Am. J. Hum. Genet. 76:510–516, 2005

Report

Identification of *C7orf11* (*TTDN1*) Gene Mutations and Genetic Heterogeneity in Nonphotosensitive Trichothiodystrophy

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We have identified *C7orf11*, which localizes to the nucleus and is expressed in fetal hair follicles, as the first disease gene for nonphotosensitive trichothiodystrophy (TTD). *C7orf11* maps to chromosome 7p14, and the disease locus has been designated "*TTDN1*" (TTD nonphotosensitive 1). Mutations were found in patients with Amish brittle-hair syndrome and in other nonphotosensititive TTD cases with mental retardation and decreased fertility but not in patients with Sabinas syndrome or Pollitt syndrome. Therefore, genetic heterogeneity in nonphotosensitive TTD is a feature similar to that observed in photosensitive TTD, which is caused by mutations in transcription factor II H (TFIIH) subunit genes. Comparative immunofluorescence analysis, however, suggests that *C7orf11* does not influence TFIIH directly. Given the absence of cutaneous photosensitivity in the patients with *C7orf11* mutations, together with the protein's nuclear localization, *C7orf11* may be involved in transcription but not DNA repair.

Trichothiodystrophy (TTD), or sulfur-deficient brittle hair (Price et al. 1980), can be associated with a spectrum of symptoms affecting organs of ectodermal and neuroectodermal origin (table 1). These include nail dystrophy, mental and growth retardation, ichthyosis, decreased fertility, and cutaneous photosensitivity, but not cancer (Bergmann and Egly 2001). Approximately half of patients with TDD display photosensitivity. These cases are associated with defects in nucleotide excision repair (NER) due to mutations in *XPD* (Botta et al. 1998), *XPB* (Weeda et al. 1997), or *TTD-A* (Giglia-Mari et al. 2004) that cause a reduction of cellular concentration of transcription factor II H (TFIIH) (Botta et al. 2002). However, the causal gene or genes for nonphotosensitive TTD are unknown.

Amish brittle-hair brain syndrome (ABHS [MIM 234050]) is an autosomal recessive disorder characterized by short stature, intellectual impairment, sulfur-deficient brittle hair, and decreased male fertility but not cutaneous photosensitivity (Jackson et al. 1974; Baden et al. 1976). Other forms of nonphotosensitive TTD, such as Sabinas brittle-hair syndrome (MIM 211390) (Howell et al. 1981) and Pollitt syndrome (MIM 275550) (Pollitt et al. 1968), were hypothesized to be allelic with ABHS, because of similar clinical presentations. Initially, to search for the ABHS disease locus, we performed homozygosity mapping on a subset of affected members from a consanguineous Amish kindred (Jackson et al. 1974) and identified a 2-Mb candidate locus on 7p14 (fig. 1*A*) (Seboun et al., in press). We then analyzed seven genes (fig. 1*A*) (Scherer et al. 2003; The

Received November 8, 2004; accepted for publication December 16, 2004; electronically published January 11, 2005.

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0002-9297/2005/7603-0014$15.00

