Mutations in *CUL4B,* Which Encodes a Ubiquitin E3 Ligase Subunit, Cause an X-linked Mental Retardation Syndrome Associated with Aggressive Outbursts, Seizures, Relative Macrocephaly, Central Obesity, Hypogonadism, Pes Cavus, and Tremor

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We have identified three truncating, two splice-site, and three missense variants at conserved amino acids in the *CUL4B* gene on Xq24 in 8 of 250 families with X-linked mental retardation (XLMR). During affected subjects' adolescence, a syndrome emerged with delayed puberty, hypogonadism, relative macrocephaly, moderate short stature, central obesity, unprovoked aggressive outbursts, fine intention tremor, pes cavus, and abnormalities of the toes. This syndrome was first described by Cazebas et al., in a family that was included in our study and that carried a *CUL4B* missense variant. CUL4B is a ubiquitin E3 ligase subunit implicated in the regulation of several biological processes, and *CUL4B* is the first XLMR gene that encodes an E3 ubiquitin ligase. The relatively high frequency of *CUL4B* mutations in this series indicates that it is one of the most commonly mutated genes underlying XLMR and suggests that its introduction into clinical diagnostics should be a high priority.

Mental retardation (MR) affects ~1%–3% of the population and is ~30% more prevalent in males than in females.[1] To date, mutations in >60 (~6%) of the X-linked genes annotated in the Vega Genome Browser have been associated with an MR phenotype (for review, see the work of Chelly et al.[2] and Ropers and Hamel[3]). Traditionally, families with X-linked MR (XLMR) have been divided into syndromic and nonsyndromic categories. In nonsyndromic XLMR, MR is the only clinical feature, whereas, in syndromic XLMR, there are other associated clinical or biochemical abnormalities. Recently, it has become clear that this classification is too rigid and arbitrary. For example, patients in most families with mutations in *RPS6KA3* have Coffin Lowry syndrome, but one family has been reported with nonsyndromic XLMR.[4]

Each reported XLMR gene appears to be responsible for only a small fraction of affected families; the exceptions are *FMR1* (MIM 309550), which accounts for ~20% of families with XLMR, and *ARX* (MIM 300382), which is mutated in ~9.5% of X-linked families and ~2.2% of small families with multiple affected males (brother pairs).[5,6] Therefore, despite considerable success in the identification of XLMR genes, the XLMR in most affected families has not been attributed to any of the known genes. Genetic heterogeneity has hindered the pursuit of further XLMR genes by conventional positional-cloning strate-

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gies, because genetic linkage information from different families cannot be combined with confidence. As a result, individual families with XLMR are mapped to large areas of the X chromosome that contain substantial numbers of genes, rendering the underlying mutations hard to identify.

We commenced a systematic mutational screen of the X chromosome in 250 families with multiple members with MR, to provide an alternative strategy to positional cloning. The approach is not dependent on mapping by genetic linkage and is a direct search for putative disease-causing mutations. Each family in the screen has a normal karyotype by conventional 500 G-banding resolution and is negative for an expansion of the trinucleotide repeat in the *FMR1* gene. For the 250 families, a causative mutation was not found after prescreening of 61 known syndromic and nonsyndromic XLMR genes. The families were investigated by bidirectional sequencing of 676 Vega-annotated genes. In the course of the screen, we noted truncating and missense variants in *CUL4B* (MIM 300304; GenBank accession number NM_003588), in Xq24 (table 1).

CUL4B is a member of the family of cullin proteins that function primarily as scaffold proteins for a series of ubiquitin-protein ligase complexes that regulate the degradation of cellular proteins. The *CUL4B* gene is composed of 22 exons and encodes a protein of 913 aa (GenBank accession number NP_003579). The cullin domain is located between amino acid residues 217 and 815 and is characterized by a C-terminal globular domain (cullin homology domain) and a series of N-terminal repeats (cullin repeats).

