New Subtype of Spinocerebellar Ataxia With Altered Vertical Eye Movements Mapping to Chromosome 1p32

Carmen Serrano-Munuera, MD; Marc Corral-Juan, BSc; Giovanni Stevanin, PhD; Hector San Nicolás, BSc; Carles Roig, MD, PhD; Jordi Corral, BSc; Berta Campos, PhD; Laura de Jorge, BSc; Carlos Morcillo-Suárez, PhD; Arcadi Navarro, PhD; Sylvie Forlani, MD, PhD; Alexandra Durr, MD, PhD; Jaime Kulisevsky, MD, PhD; Alexis Brice, MD, PhD; Ivelisse Sánchez, PhD; Victor Volpini, MD, PhD; Antoni Matilla-Dueñas, PhD

Importance: To provide clinical and genetic diagnoses for patients’ conditions, it is important to identify and characterize the different subtypes of spinocerebellar ataxia (SCA).

Objective: To clinically and genetically characterize a Spanish kindred with pure SCA presenting with altered vertical eye movements.

Design: Family study of ambulatory patients. Electro-oculographic and genetics studies were performed in 2 referral university centers.

Setting: Primary care institutional center in Spain.

Participants: Thirty-six participants from a large Spanish kindred were clinically examined, and 33 family members were genetically examined. Detailed clinical data were obtained from 9 affected relatives. Two ataxic siblings and 2 asymptomatic family members were examined using an enhanced clinical protocol for a follow-up period of 7 years.

Main Outcomes and Measures: High-density genome-wide single-nucleotide polymorphism arrays, along with microsatellite analysis, and genetic linkage studies were performed. Whole-exome sequencing was used for 2 affected relatives. For most patients, the initial symptoms included falls, dysarthria, or clumsiness followed by a complete cerebellar syndrome. For all 9 affected relatives, we observed altered vertical eye movements, as initial ocular signs for 3 of them and for the 2 asymptomatic family members, all having inherited the risk haplotype. Neuroimaging showed isolated cerebellar atrophy.

Results: Initial genome-wide linkage analysis revealed suggestive linkage to chromosome 1p32. Multipoint analysis and haplotype reconstruction further traced this SCA locus to a 0.66-cM interval flanked by D1S200 and D1S2742 ($z_{\text{max}}=6.539; P<.0001$). The causative mutation was unidentified by exome sequencing.

Conclusions and Relevance: We report a new subtype of SCA presenting in patients as slow progressing ataxia with altered vertical eye movements linked to a 11-megabase interval on 1p32. The Human Genome Nomenclature Committee has assigned this subtype of ataxia the designation SCA37.


Original Contribution

©2013 American Medical Association. All rights reserved.

Autosomal dominant spinocerebellar ataxias (SCAs) are a highly heterogeneous group of movement disorders characterized by progressive cerebellar ataxia of the gait and limbs variably associated with ophthalmoplegia, pyramidal and extrapyramidal signs, dementia, pigmentary retinopathy, seizures, lower motor neuron signs, or peripheral neuropathy. Genetic has a significant role to play in the etiology, and actually 32 different loci have been associated with SCA phenotypes with 23 defective genes identified, although these numbers are still in flux (ie, increasing). Few mutations cause pure cerebellar syndrome and isolated neurodegeneration. In fact, most SCAs are multisystemic disorders presenting with clinical and neuropathological variabilities. The prognosis is variable, and drug treatments have shown limited effectiveness.

Several clinical scales have been developed to measure the severity of SCAs. The Scale for the Assessment and Rating of Ataxia (SARA) is the most widely used. Since its design, SARA has demonstrated construct validity, internal consistency, and interrater reliability, together with favorable reproducibility and responsiveness.
In our study, we report the clinical and genetic findings in a Spanish kindred presenting with a pure cerebellar phenotype consisting of ataxia with altered vertical eye movements and with no evidence of anticipation. The causative genetic defect for this disorder localizes to an 11-megabase interval on chromosome 1p32. The Hu-
man Genome Nomenclature Committee has assigned this new ataxia subtype the designation SCA37.