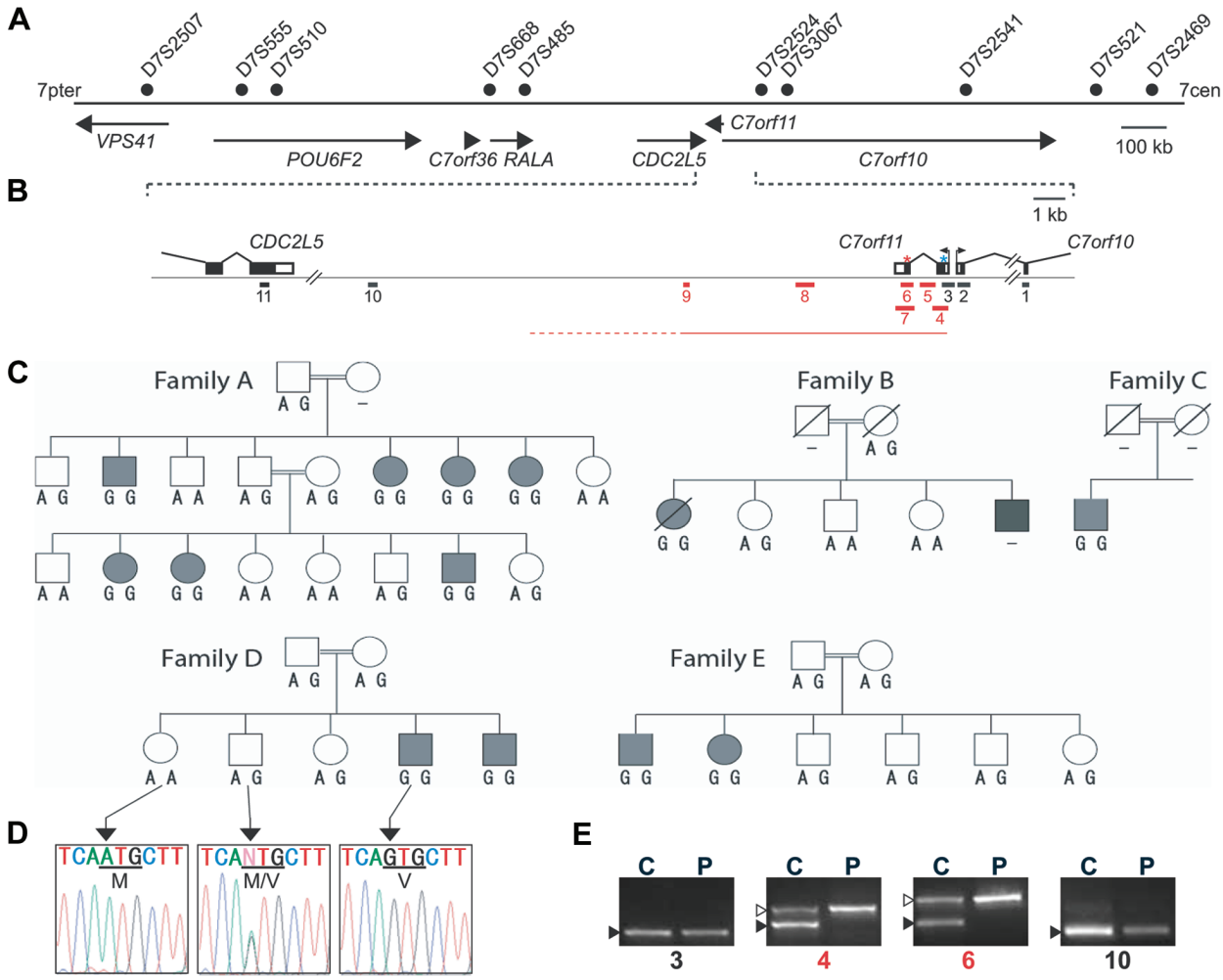
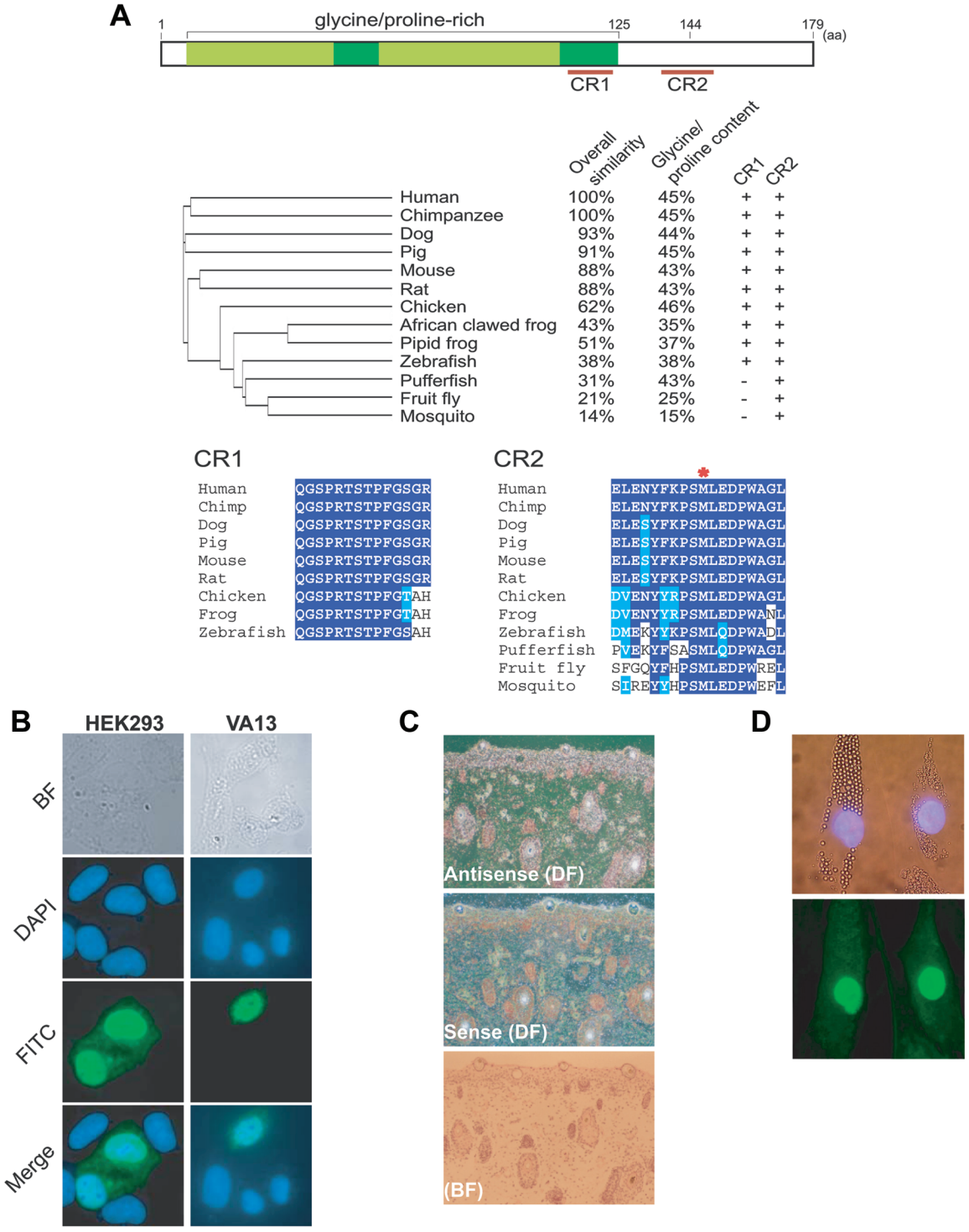