Three mutations that introduce premature termination codons were identified (figs. 1 and 2). In family 42, there is a c.1007_1011delTTATA deletion, which introduces a translational frameshift, resulting in the inclusion of a single novel amino acid and a premature termination at codon 337. Genetic linkage analysis demonstrated that the three affected male siblings in this family share a haplotype between *DXS1106* and *DXS1073* on Xq22-Xq28, which is consistent with the localization of *CUL4B*. It was confirmed that the c.1007_1011delTTATA mutation segregates in the three affected males and their mother. In family 307, there is a p.R388X (c.1162C→T) nonsense mutation that was found in the proband and his two affected maternal uncles. In family 43, there is a p.R856X (c.2566C→T) nonsense mutation. This family had linkage data consistent with Xq24-q27.1, and the R856X mutation was confirmed in all eight affected males.

Two families carried variants in splice sites, which alter splicing such that the protein is prematurely truncated. In family 329, a base change, 901–2A→G, was found. To investigate the effect of this variant on splicing, *CUL4B* exons 6–11 were amplified from patient and control lymphocyte cDNA. The 901–2A→G alteration results in aberrant splicing of the *CUL4B* transcript (fig. 3*a*). Sequence analysis shows that the mutated exon 7 splice-acceptor site is ignored, and, as a result, exon 7 (74 bp) is excluded from the mature transcript. Removal of exon 7 results in the introduction of a translational frameshift, with the inclusion of 7 novel aa and a premature termination at codon 308. The 901–2A→G change was found in the proband and his two affected brothers.

In family 363, an apparently silent variant, p.T831T (c.2493G→A), affecting the last base of exon 20, was found (fig. 3*b*). *In silico* analysis indicated that this nucleotide change weakens the consensus splice-donor site for intron 20 (BDGP: Splice Site Prediction by Neural Network). To examine directly whether this variant has any affect on splicing, *CUL4B* exons 18–22 were amplified from patient and control lymphocyte cDNA. Sequence analysis of the RT-PCR product shows that the splice-donor site of intron 20 is ignored, and two new cryptic TG/GT splice-donor sites are activated. The major transcript used a cryptic donor site 80 bp upstream in exon 20. The outcome is the exclusion of 80 bp at the end of exon 20 from the *CUL4B* transcript, with consequent introduction of a premature translational termination at codon 806. A second minor transcript used a cryptic donor site 65 bp upstream in exon 20. The deletion of the terminal 65 bp of exon 20 results in the introduction of a premature termination at codon 811. Wild-type transcript was not observed. The

Table 1. Identified *CUL4B* Variants

CUL4B Variant	Mutation Class	Family	No. of Affected Individuals	No. of Generations	Control	Allele Frequency
Identified in MR samples:						
c.1007_1011delTTATA	Deletion	42	7	2	…	…
c.1162C→T; p.R388X	Nonsense	307	3	2	…	…
c.2566C→T; p.R856X	Nonsense	43	8	3	…	…
c.901–2A→G	Splice	329	3	1	…	…
c.2493G→A; p.T831T	Splice[a]	363	3	3	…	…
c.1714C→T; p.R572C	Missense	180	6	2	…	…
c.2234T→C; p.V745A	Missense	64	4	2	…	…
c.638C→T; p.T213I	Missense	432	5	2	…	…
Identified in control samples:						
c.308T→C; p.L103P	Missense	…	…	…	AC0302	1/639
c.732A→G; p.V244V	Silent	…	…	…	AC0553	1/634

[a] Cryptic splice site.