Figure 1. Pedigree of the Spanish kindred (subtype SCA37 of spinocerebellar ataxia) showing the reconstructed haplotypes resulting from the analysis of 10 polymorphic markers spanning 20.38 cM on chromosome region 1p32.

CLINICAL STUDIES

Our study was approved by the local Human Subjects Protection Committee (ie, Comité Éticos de Investigación Clínica) of the University Hospital Germans Trias i Pujol in Badalona, Spain, and included patient consent forms for both genetic testing and research for all relatives participating in the study. Figure 1 shows the genealogical tree of the Spanish family with 68 members spanning 6 generations. A neurological examination was performed by the first author (C.S.M.) for 9 ataxic patients (ie, patients IV:5, IV:6, IV:7, IV:10, IV:11, IV:16, IV:19, IV:21, and V:15), 8 spouses, and 19 asymptomatic relatives. Data on the medical histories of the remaining members of the family were collected. The SARA scores\(^{10}\) were assessed for 8 ataxic patients during the first visit, twice during a 5-year period for 1 affected patient (IV:10) and at least once a year during follow-up visits for 7 years for 2 affected relatives (patients IV:5 and IV:6). These 2 affected siblings were further investigated using an enhanced clinical protocol, including electrocardiograms, echocardiograms, audiometric tests, nerve conduction studies, magnetic resonance imaging of the brain, evoked potentials, transcranial magnetic stimulation, and electro-oculographic studies during follow-up visits. Two asymptomatic relatives, patients IV:3 and V:7, were also examined using the same enhanced clinical protocol for the same period of time. All the studies were performed in the absence of medication treatment. Eye movements were recorded using an automated, computerized electronystagmographic package (Nystar; Nicolet Audi-diagnostics). Detailed methods for random and fixed saccades, smooth pursuit tests, and optokinetic nystagmus (ON) tests are described in the eAppendix (http://www.jamanetwork.com).\(^{11}\) Oculographic data from 6 healthy controls (ranging in age from 40 to 74 years) were registered.

GENETICS STUDIES

Genomic DNA samples were isolated from blood leukocytes or fibroblasts expanded from skin biopsy samples using automated DNA purification (Chemagen). DNA samples were obtained from 23 unaffected and 10 affected relatives. Affected relatives were first tested for mutant CAG expansions within the SCA1, SCA2, SCA3, SCA6, SCA7, SCA10, SCA12, SCA17, and DRPLA genes. Relatives with linkage to the SCA4 locus and mutations in the KCND3 gene were excluded. Twelve relatives, 6 healthy and 6 affected, were included in the initial genetic linkage study that used the Infinium HumanLinkage-12 Genotyping BeadChip (Illumina Inc). The panel included 6009 single-nucleotide polymorphism (SNP) markers with an average gap of 441 kilobases and 0.58 cM across the genome. Genotypes were assigned using the Bead Studio genotyping module software (Illumina Inc), and linkage was analyzed using Merlin.\(^{14}\) Penetrance was set to 80% for all participants. To confirm linkage and refine mapping, 10 affected and 23 healthy relatives of the pedigree were further genotyped for microsatellite markers located on chromosome 1 and for SNPs using the Genome-Wide Human SNP Array 6.0 (Affymetrix), which contains 906,600 SNPs. Two-point and multipoint genetic linkage analyses were then performed with the MLINK and
LINKMAP modules (both version 5.10), respectively, from FASTLINK (version 4.1P). For the multipoint analysis, we used the framework maps from the Marshfield Medical Research Foundation, deCODE Genetics, and Généthon. Whole-exome sequencing was performed with DNA samples from 2 affected relatives. The method is described in the eAppendix. Known variants were discarded from further analysis based on the information from the Ensembl version 62 database, which hosts data from the most important human variation resources such as 1000 Genomes, dbSNP, and HapMap. Candidate genes were prioritized based on potentially damaging variants, as previously described.

