. Confirmation that the mutation segregated with MEN1 was achieved by direct sequencing of PCR products from other affected family members. Independent confirmation of the sequence change in affected individuals was achieved by restriction digestion of the appropriate exon PCR product for 512delC (creates an Afl II site), W436R (creates Msp I and Nci I sites), and R527X (creates a Bsu 36I site). For the remainder, analysis was carried out with radioactively labeled allele-specific 16- to 20-nucleotide oligomers, corresponding to the wild-type or mutant sequence, that were hybridized to slot blots of exon PCR products as described [J. Lyons *et al.*, *Science* **249**, 655 (1990)].
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