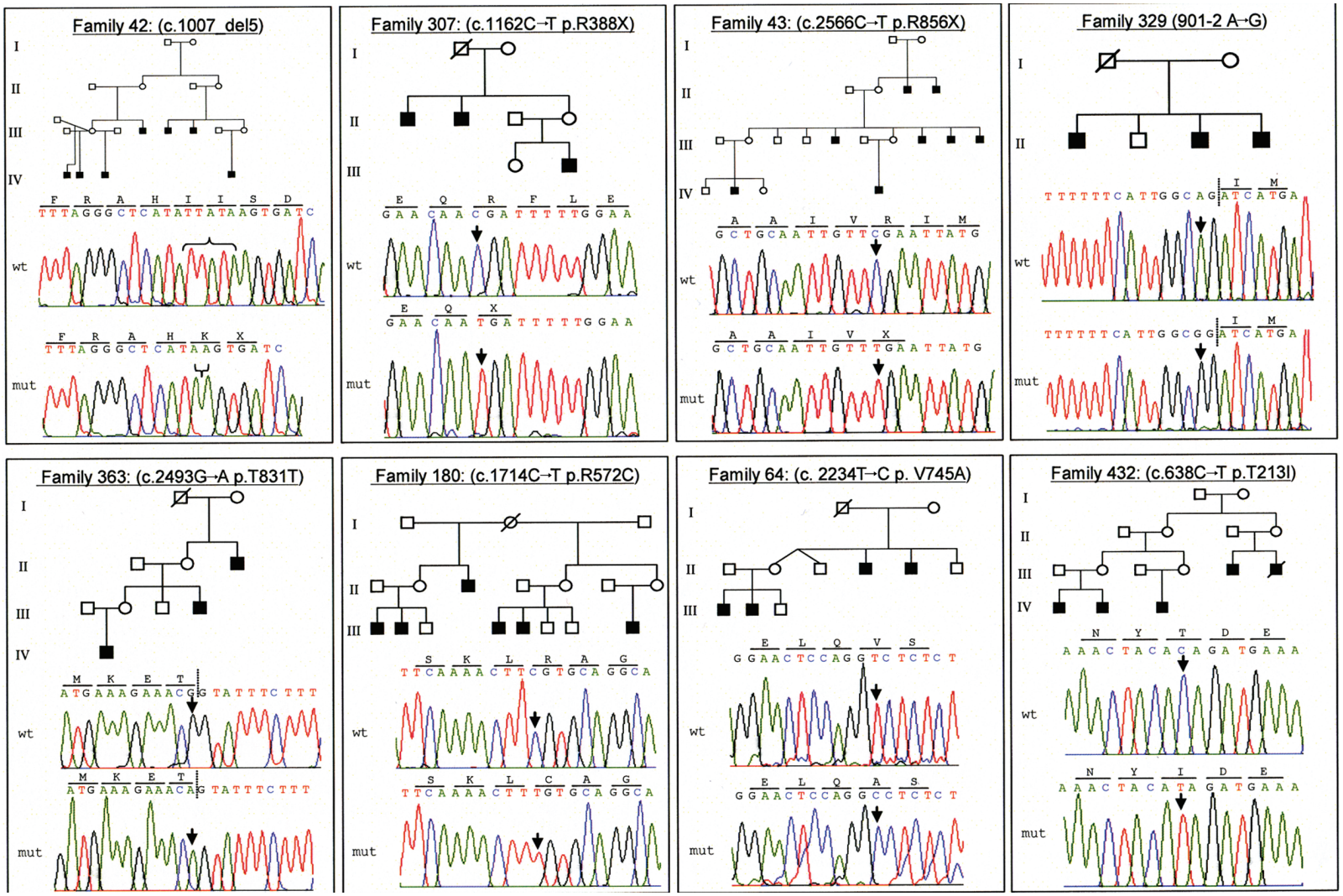

Figure 1. Families with mutations in *CUL4B*. Below the pedigree for each family, a wild-type (wt) and a mutant (mut) representative trace are shown. The position of the mutation is indicated by an arrow, and the numbering is according to reference sequences (GenBank accession numbers NM_003588 and NP_003579).

