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Report

A Mutation in the *Fibroblast Growth Factor 14* Gene Is Associated with Autosomal Dominant Cerebral Ataxia

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Hereditary spinocerebellar ataxias (SCAs) are a clinically and genetically heterogeneous group of neurodegenerative disorders for which ⩾14 different genetic loci have been identified. In some SCA types, expanded tri- or pentanucleotide repeats have been identified, and the length of these expansions correlates with the age at onset and with the severity of the clinical phenotype. In several other SCA types, no genetic defect has yet been identified. We describe a large, three-generation family with early-onset tremor, dyskinesia, and slowly progressive cerebellar ataxia, not associated with any of the known SCA loci, and a mutation in the *fibroblast growth factor 14* (*FGF14*) gene on chromosome 13q34. Our observations are in accordance with the occurrence of ataxia and paroxysmal dyskinesia in Fgf14-knockout mice. As indicated by protein modeling, the amino acid change from phenylalanine to serine at position 145 is predicted to reduce the stability of the protein. The present *FGF14* mutation represents a novel gene defect involved in the neurodegeneration of cerebellum and basal ganglia.

Spinocerebellar ataxias (SCAs) are a growing group of hereditary neurodegenerative diseases for which ⩾14 different genetic loci have been identified. An expansion of an unstable trinucleotide repeat in the coding or noncoding region has been found for nine different SCA types (Holmes et al.1999; Koob et al. 1999; Zoghbi et al. 1999; Nakamura et al. 2001), whereas a pentanucleotide repeat expansion has been found in SCA10 (MIM 603516) (Matsuura et al. 2000). Anticipation has been described in several SCA types (Nakamura et al. 2001). Although ataxia is the unifying clinical characteristic, other noncerebellar symptoms, such as dopamine-responsive parkinsonism, early-onset tremor, or epilepsy, may develop early or late in a specific SCA type (Gwinn-Hardy et al. 2000; O'Hearn et al 2001; Rasmussen et al. 2001).

We describe a large, four-generation white family of Dutch descent with an autosomal dominant cerebellar ataxia slowly progressing over decades, in which the known candidate genes involved in other SCA types did not show a repeat expansion. The proband of this family was a 45-year-old woman (individual III:9 in fig. 1) who was referred for tremor and progressive ataxia. She reported that her 69-year-old father had severe ataxia, whereas her 24-year-old daughter complained of tremor and mild unsteadiness. Testing for trinucleotide-repeat expansions in SCA1, SCA2, SCA3, SCA6, SCA7, and DRPLA (MIM 164400, 183090, 109150, 183086, 164500, and 125370) of the proband gave results in the normal population range.

Twenty-one members of this three-generation family were examined by two neurologists. Ataxia, tremor, or both was seen in 14 members (7 men and 7 women) and transmitted as an autosomal dominant trait (fig. 1). Individual III:1 was not willing to participate in the study, although by family report he was considered to be affected. We could neither perform neurological examination of this patient nor obtain blood for DNA isolation. For the 21 family members examined, the medical records and, if available, hard copies of structural brain imaging were reviewed. Two patients underwent nerve