Figure 1 Identification of *C7orf11* mutations. To screen the two exons and the 5′ upstream region of the *C7orf11* gene, we used three sets of primer pairs: C7orf11-5upF/ex1R1, C7orf11ex1-F2/R3, and C7orf11ex2-F/R2 (for primer sequences, see table A1 [online only]). The cycling conditions were initial denaturation at 94°C for 3 min followed by 35 cycles of denaturation at 94°C for 30 s, annealing at 58°C for 30 s, and extension at 72°C for 60 s. PCR products were purified using microCLEAN (Microsone) and were used as the sequencing template. Sequencing reactions were performed using the Big Dye Terminator kit (Applied Biosystems), and an ABI-3730 DNA Sequencer (Applied Biosystems) was used to obtain sequences. *A,* Physical map of the 2-Mb region on 7p14 showing homozygosity in a consanguineous Amish kindred. *B,* Diagram of *C7orf11,* consisting of two exons spanning 2 kb. The coding and untranslated regions are shown as blackened and unblackened boxes, respectively. The red and blue asterisks (*) indicate the position of the M144V mutation in the Amish kindred and the 2-bp deletion in the Moroccan siblings with TTD, respectively. Black and red bars (numbered from 1 to 11) represent the size and location of the PCR products in the deletion mapping for patient 6474. The fragments that were not amplified from patient 6474 (because of homozygous deletion) are indicated by red bars. *C,* Five affected families from the Amish kindred. Gray and blackened symbols indicated affected members, and unblackened symbols indicate unaffected members. The member of family B represented by the blackened symbol is the proband, who had a more severe phenotype, presumably due to a de novo chromosomal abnormality (46,XY,14q^{-}) (Jackson et al. 1974). The genotype at the M144V mutation site (A, wild-type; G, mutated) is shown for each member. *D,* Electropherograms for the M144V site. *E,* Representative results (from test primers 3, 4, 6, and 10) of the PCR-based deletion mapping of the *C7orf11* locus in patient 6474 (lane C, control; lane P, patient 6474). Unblackened triangles indicate the 704-bp fragment amplified by control primer DJg5/g6. The blackened triangles indicate the fragment amplified by a test primer pair. The cycling conditions were initial denaturation at 94°C for 3 min followed by 36 cycles of denaturation at 94°C for 30 s, annealing at 58°C for 30 s, and extension at 72°C for 75 s. Detailed information for the 11 test primers pairs and the control primer pair is available in table A1 (online only).