RESULTS

CLINICAL FEATURES

The index patient (IV:7) was evaluated for the first time at the age of 54 years. He had a 2-year history of falls and abnormal speech. A neurological examination disclosed dysmetric vertical saccades and irregular vertical ocular pursuit, whereas his horizontal eye movements appeared to be normal. Additional clinical signs included scanning speech, mild trunk ataxia, severe dysmetria in both legs, and irregular fast alternating movements and dysmetria with the left hand. His deep tendon reflexes were normal, and further examination revealed no cognitive impairment, long tract signs, myoclonus, tremor, sensory loss, cogwheel rigidity, or other extrapyramidal signs. Computed tomography revealed diffuse cerebellar atrophy. No further clinical information is available from this patient because he died of disseminated adenocarcinoma 4 months after his first visit. Patient IV:5 was first seen at the age of 64 years. A neurological examination showed slight clumsy tandem walking. Vertical saccades were remarkably inaccurate, and vertical pursuit was irregular, with a cogwheel pattern revealed during the eye movement examination. By contrast, his horizontal eye movements were normal. Abnormal horizontal pursuit and horizontal nystagmus appeared during follow-up. Remarkably, horizontal saccades remained normal. Clinical progression of the ataxia in patient IV:5 outlines a more benign phenotype than that in the index patient IV:7. After 7 years of disease progression, tandem walking is still possible for patient IV:5, and he does not report falls and has no major difficulties in activities of daily living. Magnetic resonance imaging of the brain first showed cerebellar atrophy of the vermis with normal brainstem (Figure 2A), evolving to generalized cerebellar atrophy after 2 years (Figure 2B). His brainstem remained normal during follow-up. The brainstem auditory evoked potentials detected endocochlear mild and bilateral loss that persisted unchanged in time. Patient IV:6 was examined for the first time at 59 years of age. She complained of mild unsteadiness while walking. A neurological examination revealed subtle difficulty in tandem walking, inaccurate vertical saccades, and clumsy vertical pursuit. Her horizontal eye movements were normal. She developed cerebellar syndrome involving the trunk and lower limbs and experienced frequent falls. Dysarthria became evi-

Figure 2. A and B, Sagittal and coronal T1-weighted magnetic resonance imaging scans of the brain of patient IV:5. The eye movements during vertical fixed saccades (C) (20° amplitude; top line, upward saccades; bottom line, downward saccades [arrows]) and smooth pursuit (D) (0.4 Hz; 16° amplitude; and peak velocity, 40°/s) are shown for patient IV:6. The asterisks indicate saccadic intrusions.
dent 1 year later. Abnormal horizontal saccades and pursuit, as well as dysphagia, were clearly noted 5 years from onset. She is currently 66 years of age and needs help in activities of daily living. Baseline magnetic resonance imaging of her brain revealed general cerebellar atrophy with sparing of the brainstem. The brainstem auditory evoked potentials yielded normal results. Electrocardiography, echocardiography, transcranial magnetic stimulation tests, and nerve conduction studies (eTables 1 and 2) all yielded normal results, and the results remained normal during follow-up for both patient IV:5 and patient IV:6.

Clinical data were obtained from 6 additional patients with ataxia (ie, patients IV:10, IV:11, IV:16, IV:19, IV:21, and V:15). They were first seen 10 to 38 years after onset. Their initial symptoms included falls, dysarthria, or clumsiness. Clinical progressions were slow albeit variable. Four patients who were still alive (ie, patients IV:10, IV:11, IV:19, and IV:21) became wheelchair-bound 10 to 33 years from onset. All 6 patients had abnormal eye movements in both vertical and horizontal planes, with mainly hypometric saccades and cogwheel pursuit. Of these 6 patients, 4 had dysphagia (patients IV:16, IV:19, IV:21, and V:15), 3 had cerebellar tremor (patients IV:10, IV:11, and IV:21), and 1 had nystagmus (patient IV:10). None of them presented with motor or sensory deficits, extensor plantar reflexes, fasciculations, epileptic seizures, or cognitive impairment. Computed tomographic or magnetic resonance imaging scans were available for 5 patients, and general cerebellar atrophy with sparing of the brainstem was detected on the scans of all 5 patients. The SARA scores for all patients, except for patient IV:7 (because he died before the SARA scores were made available), are shown in Figure 3.