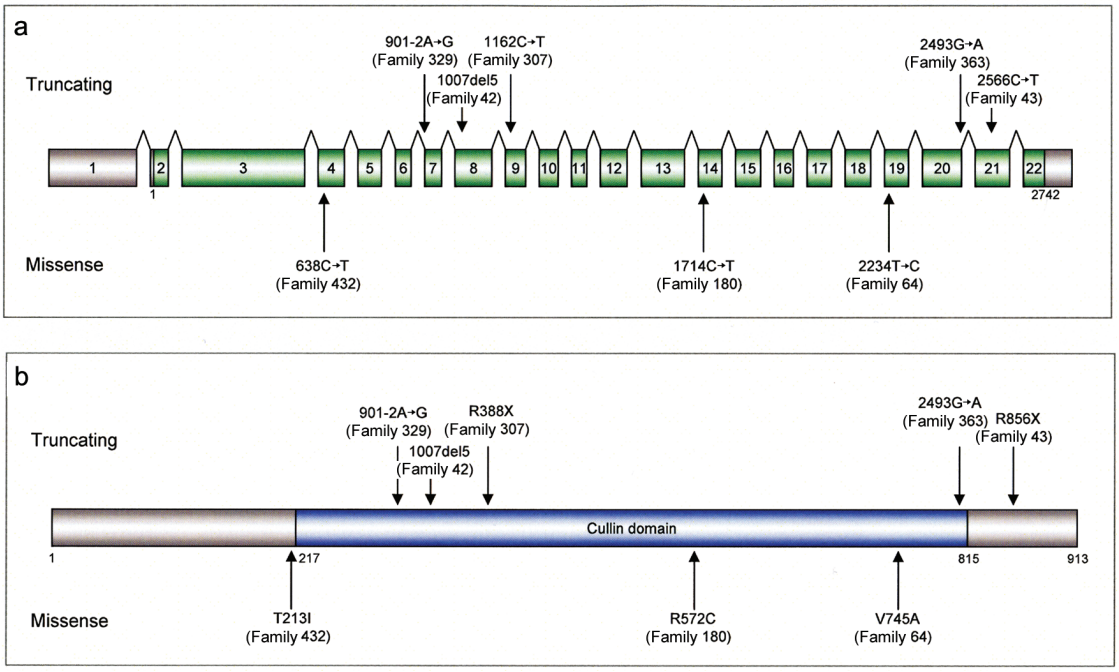

Figure 2. *a,* Schematic representation of the genomic structure of *CUL4B,* with positions of mutations found in eight families with XLMR. *b,* Schematic representation of the protein sequence. The cullin domain is marked, and the positions of the eight mutations are indicated.

c.2493G→A change was found in the proband of family 363 and his affected nephew.

Three missense variants were identified in the screen. In family 180, there is a p.R572C (c.1714C→T) change. Residue R572 is highly conserved throughout evolution (fig. 4) and is located within the cullin domain, and the arginine→cysteine change is a nonconservative substitution. MR in family 180 has previously been mapped to Xq23-Xq25, with a maximum LOD score of 2.8 at *DXS1212,* which is compatible with the location of *CUL4B*.[7] The c.1714C→T change segregates with MR in family 180, and the affected males share many phenotypic features with others who carry truncating *CUL4B* mutations, including tremor and pes cavus. Taken together, the results strongly indicate that p.R572C (c.1714C→T) is the mutation causing XLMR in family 180.

In family 64, a c.2234T→C change was found that gave rise to the missense mutation p.V745A. Residue V745 is highly conserved throughout evolution (fig. 4) and is located within the cullin domain. Linkage was demonstrated between *DXS6064* in Xq23 and *DXS1205* in Xq27.1, which is consistent with the location of *CUL4B*. The V745A variant was found in four affected males and one obligate female and was absent in two unaffected males.

In family 432, missense mutation p.T213I (c.638C→T) was found. Residue T213 is conserved during evolution, although not as extensively as residues R572 or V745 (fig. 4). Residue T213 is just outside the cullin domain. However, there is clearly conservation of amino acids immediately adjacent to it, indicating that it is probably part of a functional domain. Previous results have demonstrated that family 432 exhibits genetic linkage to Xq24, and the variant segregates with the disease in the two available affected males and their mother. It is plausible that c.638C→T (p.T213I) is responsible for XLMR in this family. It is also possible that it is a rare variant. However, we did not find another instance of this variant after sequencing exon 4 in 637 additional X chromosomes, although these controls were ethnically unmatched to family 432, which is of Asian descent. Further biological studies may be required to unequivocally determine whether the identified *CUL4B* missense variants are disease-associated or represent rare polymorphisms.