A
glycine/proline-rich
1
125
144
179
(aa)
CR1
CR2
Overall similarity
Glycine/ proline content
CR1
CR2
Human 100% 45% + +
Chimpanzee 100% 45% + +
Dog 93% 44% + +
Pig 91% 45% + +
Mouse 88% 43% + +
Rat 88% 43% + +
Chicken 62% 46% + +
African clawed frog 43% 35% + +
Pipid frog 51% 37% + +
Zebrafish 38% 38% + +
Pufferfish 31% 43% - +
Fruit fly 21% 25% - +
Mosquito 14% 15% - +
CR1
Human QGSPRTSTPFGSGR
Chimp QGSPRTSTPFGSGR
Dog QGSPRTSTPFGSGR
Pig QGSPRTSTPFGSGR
Mouse QGSPRTSTPFGSGR
Rat QGSPRTSTPFGSGR
Chicken QGSPRTSTPFGTAH
Frog QGSPRTSTPFGTAH
Zebrafish QGSPRTSTPFGSAH
CR2
Human ELENYFKPSMLEDPWAGL
Chimp ELENYFKPSMLEDPWAGL
Dog ELESYFKPSMLEDPWAGL
Pig ELESYFKPSMLEDPWAGL
Mouse ELESYFKPSMLEDPWAGL
Rat ELESYFKPSMLEDPWAGL
Chicken DVENYYRPSMLEDPWAGL
Frog DVENYYRPSMLEDPWANL
Zebrafish DMEKYYKPSMLQDPWADL
Pufferfish PVEKYFSASMLQDPWAGL
Fruit fly SFGQYFHPSMLEDPWREL
Mosquito SIREYYHPSMLEDPWEFL
B
HEK293
VA13
BF
DAPI
FITC
Merge
C
Antisense (DF)
Sense (DF)
(BF)
D

Chromosome 7 Annotation Project [see Web site]) by DNA sequencing and identified three homozygous sequence variations in the affected members of family E (fig. 1*C*): a T→C variant in intron 7 of *C7orf10,* a G→A variant in exon 1 of *CDC2L5* causing an arginine-to-lysine substitution (R21K), and an A→G variant in exon 2 of *C7orf11* causing a methionine-to-valine substitution (M144V). The first two sequence variations were excluded from further analysis, because the same genotype was found in either normal controls or the unaffected parents in family E. We have shown elsewhere that *C7orf11* encodes a 179-aa protein of unknown function (Nakabayashi et al. 2002) and that it is variably expressed in many tissues, including fibroblasts and brain. By sequencing all available members of the Amish kindred, we confirmed that all 13 affected cases were homozygous for the A→G variant and that 26 unaffected members were either heterozygous carriers (18/26) or homozygous for the normal allele (8/26) (fig. 1*C* and 1*D*). We genotyped 148 controls (296 chromosomes), including 48 unrelated Amish individuals, and confirmed cosegregation of the M144V variant in only carrier or disease chromosomes.