To calculate the mean age at onset and the mean duration of disease, additional information from 2 deceased ataxic patients (III:3 and III:5) was included. Thus, the mean age at onset of our patients is 48 years (range, 38-64 years), and the mean disease duration for both deceased patients was 49.5 years. Patient IV:7 was excluded from this average because he died earlier of an unrelated disease. There is no evidence of anticipation in the age at onset in the 3 generations for which data are available.

Nineteen asymptomatic relatives were identified and examined (mean age, 42 years [range, 9-75 years]). Of these, 2 patients (V:7 and V:10), 32 and 40 years of age, respectively, showed dysmetric vertical saccades and irregular vertical pursuit; their horizontal eye movements and the results of their remaining standardized neurological examinations were normal. Patient V:7 participated in the enhanced serial clinical investigation, and the electro-oculographic studies (Tables 1, 2, and 3) confirmed this clinical finding. Electrocardiography, echocardiography, transcranial magnetic stimulation tests, magnetic resonance imaging, and nerve conduction studies yielded normal results. Both individuals (ie, patients V:7 and V:10) were later found to carry the risk haplotype. The results of the neurological and eye movement examinations were normal for the other 17 asymptomatic relatives. Among them, patients V:8 and VI:7 were also later found to carry the risk haplotype. Patient V:8 was excluded from the clinical study because of a history of drug abuse, and, as expected, patient VI:7 had normal eye movements, given that he is currently 22 years of age, which is well before the average age at onset. As for the second asymptomatic patient who participated in the enhanced serial clinical protocol (patient IV:3, who was last assessed at 74 year of age), all the ancillary tests, including electro-oculographic studies, yielded normal results, and he was later found not to carry the risk haplotype.

**ELECTRO-OCEULOGRAPHIC STUDIES OF PATIENTS IV:5 AND IV:6**

From the results of the first electro-oculographic study (2 years after disease onset), it was found that patient IV:5 was more severely affected than patient IV:6. Patient IV:5 showed both downward and upward hypermetric saccades, and patient IV:6 revealed hypometric upward saccades and hypermetric downward saccades. For both patients, the latency and velocity of the vertical saccades were normal. For both patients, vertical smooth pursuit was diminished, and vertical ON showed slow pursuit velocity. Patient IV:5 showed an altered horizontal ON as the unique abnormal finding in the horizontal plane because the horizontal ON was normal in her sister (patient IV:6) and because the horizontal saccades and smooth pursuit were normal for both patients.

Electro-oculographic data are included in Tables 1-3 from the second electro-oculographic study (5 years after disease onset). The accuracies of the vertical saccades were abnormal (Table 1), the vertical smooth pursuits were deficient (Table 2), and vertical ON showed slow pursuit velocities (Table 3) for both siblings (ie, patients IV:5 and IV:6). The latencies and velocities of the vertical saccades remained normal (data not shown). The vertical eye movements of patient IV:5 remain unchanged. For patient IV:6, the altered vertical eye movements worsened, particularly in the downward direction. Figure 2C shows downward hypermetric and saccadic intrusions, particularly in downward saccades. Figure 2D shows cogwheel pursuit in both upward and downward pursuit. For patient IV:5, horizontal saccades were normal, whereas for patient IV:6, horizontal saccades were hypermetric in both directions.
(Table 1), with normal velocity (data not shown). Horizontal smooth pursuit was impaired for both siblings (Table 2). Horizontal ON showed a slow automatic pursuit velocity for both siblings, with velocity down to 19°/s at 40°/s for patient IV:5 (Table 3).