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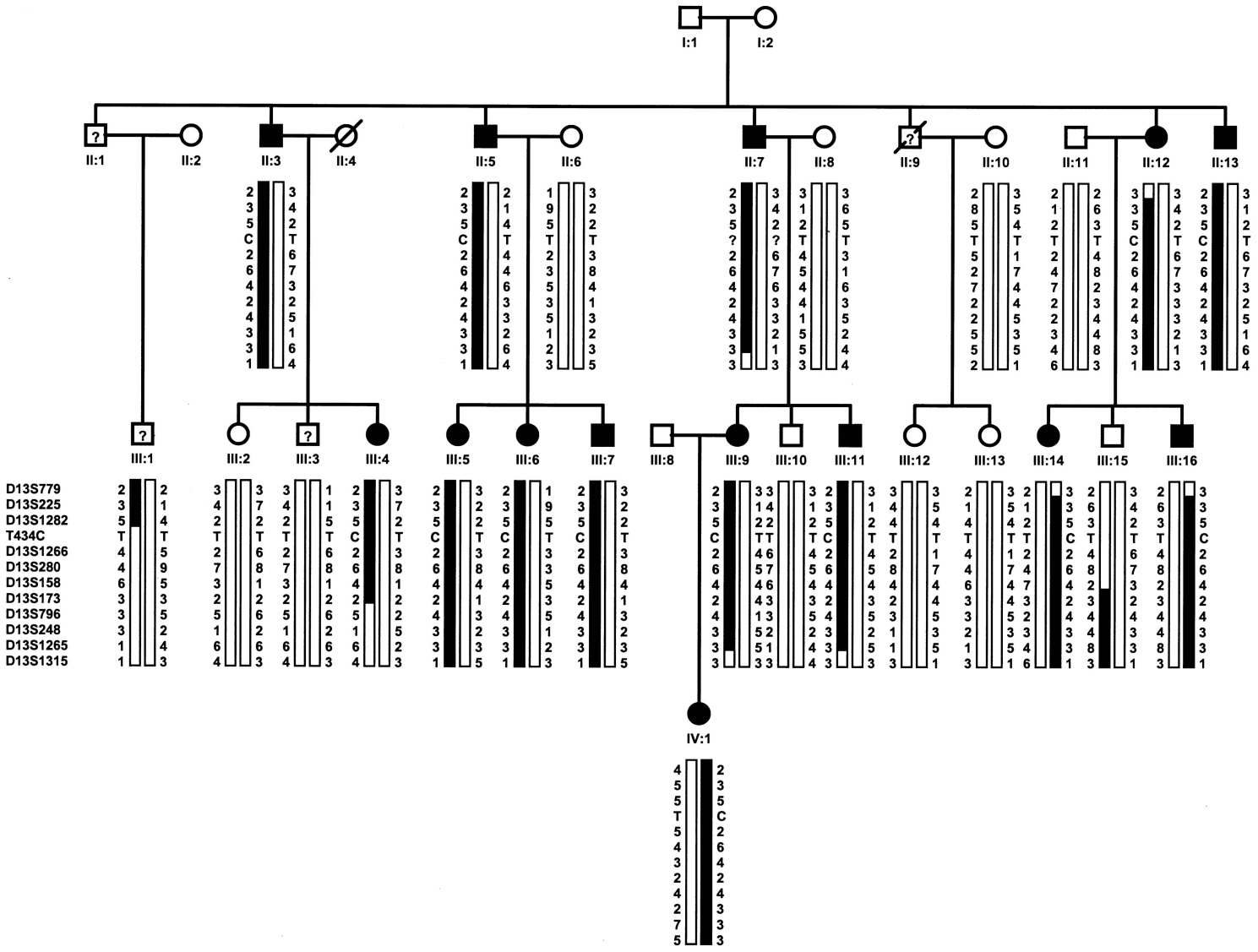

Figure 1 Pedigree structure of a family with autosomal dominant ataxia and haplotype reconstruction of chromosome 13q34 STR markers. Black symbols represent affected individuals; open symbols represent unaffected individuals. Question marks within symbols denote individuals with clinical status that is unknown because of either lack of data or uncertain diagnosis (see text). Black bars indicate a shared "risk" haplotype.

conduction studies, and five patients were evaluated by means of a battery of neuropsychological tests. Clinical data for the 14 affected family members are summarized in table 1. The age at examination was 48.8 ± 17.9 years (range 24–79 years). All had noticed trembling of both hands since childhood; the trembling was exacerbated by emotional stress and physical exercise. Patients first experienced mild unsteadiness and ataxia of upper limbs, especially under unusual circumstances, at age 15–20 years. The age at onset of gait ataxia was retrospectively determined by rough estimation based on the extremely slow progression of the disease process. Historical data showed no indication of anticipation in consecutive generations. Six patients did not complete primary education, and only 4 of the 14 patients attended secondary school. Aggressive outbursts were mentioned in five patients and depression in three patients. Neurological examination showed dysmetric saccades, disrupted ocular pursuit movements, gaze-evoked nystagmus, cerebellar dysarthria, and a high-frequency, small-amplitude tremor in both hands in most of the patients. Six patients showed head tremor, and subtle orofacial dyskinesias were seen in eight patients. Severe limb and gait ataxia was present in the three oldest patients. One at-risk individual (III:1, age 48 years), with known chronic alcohol abuse, showed a gaze-evoked nystagmus, although he did not have tremor, dyskinesia, or ataxia. Further neurological examination was unremarkable except for brisk knee jerks and diminished vibration sense at ankles in several patients. Neuropsychological testing showed low IQ scores (four patients) and impairment of memory functions (three patients), abstract thinking (three patients), and word fluency (one patient).