We then examined *C7orf11* in 12 additional cases of nonphotosensitive TTD and found two deleterious homozygous deletions. In siblings of Moroccan origin with TTD (Przedborsk et al. 1990), we found a 2-bp homozygous deletion in exon 1 (nucleotides 187 and 188 of *C7orf11* mRNA [GenBank accession number NM_138701]) (data not shown), which predicts a 57-aa truncated protein. In another case—an Italian patient with TTD and severe nervous-system impairment (patient 6474) (Rizzo et al. 1992)—our attempts to amplify the coding regions of *C7orf11* failed. By multiplex PCR using a primer pair that amplifies a 704-bp control fragment, we determined that part of exon 1 and the entire exon 2 of *C7orf11* were homozygously deleted, whereas the flanking genes (*CDC2L5* and *C7orf10*) were not (fig. 1*B* and 1*E*). These patients with homozygous deletions are likely to be genetically null for *C7orf11,* which might explain their more-severe neurological phenotype in comparison with that of the patients with ABHS. We did not find any mutations in the two exons and 5′ upstream region of *C7orf11* in the other 10 cases of nonphotosensitive TTD, including two cases of Sabinas syndrome and one case of Pollitt syndrome, which suggests that genetic heterogeneity exists in nonphotosensitive TTD. The fibroblasts derived from all but two patients with Sabinas syndrome were tested for UV sensitivity by use of various NER parameters, including unscheduled

Figure 2 *A,* The human *C7orf11* protein. The glycine/proline–rich region is shown in green (the low-complexity regions detected by the BLASTP program are in light green). There are two highly conserved C terminal regions (CR1 and CR2) among the candidate orthologues. The evolutionary tree (*middle*) was drawn by the ClustalX program (Thompson et al. 1997). The protein sequences used for phylogenetic analysis are human C7orf11 (NCBI accession number NP_619646) and orthologues from chimpanzee (Ensembl accession number ENSPTRP00000032652), mouse (NCBI accession number BAB27916), rat (Ensembl accession number ENSRNOP00000018746), chicken (Ensembl accession number ENSGALP00000020100), frog (*Xenopus tropicalis* [NCBI accession number NP_989025]), pufferfish (*Tetraodon nigroviridis* [NCBI accession number CAF91712]), fruit fly (*Drosophila melanogaster* [NCBI accession number NP_648690]), and mosquito (*Anopheles gambiae* [NCBI accession number XP_318005]). Deduced protein sequences were derived from cDNA sequences from zebrafish (*Danio rerio* [GenBank accession number BC062385]) and pig (GenBank accession number BP456435). The dog protein sequence was predicted from the genomic DNA sequence (see UCSC Genome Browser Web site). For each species, the overall amino acid similarity with the human protein sequence, the percentage ratio of glycine/proline content in the region from the N terminus to CR1, and the presence (+) or absence (−) of CR1 and CR2 are shown. Multiple sequence alignments for CR1 and CR2 are at bottom. The position of M144V in CR2 is indicated by a red asterisk (*). Identical and similar amino acids are highlighted in dark and light blue, respectively. *B,* Subcellular localization assay. Transiently expressed Myc-tagged C7orf11 in human cultured cells (transformed human embryonic kidney cells [HEK293] and SV40-transformed WI38 human embryonic fibroblasts [VA13]) was examined by immunostaining, by use of anti-Myc antibody and a secondary antibody conjugated with fluorescein isothiocyanate (FITC). Bright-field (BF), 4'-6-diamidino-2-phenylindole (DAPI), FITC, and the merged image of DAPI and FITC signals are shown for each cell line. The Myc-tagged cDNA construct for *C7orf11* was generated by inserting the coding region of *C7orf11* (nucleotides 51–590 of mRNA) in pcDNA3.1+ Myc-His A (Invitrogen). DNA transfection was performed using Lipofectamine Plus (Invitrogen). Two days after transfection, cells were washed in PBS and were fixed in 50% acetone plus 50% methanol at −20°C for 15 min. The samples were blocked with 10% BSA in PBS (blocking buffer) for 1 h and were incubated in blocking buffer containing anti-Myc antibody (Santa Cruz Biotechnology) for 45 min. Cells were washed three times with PBS, were incubated with FITC-conjugated anti-mouse IgG antibody for 30 min, and were washed three times with PBS. After DAPI staining, the samples were analyzed by deconvolution microscopy (Zeiss). *C,* In situ RNA hybridization for *C7orf11* on human fetal skin tissue. A 556-bp cDNA fragment (corresponding to nucleotides 303–858 of mRNA) was subcloned in pCR-Script (Stratagene) and was used as template DNA to synthesize [^{35}S]UTP-labeled riboprobes. [^{35}S]UTP-labeled riboprobes (sense and antisense) were hybridized to the sections. Radioactive signals were detected by autoradiography with 38 d of exposure. Slides were counterstained with hematoxylin-eosin and were photographed under dark-field (DF) and bright-field (BF) illumination. The signal detected in epidermis and hair follicles is specific to the antisense probe. The detail conditions used for hybridization, washing, and signal detection were described elsewhere (Saarialho-Kere et al. 1992). *D,* Normal level of TFIIH in fibroblast cells from one of the Moroccan siblings with the 2-bp deletion. Mixed DAPI/phase contrast image (*top*) showing a normal (with large beads) and TTD (with small beads) cells. Immunofluorescence with anti-XPB antibody (*bottom*). For exact quantitative comparison of fluorescence signals between normal and TTD fibroblasts without slide-to-slide variability, two types of fibroblasts were preloaded with cytoplasmic plastic beads of different sizes (large beads for normal and small beads for TTD) and then were mixed, cultured overnight, and processed for immunofluorescence.