None of the proposed XLMR-causing variants was found in a screen of the complete coding sequence and splice sites of *CUL4B* in 637 normal X chromosomes, nor were any other clearly truncating or splice-site variants found among these controls. Indeed, *CUL4B* exhibits relatively little variation in the general population. Two variants were identified after the screening of 637 control chromosomes (fig. 1*b*). A synonymous variant (c.732A→G; p.V244V) was identified in a single female sample, and a nonsynonymous variant (c.308T→C; p.L103P) was observed in a single male sample. In contrast to the likely disease-causing variants found in the families with XLMR,

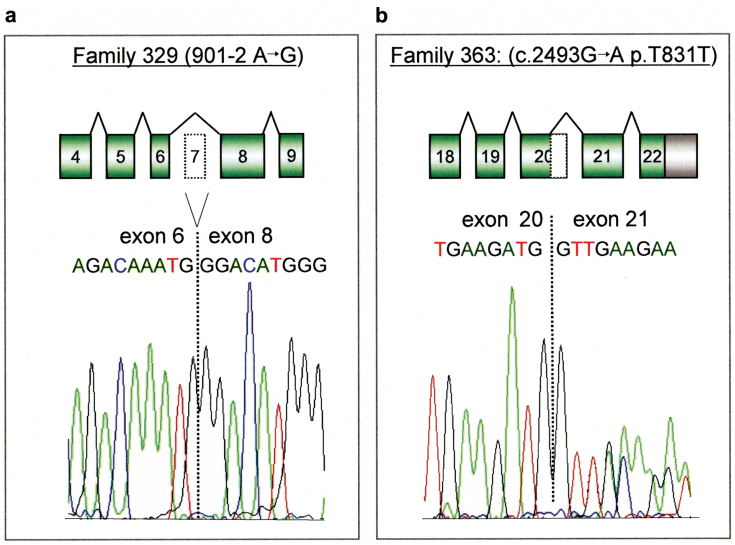

Figure 3. RT-PCR analysis. *a,* Analysis of family 329, demonstrating the skipping of exon 7 in the *CUL4B* transcript. *b,* Analysis of family 363, showing deletion of the terminal 80 bp of exon 20, which results from the activation of a cryptic splice-donor site upstream from the normal donor site.

residue L103 is poorly conserved through evolution, and it is likely that these variants represent rare polymorphisms.

The main clinical features of the syndrome were first described in a single family by Cabezas et al.[7] The clinical features of this family and the seven additional families with *CUL4B* mutations are summarized in table 2, and the pedigrees are presented in figure 1. Seven families were white, and one was of Asian descent. Affected individuals from families 42, 43, and 363 are presented in figure 5. There were 39 affected males, with variable clinical data available for 28. Five of them were children younger than 15 years at their last assessment; the remainder of the affected individuals were aged 16–56 years.

All the males had an intellectual disability. This was usually moderate but varied widely, such that some men were institutionalized and others were able to live semi-independently. Speech delay was evident in early childhood and remained disproportionately severe given the degree of intellectual impairment. In adults, speech was very limited or nonexistent; nevertheless, affected individuals could understand simple commands and were often cooperative in tasks. Short outbursts of aggression were common. Some were provoked, but many were not. They ranged from shouting, stamping, and running away to smashing windows and furniture, punching, and attempted strangulation.

Several neurological features were evident—notably, a fine intention tremor that was seen in the hands, with some impairment of motor activities. Seizures, usually single febrile fits, were common in young children but uncommon in adults. Ataxia was sufficient to suggest a diagnosis of Angelman syndrome (MIM 105830) in one child but was usually regarded as clumsiness in adults. Some unexplained wasting of the calf muscles, with retained tendon reflexes, and pes cavus were seen.