Moderate cerebellar atrophy on structural imaging was seen in two patients (fig. 2), whereas findings were normal in seven other patients. The individual with chronic alcoholism showed generalized cerebral atrophy. Imaging of dopamine-D2 receptors, using [123I]iodobenzamide single-photon-emission computed tomography (IBZM-SPECT), in one patient (II:7) showed a reduced dopamine D2-receptor binding of the left striatum. Normal binding ratios in striatum of the same patient were found on iodine-123-N-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane (FP-CIT) SPECT. Nerve conduction studies revealed mild axonal polyneuropathy on electromyography in both patients examined (II:7 and II:12).

After approval by the medical ethics committee of the Erasmus Medical Center, Rotterdam, genomic DNA was isolated from peripheral blood from all 14 affecteds, 4 spouses, and 7 at-risk individuals, as described elsewhere (Miller et al. 1988). We performed a systematic genome screen, using STRs from the ABI PRISM Linkage Mapping Set MD-10 (Applied Biosystems). Additional markers for fine mapping were obtained from Généthon and from the Center for Medical Genetics (Marshfield Medical Research Foundation) genetic marker sets. Marker order and distances were obtained from the Marshfield integrated linkage map. Markers were amplified accord-

Table 1

Clinical Phenotype of 14 Affected Family Members with Early-Onset Tremor and Cerebellar Ataxia

	Age (in years) at		Result of Neurological Examination[a]							
Individual	Examination	Onset of Ataxia[b]	W	P	N	D	T	LA	GA	Imaging Finding
II:3	79	30	WC	A	+	U	+	++	Unable	NA
II:5	71	34	WC	Dp	−	U	+	++	Unable	Cerebellar atrophy
II:7	69	27	C	−	+	++	+	++	++	Cerebellar atrophy
II:12	64	40	↓↓	−	−	++	+	+	++	Normal[c]
II:13	61	30	↓	−	+	++	+	+	+	NA
III:4	54	40	↓	−	+	++	+	+	+	Normal
III:5	31	30	↓	A	+	+	+	+	+	NA
III:6	30	−	Normal	A	+	+	−	+	−	NA
III:7	27	−	Normal	A	+	+	+	−	+	Normal
III:9	48	28	↓	−	+	+	+	+	+	Normal
III:11	42	37	↓	−	+	+	+	−	+	Normal
III:14	43	40	↓	−	+	+	−	−	+	Normal
III:16	39	−	↓	A	+	−	+	−	−	NA
IV:1	24	−	Normal	Dp	+	−	+	+	+	Normal

[a] A = aggressive outbursts; C = walking with a cane; D = dysarthria; Dp = treated for depression; GA = gait ataxia; LA = limb ataxia; N = gaze-evoked nystagmus; NA = not available; P = psychiatric episodes; T = tremor; U = unintelligible speech; W = walking; WC = wheelchair; ↓ = mild unsteadiness; ↓↓ = impaired walking; + = present or mild; − = absent; ++ = moderate; unable = unable to walk without assistance.

[b] Age at onset of gait ataxia was estimated retrospectively by patient.

[c] CT scan of the brain at age 60 years.