Table 1

Clinical Features and *C7orf11* Mutations in Patients with Nonphotosensitive TTD

	Finding[a] for						
Study	Isolated TTD[b]	Sabinas Syndrome	ABHS	Moroccan Siblings	Pollitt Syndrome	Patient 6474 (Present Study)	IBIDS[b]
Clinical features:							
Hair defect	+	+	+	+	+	+	+
Nail dystrophy	−	+	+	−	+	+	+
Mental retardation	− (IQ 80)	+ (IQ 50–60)	+[c] (IQ 90)	+ (IQ 25–40)	+	+	+
Growth retardation	−	−	+[c]	+	+	+	+
Ichthyosis	−	−	−	−	−	−[d]	+
Decreased fertility		+	+[e]	+[f]			
Other features				Ataxia	Ataxia, dental caries	Severe nervous-system impairment	Cataract, collodion skin at birth
UV sensitivity of fibroblasts[g]	ND	ND	ND	No UV sensitivity	No UV sensitivity	No UV sensitivity	ND
Mutations in *C7orf11*[h]	ND	No mutation	480A→G (M144V)	187_188delGG	No mutation	Deletion: part exon 1 and entire exon 2	ND
Reference	Alfandari et al. 1993	Howell et al. 1981	Baden et al. 1976; Jackson et al. 1974	Przedborski et al. 1990	Pollitt et al. 1968	Rizzo et al. 1992; Stefanini et al. 1992	Jorizzo et al. 1982

[a] ND = not determined; + = presence; − = absence.

[b] The isolated TTD cases and the ichthyosis, brittle hair, impaired intelligence, decreased fertility, and short stature (IBIDS) cases were not analyzed in this study but are included in the table to show the extent of the spectrum of TTD symptoms.

[c] Mild.

[d] Ichthyosiform areas present only on the lower limbs.

[e] Male only.

[f] Gonadal dysfunction tested.

[g] UV sensitivity tests were performed using various NER parameters, including unscheduled DNA synthesis (global NER), recovery from transcription inhibition (transcription-coupled NER), and overall clonogenic cell survival after UV exposure.

[h] GenBank accession number NM_138701.

DNA synthesis, recovery from transcription inhibition, and overall clonogenic cell survival after UV exposure. Microsatellite analysis also excluded the 2-Mb *C7orf11* locus from involvement in Sabinas syndrome. Therefore, we have designated *C7orf11* with the symbol *TTDN1* (TTD nonphotosensitive 1).