In addition to the alterations already described, from the results of the third electro-oculographic study (7 years after disease onset), it was found that patient IV:5 showed horizontal nystagmus, but her horizontal saccades remained normal. For patient IV:6, vertical saccadic intrusions began to appear. The results of a study of patient V:7 (32 years of age) were that this asymptomatic patient's horizontal movements were strictly normal, that abnormal accuracy was detected for vertical saccades (Table 1), and that abnormal velocity was noted for vertical pursuit (Table 2) and vertical ON (Table 3).

**GENETICS STUDIES**

The initial genome-wide linkage analysis of 6 healthy and 6 affected relatives using the Illumina LINKAGE_12 array, including 6609 SNPs, revealed suggestive genetic linkage to 1p32 ($z_{max} = 2.03; \theta = 0.00$). Further linkage analysis with 21 additional family members revealed a significant
Herein, we report a new SCA subtype of late onset associated with chromosome 1p32, which the Human Genome Nomenclature Committee has assigned as SCA37. The phenotype is characterized by a relatively pure cerebellar ataxia. As a distinct clinical feature, an accurate examination of the eye movements detected vertical abnormalities in early stages of the disease, which correlated with the results of the electro-oculographic studies. This initial subtle sign later became very evident during the follow-up visits and was identified in all affected patients. Diffuse horizontal eye movement abnormalities were also detected in this family. They were milder and appeared later in patients IV:5 and IV:6 and were common in all patients with a long-standing disease. Remarkably, patient IV:5 exhibited normal horizontal saccades 7 years after disease onset. Impaired horizontal eye movements are regarded as a well-known clinical sign in several SCA subtypes: SCA1, SCA2, SCA3, SCA4, SCA5, SCA6, SCA7, SCA9, SCA12, SCA17, and SCA18. In SCA1, SCA6, SCA7, and SCA17,28 those abnormalities may appear even in presymptomatic stages. However, vertical eye movement abnormalities have been rarely reported. Abnormal vertical saccades were detected in SCA6 and SCA30, whereas impaired vertical smooth pursuit has been described in SCA6 and SCA26.31 Interestingly, the vertical abnormalities reported in these SCA subtypes are usually part of diffuse ocular abnormalities or well-developed cerebellar syndromes. However, we suggest that the vertical ocular alterations identified in our patients may constitute a predominant or a presymptomatic clinical sign. We found that one of our patients (patient IV:5) supported this hypothesis by having initial severe vertical eye movement abnormalities that were extensively confirmed by the electro-oculographic studies and that appeared much earlier than his only mild ataxic signs or than the horizontal eye movement alterations. Furthermore, vertical eye movement abnormalities were clinically identified in 2 at-risk asymptomatic young patients (V.7 and V.10) and were confirmed by electro-oculography for patient V.7. Genetics studies revealed thereafter that all 3 patients had inherited the risk haplotype.

Table 4. Two-Point Logarithm of Odds Scores Between the Locus Trait and the 10 Markers Analyzed on Chromosome 1p32