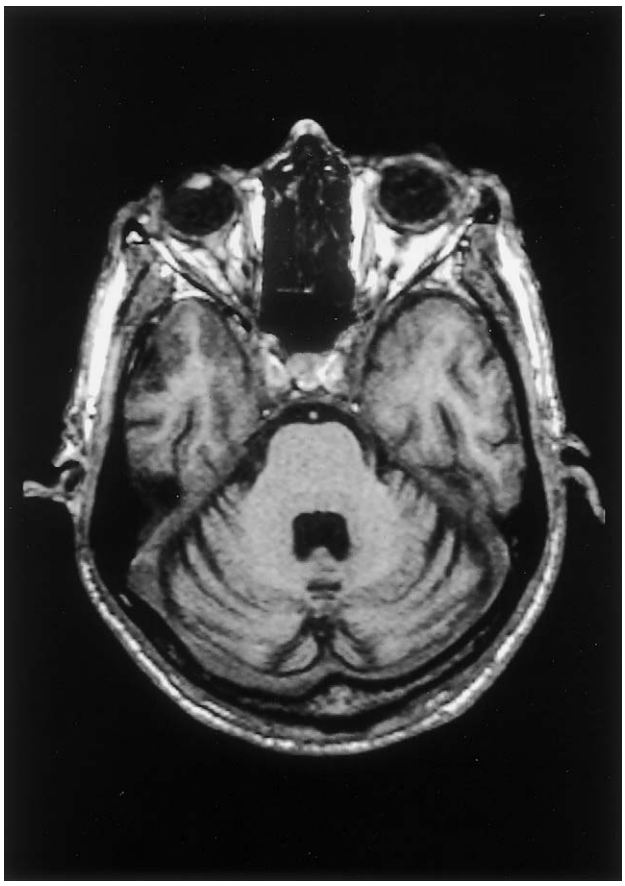

Figure 2 MRI of the brain of patient II:7 showed atrophy of cerebellar hemispheres (T1-weighted axial images).

ing to methods specified by the manufacturers. PCR products were loaded on an ABI 3100 automated sequencer (filter set D), and the data were analyzed with ABI GeneMapper (version 2.0) software.

Two-point linkage analysis was performed with the MLINK program of the LINKAGE package (version 5.1) (Lathrop and Lalouel 1984). Maximum LOD and location scores were calculated for each marker, assuming ataxia to be an autosomal dominant disorder with 90% penetrance and with a gene frequency of 1:10,000; no phenocopies were allowed, and equal allele frequencies of the genotyped markers were used in the calculations. Individuals with unknown clinical status (question marks in fig. 1) were regarded as unknown in the linkage analysis. We obtained positive LOD scores for adjacent markers on chromosome 13q34 (D13S158, D13S173, and D13S1265). Further refinement of this region by saturation with additional markers confirmed these findings, and two-point linkage analysis yielded a maximum LOD score of $Z = 4.28$ at recombination fraction 0 for marker D13S280. Changing allele frequencies of the polymorphic markers did not significantly alter LOD and location scores. Subsequently, haplotypes for 11 adjacent markers on chromosome 13q34 were then constructed by parsimony (fig. 1), and several recombinants that defined the limits of the ataxia-susceptibility region were detected. The recombination events in affected individuals demonstrate that the region is limited by marker D13S779 on the centromeric side (individuals II:12, III:14, and III:16) and by marker D13S796 on the telomeric side (individual III:4), showing the critical region to be 10.6 cM on the sex-averaged linkage map. The SCA8 locus could be excluded by testing the following markers flanking the SCA8 locus (MIM 603680) on chromosome 13q21: D13S1309, D13S1268, D13S275, D13S1296, D13S279, and D13S18. SCA8 CTG-repeat length was determined by radioactive PCR essentially as described by Weber and May (1989) and was within the normal range for affected and unaffected family members (data not shown) (Koob et al. 1999).

According to Ensembl and the Human Genome Browser, within this critical region, ⩾10 genes with a known function and 58 predicted transcripts with unknown function are located, including *fibroblast growth factor 14* (*FGF14*) or *fibroblast growth factor homologous factor 4* (*FHF4*) (MIM 601515). A recently published mouse model lacking *Fgf14* showed ataxia and paroxysmal dyskinesia (Wang et al. 2002). This led us to begin our candidate-gene mutation analysis with the *FGF14* gene in this family. The *FGF14* gene encompasses ~200 kb on the genomic level. Two major mRNA transcripts are produced, FGF14a and FGF14b, which differ in the definition of exon 1 (Wang et al. 2000). The two transcripts encode protein isoforms of 247 and 252 amino acids, respectively. For mutation analysis, the genomic structure of *FGF14* was determined by aligning cDNA (GenBank accesssion number NM_004115) to genomic sequence (GenBank accesssion number NT_009952). Primers were designed to amplify DNA from coding regions, splice sites, and ⩾50 bases of flanking intronic sequence on both sides of each exon. Amplification was performed with 10-min initial denaturation at 94°C; 35 cycles of 30-s denaturation at 94°C, 30-s annealing at 55°C (for exons 2, 3, and 4), at 57°C (for