A physical habitus of short stature and central obesity was observed in some affected males and was often accompanied by gynecomastia and striae. Puberty was delayed, and abnormalities of the genital tract were reported, including undescended and/or small testes, hypospadias, and small penis. The average adult height was in the 5th percentile, and the average head circumference was in the 97th percentile. The feet were often noted to be small with abnormal toes and a wide sandal gap. Diagnoses of Prader-Willi syndrome (MIM 176270), Börjeson-Forssman-Lehman syndrome (MIM 301900), and Wilson-Turner syndrome (MIM 309585) had all been considered. Numerous biochemical investigations and magnetic resonance imaging and CT scans showed no abnormalities except for a porencephalic cyst (table 2). The known heterozygote females were essentially normal, except for one who had borderline intelligence; one 12-year-old with multiple tics, attention deficit disorder, and a fine tremor; one with severe recurrent alopecia; and one with achalasia of the cardia that required surgery. Overall, the only consistent feature in all affected individuals was MR, but the presence of relative macrocephaly, short stature, obesity, genital tract abnormalities, tremor, aggressive outbursts, seizures, and pes cavus are indicative of the syndrome associated with mutations in *CUL4B*.

CUL4B is a component of the ubiquitin system. Ubiquitin-dependent proteolysis is a fundamental cellular mechanism for regulating protein activity.[8] It is implicated in a diverse set of biochemical processes, including signal transduction, transcription receptor down-regulation, and

endocytosis and has been implicated in regulation of the cell cycle, immune response, development, and programmed cell death. The proteolytic effects of ubiquitination are the most extensively characterized, but there is also evidence that it can influence activities of proteins through processes other than degradation.[9–14]

Ubiquitination generally results from the formation of a peptide bond between the C-terminus of the 76-aa ubiquitin peptide and an amino group of a substrate lysine residue. The process of ubiquitination involves several enzymatic activities. A ubiquitin-activating enzyme (E1) activates the ubiquitin peptide in an ATP-dependent reaction by forming an athioester bond with the C-terminal glycine of ubiquitin. The ubiquitin is then transferred to a specific sulfhydryl group on a ubiquitin-conjugating enzyme (E2). A ubiquitin-protein ligase (E3) then transfers the activated ubiquitin from E2 to a lysine residue of a bound substrate forming a peptide bond. The substrate specificity of the process is determined predominantly by E3 ligases, which bind both the protein substrate and the cognate E2. Once the polyubiquitin chain has been assembled on a protein substrate by the cooperation of E1, E2, and E3 enzymes, the target protein is recognized and degraded by the 26S proteasome.[15]

A large number of E3s are found in mammalian cells. However, all known E3s have one of three structural elements. These are the ~350-aa HECT domain (homologous to E6-AP carboxy terminus), the RING (really interesting new gene) finger, and the U-box domain.[16–18] In turn, there are two classes of RING E3s. In one class, the E3 consists solely of the RING-finger protein itself. For this class, the RING E3 together with E2 is sufficient for ubiquitination. In the second class of RING E3, the RING-finger protein is part of a multisubunit protein complex. The cullin family of proteins constitute one of the other subunits of the complex and, by associating with the RING-finger protein and a cognate E2, form the integral catalytic core necessary for ubiquitination.

Cullin 4 (CUL4) is a conserved core component of a class of ubiquitin E3 ligases that also contains the UV-damaged DNA-binding protein 1 (DDB1) and RING-finger protein ROC1 (also called "RBX1" or "HRT1"). There are two paralogues in mammals, CUL4A and CUL4B. CUL4A and CUL4B are coexpressed in many cell types, and the functional differences between them remain unclear. The specific targets of CUL4B are only partially understood and may overlap with other E3 ubiquitin ligases. There is evidence that CUL4-containing E3 ligase complexes regulate the proteolysis of the replication-licensing protein CDT1 in response to UV or gamma-irradiation, that the CUL4A/

Table 2. Clinical Features in Affected Males of Eight Families with Mutations in *CUL4B*