<table>
<thead>
<tr>
<th>Marker Order</th>
<th>Distance, cM</th>
<th>Logarithm of Odds Score</th>
<th>zmax</th>
<th>θmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1S139</td>
<td>75.66</td>
<td>0.00 0.05 0.10 0.15 0.20 0.25 0.30 0.35 0.40 0.45</td>
<td>0.05 0.25</td>
<td></td>
</tr>
<tr>
<td>D1S2661</td>
<td>78.25</td>
<td>1.68 1.32 0.65 0.38 0.20 0.12 0.04 0.00 0.00 0.00</td>
<td>0.00 0.00</td>
<td></td>
</tr>
<tr>
<td>D1S147</td>
<td>79.80</td>
<td>2.97 2.57 2.17 1.77 1.37 0.99 0.62 0.36 0.19 0.09</td>
<td>0.00 0.00</td>
<td></td>
</tr>
<tr>
<td>D1S2652</td>
<td>80.77</td>
<td>0.64 0.53 0.42 0.35 0.27 0.19 0.13 0.06 0.02 0.00</td>
<td>0.00 0.00</td>
<td></td>
</tr>
<tr>
<td>D1S475</td>
<td>82.41</td>
<td>3.03 2.64 2.24 1.85 1.47 1.10 0.75 0.44 0.20 0.04</td>
<td>0.00 0.00</td>
<td></td>
</tr>
<tr>
<td>D1S200</td>
<td>82.41</td>
<td>2.54 2.23 1.92 1.61 1.31 1.02 0.50 0.20 0.07 0.00</td>
<td>0.00 0.00</td>
<td></td>
</tr>
<tr>
<td>D1S2742</td>
<td>83.07</td>
<td>3.83 3.42 3.00 2.57 2.13 1.70 1.27 0.82 0.51 0.21</td>
<td>0.00 0.00</td>
<td></td>
</tr>
<tr>
<td>D1S2690</td>
<td>83.07</td>
<td>0.32 0.33 0.32 0.29 0.25 0.20 0.15 0.10 0.05 0.01</td>
<td>0.00 0.00</td>
<td></td>
</tr>
<tr>
<td>D1S2867</td>
<td>85.68</td>
<td>0.62 0.60 0.53 0.45 0.38 0.26 0.17 0.10 0.05 0.01</td>
<td>0.00 0.00</td>
<td></td>
</tr>
<tr>
<td>rs151062149</td>
<td>96.04b</td>
<td>0.05 0.36 0.31 0.22 0.17 0.10 0.05 0.01 0.00 0.00</td>
<td>0.00 0.00</td>
<td></td>
</tr>
</tbody>
</table>

aThe maximum logarithm of odds score obtained with maker D1S2742 is shown in bold, along with its zmax and θmax values (ie, zmax = 3.831, θ = 0.0).
bThe relative distance in centimorgans of marker rs151062149 is estimated with the closest marker obtained in the Marshfield Medical Research Foundation map.16

2-point logarithm of odds score between the locus trait and the marker D1S2742 (zmax = 3.83; θ = 0.00) (Table 4). A multipoint linkage analysis using the LINKMAP function of FASTLINK further located the SCA37 locus to a 0.66-cM interval flanked by markers D1S200 and D1S2742 (zmax = 6.539; P < .0001). Significant linkage (zmax = 3.27) was also obtained in an affected-only analysis that avoided any influence of considerations of penetrance of the unaffected members of the pedigree. Whole-exome sequencing identified 26,974 single-nucleotide variants and 472 insertions or deletions in patient IV:16, and 25,754 single-nucleotide variants and 894 insertions or deletions in patient V:15. After database filtering, we identified 6 predicted damaging heterozygous coding variants shared by both patients. Although none of these variants segregated with the disease in all affected members, a rare single-nucleotide variant undetected in whites, rs151062149 (c.1438A>G) within the USP1 gene, was identified with significant linkage proximally located on 1p32 (zmax = 3.65; θ = 0.05; Table 4).