Table 2

Primer Sequences and Amplified Product Sizes

Exon	Forward 5′→3′	Reverse 5′→3′	Size (bp)
1a	agggcgagccacggtctg	gagggaaggagcctggagaa	373
1b	aatcactgagaagtctcaaag	ctgcagatctagctcgatga	362
2	gcctgtttctgtggcttact	aactatgtaactggtggcctga	357
3	tattgtcgcatcagcccttc	ttgttgttgctgccattgtt	423
4	gtatatccggtcctccatgc	tccagcactttgtgaaggtt	428
5	ctctgtgggctggaaatga	agcaggaatgtctggtgagg	388

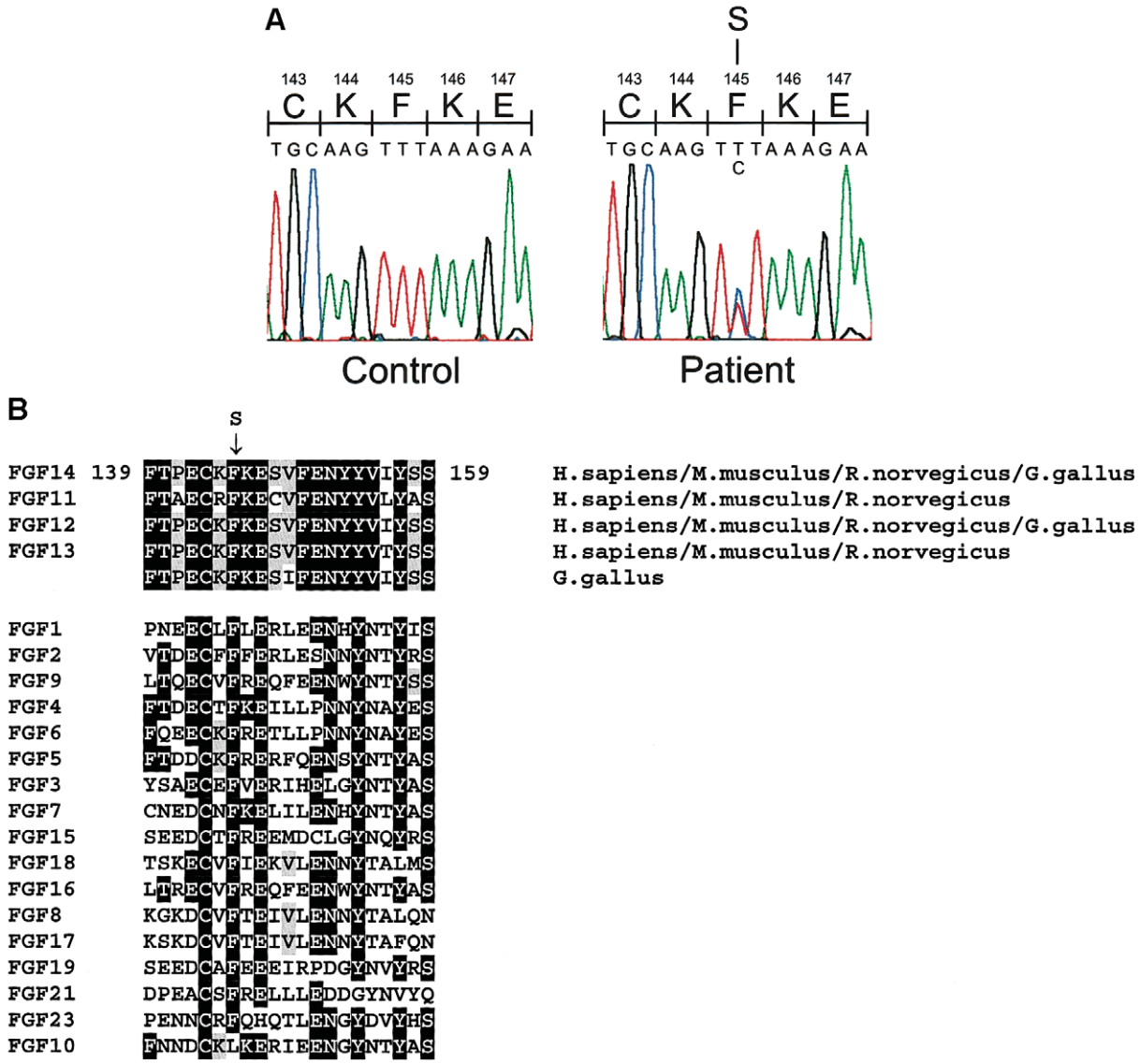

Figure 3 *A*, Sequence electropherograms of mutations found in *FGF14*. Both normal (*left*) and mutated (*right*) DNA and amino acid sequences are shown. *B* (*top*), Amino acid sequence comparison of FGF11–FGF14 homologs in *Homo sapiens*, *Mus musculus*, and *Gallus gallus*, showing the conservation of the amino acid mutated in FGF14 (F145S) in the family with ataxia. The change of a phenylalanine to a serine in patients is indicated by an arrow. Only the alignment with amino acids 139–159 of FGF14 is shown. *B* (*bottom*), Amino acid sequence comparison around the mutated F145S for all FGFs found in *Homo sapiens*. Amino acid alignments were performed with ClustalW.

exon 5), or at 61°C (for exon 1), and 90-s extension at 72°C; and 5-min final extension at 72°C. Primer sequences and sizes of amplified fragments are listed in table 2. PCR reactions for all exons were performed in 50 μl containing 10 × PCR buffer (Gibco/Invitrogen); 1.5 mM $MgCl_2$; 200 μM dNTP; 0.8 μM forward primer; 0.8 μM reverse primer; 2.5 U *Taq* polymerase (Gibco/Invitrogen); and 50 ng genomic DNA. PCR products were purified with the Amersham GFX-PCR, DNA, and Gel Band Purification Kit, and their approximate concentration was determined by use of Low DNA Mass Ladder (Gibco BRL). Sequencing reactions were essentially performed as specified by the manufacturers, using BigDye Terminator chemistry, version 1 (Applied Biosystems). Products were loaded on an ABI 3100 automated sequencer and analyzed with SeqScape (version 1.1) for heterozygous base calls and sequence alignment. We identified a T→C transition at position 434 of the FGF14a ORF in exon 4, resulting in an amino acid substitution of a serine for a phenylalanine at position 145 (F145S) (fig. 3*A*).

Testing of the base change in exon 4 on all available

Figure 3*C* Molecular models of wild-type and mutant FGF14. The purple and yellow ribbons correspond to α-helix and β-sheet structures, respectively. Indicated is the position of the wild-type (F145) (*left panel*) and mutated (Ser145) residue mutated in the family.