Age Period and Clinical Feature(s)	No. of Affected Males with Feature/Total No. of Affected Males
Infancy:	
Normal pregnancy and birth	18/18
Birth weight <10th percentile	11/15
Childhood:	
Motor delay (walking at or after 2 years)	5/5
Speech delay	18/18
Seizures (before age 2 years)	8/11
Adulthood:	
Height <10th percentile	7/11
Head circumference >97th percentile	8/11
MR:	22/22
Mild	4/18
Moderate	11/18
Severe	7/18
Impaired speech and/or nonverbal communication	11/15
Aggressive outbursts	12/15
Tremor	11/13
Obesity, central	15/19
Abnormal toes, with wide 1–2 gap	11/13
Small feet	7/14
Pes cavus	7/8
Wasted lower-leg muscles	7/12
Small testes	10/15
Gynecomastia	7/10
Prominent lower lip	6/17
Gait ataxia	6/12
Kyphosis	3/18

NOTE.—In addition, there were single cases of pes planus, inguinal hernia, micropenis, strabismus, cataracts, keratoconus, sleep apnea, hemiplegia, porencephalic cyst, and acanthosis nigricans.

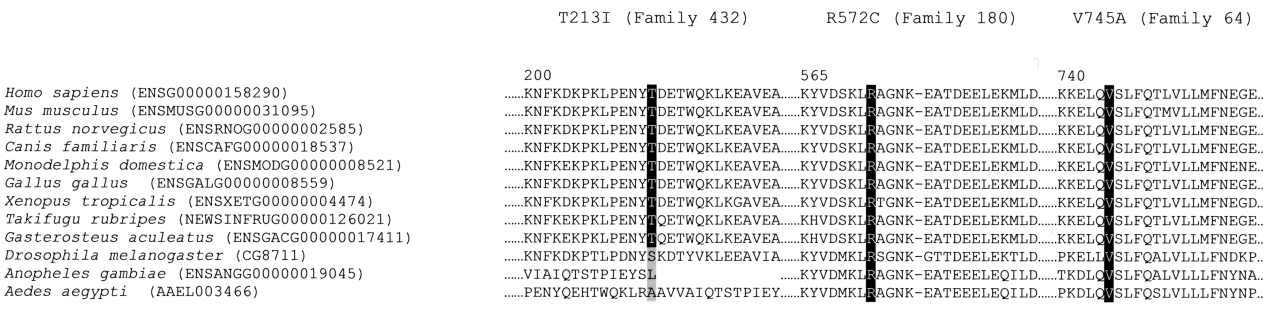

Figure 4. Alignment of available *CUL4B* protein sequences, showing the conservation of amino acid residues altered by the missense mutations. Accession numbers in parentheses are from the Ensembl Genome Browser.