In summary, of the 13 examined patients who inherited the risk haplotype (ie, patients IV:5, IV:6, IV:7, IV:10, IV:11, IV:16, IV:19, IV:21, V.7, V.8, V.10, V.15, and VI.7), 11 had altered vertical eye movements. The only individual with a risk haplotype who did not have altered vertical movements was patient VI.7, and he was 20 years of age. Patient V.8 was excluded from the study because of drug use. Of the 11 patients presenting with abnormal vertical eye movements, patients IV:5, IV:6, and V:7 had registered oculographic data confirming the clinical examination. Vertical eye movement abnormalities were noted in 2 young asymptomatic individuals (ie, patients V:7 and V:10) who were later found to have the risk haplotype, and these abnormalities constituted the isolated ocular involvement at onset of 3 ataxic patients (IV:5, IV:6, and IV:7), 2 of whom later developed horizontal eye abnormalities (ie, patients IV:5 and IV:6). Furthermore, vertical eye movement abnormalities, together with horizontal eye movement abnormalities, were detected in 6 ataxic patients with long-standing disease (ie, patients IV:10, IV:11, IV:16, IV:19, IV:21, and V:15). The results of neurological and eye examinations were normal for 14 asymptomatic relatives who were found not to carry the risk haplotype.
The pathological process underlying the ocular movement abnormalities in this Spanish family is unclear because postmortem studies are not yet available. From previously described observations in a few SCAs, we assume that most of the abnormal horizontal eye movements observed in our patients may be related to cerebellar structures, such as the posterior vermis (lobules VI and VII), the fastigial nucleus, the flocculus, and the ventral paraflocculus. Similar to the saccadic velocities associated with SCA17, those associated with SCA37 were poorly affected in our patients, which suggests relative sparing of the pons. However, the pathological mechanism underlying the specific vertical abnormalities in our patients is difficult to assess because it is widely accepted that both horizontal and vertical eye movements are controlled by the same cerebellar structures. Because P cells from the deep cerebellar nuclei have a distinct discharge behavior due to horizontal and vertical eye stimuli in the flocculus of primates, we suggest that they may be involved in this specific disease pattern in our patients.

The progression of the disease is slow, although variable, and the SARA scores in this family followed a linear pattern, as expected. For the initial stages of the disorder, this scale was not useful for measuring disease progression because the cerebellar syndrome was not fully developed and because SARA is not considered to be a diagnostic tool; it was originally designed to measure worsening ataxia. However, for this specific phenotype, we found the electro-oculographic studies to be very useful for detecting the progress of the ongoing pathologic process before ataxia completely developed.

The genetics studies in this family revealed a distinct genetic linkage to a 0.66-cM genomic region flanked by D1S200 and D1S2742 markers on 1p32. Remarkably, 2 other autosomal dominant SCA subtypes have also been associated with chromosome 1 deficits, SCA19 and SCA22. Both SCA19 and SCA22 have recently been associated with mutations in the potassium channel KCND3 in Chinese, Dutch, and French kindreds, where the clinical variability among SCA19/22 families was correlated with specific mutations. In contrast, none of our patients revealed mutations in the KCND3 gene.

In conclusion, we report the clinical and genetic findings of a new SCA subtype, SCA37, in a Spanish kindred. Affected patients present with a relatively pure cerebellar phenotype consisting of ataxia and altered vertical eye movements. With the genetics studies, we found an association between this clinical phenotype and a new locus on chromosome 1p32. According to the University of California Santa Cruz genome browser assembly (GRCh37/hg19), the genomic region identified spans 11,108,563 bases containing 71 known genes, 35 pseudogenes, and 10 predicted open-reading frames (eTable 3). Whole-exome sequencing identified no causative SCA37 mutation, which indicates that it may lie in a non-coding genomic region or that it may consist of large repeat expansions or structural variants within the newly identified delimited region.

Accepted for Publication: December 20, 2012.
Published Online: April 29, 2013. doi:10.1001/jamaneurol.2013.2311