family members and 376 control chromosomes from the general Dutch population was done with allele-specific oligo hybridization; PCR products containing exon 4 were blotted onto Hybond-N+ (Amersham Biosciences). The blots were hybridized for 1 h at 37°C in 5 × sodium chloride sodium phosphate EDTA, 1% SDS, and 0.05 mg/ml single-strand salmon sperm DNA with either the normal (tgcaagtttaaagaat) or mutated (tgcaagtctaaagaat) sequence primer. Filters were washed to a final stringency of 0.3 × SSC, 0.1% SDS, at 37°C. The base change in exon 4 was not found in the general Dutch population, and it segregates completely with the disease phenotype in the family. No other sequence changes segregating with the disease phenotype were identified. The individual (III:1) for whom diagnosis was uncertain did not share the disease-associated haplotype and mutation.

To investigate the structural consequences of the F145S mutation described here, the sequence of *FGF14* was submitted to the 3D-PSSM (position-specific scoring matrix) fold-recognition server (Kelley et al. 2000), which identified six homologues of known structure with E values ranging from 0.005 to 0.1. A molecular model of FGF14 was built on the basis of the known structure of human FGF9 (MIM 600921). The corresponding structure of FGF9, solved by X-ray crystallography at 2.6 Å resolution (Protein Data Bank entry 1G82), was therefore used as a modeling template (Hecht et al. 2001). Side chains were built, using WHAT IF (Vriend 1990), and the model was then refined with YASARA (Krieger et al. 2002). Validation of the model with WHAT_CHECK (Hooft et al. 1996) showed structure *Z* scores in normal ranges, slightly better than those of the template. The model coordinates are available on request. With 39% sequence identity and an almost gapless alignment spanning 144 residues, both proteins can be expected to adopt the same fold (Rost 1999). The highest scoring alignment, with 39% sequence identity, spanned residues Arg 63 to Tyr 206 and was gapless except for a single one-residue insertion. In this model, F145 is deeply buried and forms a central part of the hydrophobic core. An *in silico* mutation to serine showed that although its hydroxyl group can form a hydrogen bond with the backbone oxygen of V114, the now-missing bulky phenyl ring leaves a big space in the protein's core (fig. 3*C*). It is well known that mutations leading to empty space in the core are very destabilizing (De Vos et al. 2001), especially if the structure is rigid and cannot easily accommodate the changes. We therefore conclude that the F145S mutation does not act directly, by influencing the interaction of FGF14 with other cellular factors, but most likely indirectly, by reducing its stability.