We identified predicted proteins with sequence similarity to human *C7orf11* in six mammalian species as well as chicken, frog, fish, and insects, but not in lower eukaryotic species (*C. elegans* and yeast). The first two-thirds of the human *C7orf11* protein is remarkably glycine/proline–rich (45% in 125 aa), and this feature is more evident in higher eukaryotic species (fig. 2*A*). There are two highly conserved regions: CR1, conserved from zebrafish to human, and CR2, conserved from mosquito to human (fig. 2*A*). The mutant M144V found in patients with ABHS is located in the three amino acid residues (SML) in CR2 that are conserved in all species. To examine the subcellular localization of *C7orf11,* we transfected Myc-epitope–tagged protein into cultured mammalian cells and found that it was predominantly expressed in the nucleus (fig. 2*B*); the pattern of the Myc-epitope–mutated protein was indistinguishable from the wild type (data not shown). We performed in situ RNA hybridization analysis for *C7orf11* in human fetal skin tissue and found that it was expressed in epidermis and hair follicles, consistent with presentation of the phenotype (fig. 2*C*). *C7orf11* expression was not clearly detected in dermis by in situ hybridization, but it was found by RT-PCR in fibroblast cells.

To examine whether *C7orf11* mutations affect TFIIH cellular concentration, we performed comparative immunofluorescence analysis, using antibody against the xeroderma pigmentosum group B protein (XPB) (a core component of TFIIH), and found that the TFIIH levels in normal controls and in fibroblasts from a patient with TTD (one of the Moroccan siblings with the 2-bp deletion) are the same (fig. 2*D*). This result, combined with the observation that mutations could not be detected in any of TFIIH subunits and with the genetic mapping data (not shown), suggests that the defect in nonphotosensitive TTD is independent of TFIIH action.

To our knowledge, *C7orf11* is the first gene identified as mutated in patients with nonphotosensitive TTD. Since these mutations were found in only a subset of nonphotosensitive TTD cases, it is likely that there is more than one disease-causing gene, as was found for photosensitive TTD. Photosensitive TTD is caused by mutations in genes encoding subunits (*XPD, XPB,* and *TTD-A*) of the TFIIH complex that functions in transcription and DNA repair. Since there is an absence of cutaneous photosensitivity in the patients with *C7orf11* mutations and since the protein demonstrates a nuclear localization, it is possible that *C7orf11* may have a role in transcriptional processes but have no role in DNA repair. Moreover, the brittle hair observed in patients with TTD is thought to result from the reduced expression of high-sulfur proteins (intermediate keratin filaments and matrix proteins) in the late stage of keratinocyte differentiation (Bergmann and Egly 2001). Genes in these pathways and/or proteins associated with *C7orf11* would be the primary candidates for involvement in other nonphotosensitive TTD cases.

Acknowledgments

We thank Alli Tallqvist for skillful technical assistance in RNA in situ hybridization experiments. We acknowledge The Centre for Applied Genomics, the Genome Canada/Ontario Genome Institute, the Hospital for Sick Children Foundation, the Association Française contre les Myopathies, and the Dykstra Foundation in Detroit (grant to C.E.J.). S.W.S. is an Investigator of the Canadian Institutes of Health Research, a Scholar of the McLaughlin Centre for Molecular Medicine, and an International Scholar of the Howard Hughes Medical Institute.

Electronic-Database Information

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

The Chromosome 7 Annotation Project, http://www.chr7.org/ (for seven candidate genes on 7p14)

Ensembl, http://www.ensembl.org/ (for proteins from chimpanzee [accession number ENSPTRP00000032652], rat [accession number ENSRNOP00000018746], and chicken [accession number ENSGALP00000020100])

GenBank, http://www.ncbi.nlm.nih.gov/Genbank/ (for human *C7orf11* mRNA [accession number NM_138701] and cDNA sequences from zebrafish [accession number BC062385] and pig [accession number BP456435])

NCBI, http://www.ncbi.nlm.nih.gov/ (for human C7orf11 [accession number NP_619646] and orthologues from mouse [accession number BAB27916], frog [accession number NP_989025], pufferfish [accession number CAF91712], fruitfly [accession number NP_648690], and mosquito [accession number XP_318005])

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for Amish brittle-hair syndrome, Sabinas syndrome, and Pollitt syndrome)

UCSC Genome Browser, http://genome.ucsc.edu/

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