Author Affiliations: Neurology Unit, Department of Internal Medicine, Hospital St Joan de Deu, Martorell (Dr Serrano-Munuera), Basic, Translational, and Molecular Neurogenetics Research Unit in Neurodegenerative Diseases, Department of Neurosciences, Health Sciences Research Institute Germans Trias i Pujol, Badalona (Mr Corral-Juan and Drs Sánchez and Matilla-Dueñas), Centre de Diagnostic Genetic-Molecular-Institut d’Investigació Biomèdica de Bellvitge, l’Hospitalet (Messrs San Nicolás and Corral, Drs Campos and Volpini, and Ms de Jorge), Department of Neurology, Hospital de la Sta, Creu i St Pau (Dr Roig), and Institut de Biologia Evolutiva (UPF-CSIC), Parc de Recerca Biomèdica de Barcelona (Drs Morcillo-Suárez and Navarro), National Institute for Bioinformatics, Universitat Pompeu Fabra (Drs Morcillo-Suárez and Navarro), Movement Disorders Unit, Neurology Department, Sant Pau Hospital (IIB Sant Pau), Universitat Autonoma de Barcelona and Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (Dr Kulisevsky), and Department of Medicine, Universitat Autonoma de Barcelona (Drs Serrano-Munuera, Roig, Sánchez, and Matilla-Dueñas and Mr Corral-Juan), Barcelona, and Catalan Institution for Research and Advanced Studies, Catalonia (Dr Navarro), Spain; and Institut National de la Santé et de la Recherche Médicale, U975, Université Pierre-et-Marie-Curie, Université Paris VI, Centre de Recherche de l’Institut du Cerveau et de la Moelle epinière, EPHE, and Centre national de la recherche scientifique, Unité mixte de recherche 7225, Groupe Hospitalier Pitie-Salpêtrière, Paris, France (Drs Stevanin, Forlani, Durr, and Brice).

Correspondence: Antoni Matilla-Dueñas, PhD, Health Sciences Research Institute Germans Trias I Pujol, Ctra de Can Ruti, Camí de les Escoles s/n, Badalona, 08916 Barcelona, Spain (amatilla@igtp.cat).


Conflict of Interest Disclosures: Dr Matilla-Dueñas is a Miguel Servet Investigator in Neurosciences of the Spanish National Health System. In the last 3 years, he acted as a consultant for Ataxia UK and the European Com-
mission, and he received an award from the Spanish Federation of Ataxia Associations. Dr Kulisevsky received honoraria for scientific lectures from Abbot, UCB, and Boehringer. Dr Serrano-Munuera performed this work as a part of a PhD project in the Department of Medicine at the Universitat Autonoma de Barcelona.

**Funding/Support:** This work was funded by the Spanish Ministry of Science and Innovation (grant BFU2008-00527/BMC to Dr Matilla-Dueñas), the Carlos III Health Institute (grant CP08/00027 to Dr Matilla-Dueñas and grant PS09/02342 to Dr Volpini), the Latin American Science and Technology Development Programme (Ciencia y Tecnología del Desarrollo) (RIBERMOV grant 210RT390 to Drs Matilla-Dueñas, Sánchez, and Volpini), the European Commission (EUROSCA project LHS-M-CT-2004-503304 of Drs Matilla-Dueñas and Brice), the Fundación de la Marato de TV3 Televisió de Catalunya (grant 10073 to Drs Matilla-Dueñas, Sánchez, Serrano-Munuera, and Volpini), the Verum Foundation (Dr Brice), and the Association Contraire les Syndromes Cerebelleux (Dr Stevanin). Dr Kulisevsky has received public research funding from Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas and research grants from Fundo de Investigaciones Sanitarias (Instituto de Salud Carlos III, Spain) and restricted research grants from Merck Serono. He acted as a consultant for the Michael J. Fox Foundation for Parkinson’s Research.

**Online-Only Material:** The eAppendix and eTables are available at [http://www.jamaneurow.com](http://www.jamaneurow.com).

**Additional Contributions:** We are indebted to all the patients and family members for their generous participation in this work. We are grateful to Eveli Peral, MD, Merce Martínez, MD, Purificación Carabdos, MD, Luisa Juan, MD, PhD, Joel Puig, BSc, MSc, Ariadna Navarro Aragall, BSc, Emeline Mundwiller, BSc, and Wassila Carpenter, PhD, for technical assistance and to Sistemas Genómicos (Spain) for whole-exome sequencing studies and bioinformatics analysis. We are indebted to the Spanish Ataxia Association, the Spanish Federation for Rare Diseases, and the patients for their continuous support and motivation. The SNP genotyping services were provided by the Spanish “Centro Nacional de Genotipado” (CEGEN-ISCHII).

**REFERENCES**