The present study demonstrates for the first time that a mutation in *FGF14* is associated with autosomal dominant cerebral ataxia with apparent complete penetrance. The FGF protein family currently consists of 23 known FGFs (Smallwood et al. 1996; ADHR Consortium 2000; Ornitz and Itoh 2001). FGF11 through FGF14 share <30% amino acid identity with other FGFs but retain core conserved amino acid residues in exons 2, 3, and 4. However, FGF11 through FGF14 share 58%–71% amino acid sequence identity with each other, lack a secretory sequence as seen in the other FGFs, and are indeed not secreted in the medium of transfected cells but accumulate to high levels intracellularly instead (Smallwood et al. 1996; Wang et al. 2000). Furthermore, no interaction with FGF receptors has been identified, making it likely that their mechanism of function is different from the other FGFs.

The alternatively spliced exon 1 appears to encode dominant protein-trafficking signals to target the proteins to different subcellular compartments (Smallwood et al. 1996; Munoz-Sanjuan et al. 2000; Wang et al. 2000); FGF14a is mainly located in the nucleus, whereas FGF14b is located in the cytoplasm of transfected NIH3T3 cells (Wang et al. 2000). In addition, in the primary sequence, two nuclear-localization domains can be predicted, (89-PSASRRR-95) and (122-KKRR-125). Other functional motifs are a peroxisomal domain (125-RLRRQDPQL-133) and an endoplasmatic reticulum membrane domain (308-KSKT-311).

The expression pattern of Fgf14 in mice suggests a role in both neuronal development and adult brain function. In embryonic mice at E12.5, the gene is expressed in the ventral lining of the third and fourth ventricles of the subventricular zone, which gives rise to neurons of several brain regions, including the cerebellum. The gene is also expressed in the supraoptic and septal areas, spinal cord, and several nonneuronal tissues (Wang et al. 2000). Fgf14 is also expressed in the adult mouse brain, with highest levels of expression in the granular cells of the cerebellum and moderate to high levels in hippocampus in amygdala, cerebral cortex, striatum, and thalamus. A β-galactosidase reporter protein showed that Fgf14 is mainly present in axons and almost entirely absent in cell bodies.

Mutations in *FGF* genes are rare; only mutations in *FGF23* have been associated with autosomal dominant hypophosphataemic rickets (ADHR Consortium 2000). The F145S mutation in the present family with cerebellar ataxia is the first genetic defect found in one of the *FGF11–FGF14* genes, encoding a subgroup of FGFs that do not interact with FGF-receptor proteins. The F145S mutation found in this family affects a highly conserved amino acid and is located in a region of the protein where several other amino acids are conserved between FGFs (for example, C143 is conserved in all FGFs; see fig. 3*B*). The region of the protein is especially conserved in the subgroup of FGF11–FGF14 (MIM 601514, 601513, 300070, and 601515), indicating that it might encode

a domain that is specifically involved in the function of this subgroup of FGFs. However, the exact effect of the mutation on the function is difficult to predict, since very little is known about the function of FGF14.

The clinical presentation of the F145S mutation—tremor in childhood years, ataxia slowly progressive over decades, with normal life expectancy in the family we describe—was quite characteristic for this SCA type. The absence of genetic anticipation and of variation in clinical phenotype in the present family already made an expansion of a trinucleotide repeat unlikely before identification of the F145S mutation. The *FGF14* gene is separated from the SCA8 locus by ⩾30 cM on the sex-averaged linkage map (Koob et al. 1999). However, the controversy over the causal relation between the expanded CTG repeat and SCA8 justifies screening of the *FGF14* gene in patients with SCA8 for whom no linkage data excluding the current locus are available (Juvonen et al. 2000; Vincent et al. 2000; Sobrido et al. 2001).