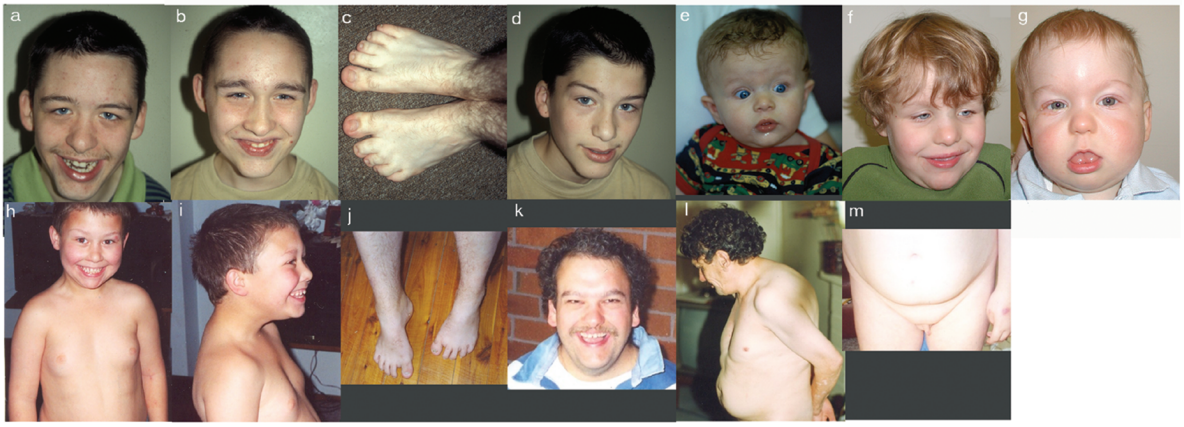

Figure 5. *a, b,* and *d,* Three half brothers from family 42 (pedigree designations IV-1, IV-2, and IV-3, respectively), aged 21, 18, and 15 years, respectively. *c,* Feet of IV-2, showing a wide sandal gap and small size. *e* and *f,* Individual IV-2 from family 43, at ages 4 mo (*e*) and 4 years (*f*). *g,* Features of an affected cousin, IV-4. *h, i,* and *j,* Individual IV-1 from family 363 at age 6 years, showing gynecomastia (*h* and *i*), and at age 13 years, showing splayed toes with a wide sandal gap (*j*). *k, l,* and *m,* Uncle (III-4) of IV-1 from family 363, showing central obesity (*k*), upper dorsal kyphosis (*l*), and micropenis (*m*).

DDB1 complex regulates the proteolysis of c-Jun and DDB2, and that CUL4 E3 ligase plays a critical role in regulating G1 cell-cycle progression through degradation of cyclin E.[19,20]

It is of interest that the abrogation of CUL4B functions results in MR with a relatively limited array of other clinical features. It may be that the E3 ligase of CUL4B is directed at a limited set of protein targets, and, therefore, most developmental processes proceed relatively normally. Alternatively, it is possible that there is substantial redundancy in the ubiquitin E3 ligase system, such that other ubiquitin ligases (e.g., CUL4A) duplicate many functions of CUL4B. In particular, there has been no indication of cancer susceptibility in families with XLMR due to CUL4B mutations, despite the likely involvement of CUL4B in processes relating to DNA repair, replication, and cell-cycle progression.

Mutated genes encoding proteins with diverse biological functions have previously been shown to be involved in XLMR. Although a truncating mutation of *UBE2A/HR6A,* which encodes an E2 ubiquitin-conjugating enzyme, was recently reported in a single family with XLMR,[21] *CUL4B* is the first ubiquitin E3 ligase mutated in XLMR. Abnormalities of E3 ligases, however, have been reported in other human genetic diseases. Mutations in the ubiquitin-protein ligase E3A gene (*UBE3A*) on chromosome 15q underlie a subset of Angelman syndrome,[22,23] in which MR is a notable clinical feature, and abnormalities of other E3 ligases have been shown to cause recessive juvenile Parkinson disease (MIM 600116) (caused by mutation in *PARK2*),[24] autoimmune polyendocrinopathy syndrome type 1 (MIM 240300) (caused by mutation in *AIRE*),[25] and von Hippel-Lindau disease (MIM 193300) (caused by mutation in *VHL*).[26]

Further prevalence studies are now needed to estimate more precisely the contribution of mutations in *CUL4B* to XLMR. However, our finding of eight families with XLMR (3% of the 250 screened) that have *CUL4B* mutations that are likely disease associated indicates that this may be one of the most frequently mutated genes underlying XLMR (for comparison, the currently most frequently mutated known XLMR gene is *DLG3,* in which we have found mutations in five families with XLMR). Moreover, the association of additional clinical features as part of the syndrome associated with *CUL4B* mutations suggests that targeted implementation of genetic testing for *CUL4B* mutations may be practical and have substantial clinical utility.

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Web Resources

Accession numbers and URLs for data presented herein are as follows:

BDGP: Splice Site Prediction by Neural Network, http://www.fruitfly.org/seq_tools/splice.html (for NNSPLICE)

Ensembl Human Genome, http://www.ensembl.org/Homo_sapiens/index.html

GenBank, http://www.ncbi.nlm.nih.gov/Genbank/ (for *CUL4B* gene [accession number NM_003588] and protein [accession number NP_003579])

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for *FMR1, ARX, CUL4B,* Angelman syndrome, Prader-Willi syndrome, Börjeson-Forssman-Lehman syndrome, Wilson-Turner syndrome, Parkinson disease, autoimmune polyendocrinopathy syndrome type 1, and von Hippel-Lindau disease)

Vega Genome Browser, http://vega.sanger.ac.uk/

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