The phenotype of the F145S mutation in the present family showed striking similarities with the findings of ataxic gait, widened stance, lack of forefoot-hindfoot correspondence, and paroxysmal hyperkinetic dyskinesia in homozygous Fgf14-knockout mice at age 3 wk (Wang et al. 2002). The cerebellar ataxia in the present patients with the F145S mutation may be caused by dysfunction of cerebellar granule cells in the internal granular layer, since FGF14N β-galactosidase staining in transgenic mice was most intense in the molecular layer where axons of granule cells extend. The findings in patients with the *FGF14* mutation and in the Fgf14-knockout mice may suggest a dysfunction in the basal ganglia circuitry. Fgf14 is not expressed by dopaminergic neurons but in other neurons of the striatopallidal and striatonigral pathways (Wang et al. 2002). The inability to complete primary education, low cognitive performances, and aggressive outbursts in several of our patients might reflect changes in the development and survival of neuronal populations in the cerebral cortex, amygdala, and basal ganglia. Fgf14 is localized in axonal projections, and it has been suggested that it plays a role in axonal function, synaptosomal function, or neurotransmission (Wang et al. 2002). The question is whether and how Fgf14 dysfunction represents a novel pathway of neurodegeneration. It seems unlikely that intranuclear inclusions, which are the pathological hallmarks of polyglutamine disorders (Zoghbi et al. 1999), will be found in the brains of patients with the F145S mutation, and we need to wait for available postmortem tissue to investigate which cell type is primarily involved and to determine the subcellular distribution of mutant FGF protein. In addition, functional studies, using model systems, will be required to help solve these questions.

It is tempting to compare the available Fgf14 knockout model directly with the clinical phenotype in the family described here, although we need to be cautious since in the family we describe the trait segregates in an autosomal dominant fashion. Each patient carrying the mutant copy of the gene still has one fully functional copy of the gene as well. However, because the F145S mutation is located in the central core of the protein and is likely to result in a decreased stability of the protein, a loss of function of the protein is a more likely explanation than increased aggregation properties of the protein. Expression studies using the mutant protein in transgenic mice and cellular models may resolve this issue in the near future. Since an animal model lacking Fgf14 is available, it is therefore important to investigate whether a heterozygous knockout mouse, which appears to be normal at age 4 wk (Wang et al. 2000), does show abnormalities when more-sensitive tests for motor and coordination are applied or when tests are performed at a later stage in life.

In conclusion, the pathogenic F145S mutation in the *FGF14* gene is a representative of a novel gene defect for cerebellar ataxia. Mutational screening in familial ataxia of unknown genetic cause, and in SCA8 in particular, will resolve the question of how frequent this gene defect is. Pathologic examination of brain tissue from ataxic patients with the F145S mutation and functional studies using model systems may shed more light on the normal function of FGF14 and characterize a new pathway to neurodegeneration.

Acknowledgments

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Electronic-Database Information

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

Center for Medical Genetics, Marshfield Medical Research Foundation, http://research.marshfieldclinic.org/genetics/ (for polymorphic STR markers)
ClustalW (European Bioinformatics Institute), http://www2.ebi.ac.uk/clustalw/ (for amino acid sequence comparisons)
Ensembl, http://www.ensembl.org/ (for identification of transcripts in the critical region)
GenBank, http://www.ncbi.nlm.nih.gov/Genbank/GenbankOverview.html (for NM_004115 and NT_009952)
Généthon, http://www.genethon.fr/php/index_us.php (for polymorphic STR markers)

Human Genome Browser, http://genome.cse.ucsc.edu/ (for identification of transcripts in the critical region)
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for SCA1 [MIM 164400], SCA2 [MIM 183090], SCA3 [MIM 109150], SCA6 [MIM 183086], SCA7 [MIM 164500], DRPLA [MIM 125370], SCA8 {MIM 603680], SCA10 [MIM 603516], FGF9 [MIM 600921], FGF11 [MIM 601514], FGF12 [MIM 604513], FGF13 [MIM 300070], and FGF14 [MIM 601515])
Protein Data Bank, http://www.rcsb.org/pdb/ (for 1G82)

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