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sporadic adult-onset degenerative ataxia

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ABSTRACT

Objective: To define the clinical phenotype and natural history of sporadic adult-onset degenerative ataxia and to identify putative disease-causing mutations.

Methods: The primary measure of disease severity was the Scale for the Assessment and Rating of Ataxia (SARA). DNA samples were screened for mutations using a high-coverage ataxia-specific gene panel in combination with next-generation sequencing.

Results: The analysis was performed on 249 participants. Among them, 83 met diagnostic criteria of clinically probable multiple system atrophy cerebellar type (MSA-C) at baseline and another 12 during follow-up. Positive MSA-C criteria (4.94 ± 0.74, $p < 0.0001$) and disease duration (0.22 ± 0.06 per additional year, $p = 0.0007$) were associated with a higher SARA score. Forty-eight participants who did not fulfill MSA-C criteria and had a disease duration of >10 years were designated sporadic adult-onset ataxia of unknown etiology/non-MSA (SAOA/non-MSA). Compared with MSA-C, SAOA/non-MSA patients had lower SARA scores (13.6 ± 6.0 vs 16.0 ± 5.8, $p = 0.0200$) and a slower annual SARA increase (1.1 ± 2.3 vs 3.3 ± 3.2, $p = 0.0013$). In 11 of 194 tested participants (6%), a definitive or probable genetic diagnosis was made.

Conclusions: Our study provides quantitative data on the clinical phenotype and progression of sporadic ataxia with adult onset. Screening for causative mutations with a gene panel approach yielded a genetic diagnosis in 6% of the cohort.

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GLOSSARY

INAS = Inventory of Non-Ataxia Signs; **MSA** = multiple system atrophy; **MSA-C** = multiple system atrophy cerebellar type; **PHQ-9** = Patient's Health Questionnaire; **SAOA** = sporadic adult-onset ataxia of unknown etiology; **SARA** = Scale for the Assessment and Rating of Ataxia; **UMSARS** = Unified MSA Rating Scale; **VAS** = visual analog scale; **VUS** = variant of uncertain clinical significance; **WES** = whole-exome sequencing.

Patients with progressive, adult-onset, nonfamilial ataxia may have an acquired ataxia. Others have a genetic cause despite a negative family history.[1–3] In most of them, however, a cause of ataxia cannot be identified, suggesting a sporadic neurodegenerative disease. In one group, the underlying disease is multiple system atrophy cerebellar type (MSA-C) clinically characterized by severe autonomic failure. Although a definitive diagnosis of MSA requires demonstration of oligodendroglial inclusions at autopsy,[4,5] a probable diagnosis can be made with high predictive

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accuracy on clinical grounds.[6] However, sensitivity of clinical criteria in early stages is low.[6,7] The second group, sporadic adult-onset ataxia of unknown etiology (SAOA), is distinguished from MSA-C by the absence of severe autonomic failure.[8,9] Because severe autonomic failure may manifest years after ataxia,[10] a portion of SAOA patients will later turn out to have MSA. The reported prevalence rates of sporadic ataxias range from 2.2 to 12.4: 100,000. Thus, they are more frequent than hereditary ataxias.[11–14]

Knowledge of the clinical phenotype and natural history of sporadic adult-onset degenerative ataxia are limited.[10,15,16] We therefore created SPORTAX, a registry of sporadic adult-onset degenerative ataxia. We present cross-sectional and longitudinal clinical data of 249 SPORTAX participants. We aimed to address the following objectives: to determine the proportion of MSA-C among patients with sporadic ataxia; to compare the phenotype and natural history of MSA-C and SAOA; to identify determinants of disease severity in sporadic ataxia; and to identify putative disease-causing mutations using an ataxia-specific gene panel.

METHODS Inclusion of study participants into the SPORTAX registry started on April 1, 2010. We recruited participants from ataxia clinics at 14 European centers. Inclusion criteria were as follows: (1) progressive ataxia, (2) ataxia onset after age 40, (3) informative and negative family history (no similar disorders in first- and second-degree relatives; parents older than 50 years, or, if not alive, age at death of more than 50 years, no consanguinity of parents), and (4) no established acquired cause of ataxia. Details of required workup are given in table e-1 at Neurology.org. Follow-up assessments were done whenever a registered patient revisited the respective study center, if possible on an annual basis. Data download was performed on March 18, 2016.

The primary measure of disease severity was the Scale for the Assessment and Rating of Ataxia (SARA).[17] We additionally used the Unified MSA Rating Scale parts I and II (UMSARS-I and II).[18] We assessed symptoms other than ataxia with the Inventory of Non-Ataxia Signs (INAS).[19] As a measure of health-related quality of life, we applied EQ-5D. EQ-5D includes a visual analog scale (EQ-5D VAS) that yields a number out of 0–100 between the anchors "worst imaginable health state" (0) and "best imaginable health state" (100).[20] Assessment of depressive symptoms was done using the Patient's Health Questionnaire (PHQ-9). To determine the proportion of patients with clinically relevant depressive symptoms, we used a cutoff score of PHQ-9 >9. All investigators were experienced in the use of the applied scales.[21]

We screened genomic DNA samples prepared from whole EDTA blood for a high-coverage custom HaloPlex gene panel (Agilent, Santa Clara, CA) using an NextSeq500 sequencer (Illumina, San Diego, CA) and paired-end 2 × 150 bp sequencing (671-kb target size). The panel included 201 genes associated with ataxia (table e-2). The mean vertical coverage was 413 reads, and a minimal coverage of 20 reads was achieved for 98.8% of the target region. The bioinformatic pipeline included read mapping with Burrows-Wheeler-Aligner and variant calling with FreeBayes. A total of 417–541 variants were identified in the target region (467 on average) and consecutively filtered for low population frequency (<1% in ExAC, 1000 Genomes, ESP6500) and for frameshift, nonsense, splicing, or missense variants. All variants were annotated with available mutation database information (HGMD professional, ClinVar) to identify known rare variants with pathogenicity. We used in silico prediction and conservation tools (SIFT, PolyPhen, MutationTaster, and PhyloP) to further evaluate rare missense variants.

Variants were classified following the joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology as pathogenic, likely pathogenic, variant of uncertain clinical significance (VUS), likely benign, and benign.[22] Rare variants with published evidence for a disease-causing effect were considered either pathogenic or likely pathogenic depending on the amount of published evidence. Variants were classified as likely pathogenic when they were rare (minor allele frequency <1% in public databases) and had a strong effect on protein function (frameshift variant, nonsense variant, or splicing variant at the consensus site within 2 bp from exon-intron boundaries), but no or insufficient published evidence. Missense variants that did not fulfill the criteria of likely pathogenicity were assigned as VUS.

Based on the genetic findings and clinical phenotype, study participants were assigned to definitive genetic diagnosis, probable genetic diagnosis, and no genetic diagnosis. A definitive genetic diagnosis was assumed when participants had pathogenic or likely pathogenic variants including an ultrarare VUS in one patient with 2 heterozygous variants in the *ATM* gene and a perfectly compatible phenotype. A probable genetic diagnosis was assumed for patients with pathogenic or likely pathogenic variants and less consistent phenotypes. All others were assigned to the group without genetic diagnosis.

An analysis of covariance was performed with the SARA score as the dependent variable and sex, age at onset, disease duration, and fulfillment of probable MSA-C criteria as independent variables. A multivariate model included variables with a p value <0.10 in univariate analysis, and a backward selection procedure was carried on. Comparisons between subgroups of patients were made using the Student t test for the quantitative variables and the χ^2 or Fisher exact test for the qualitative variables. To estimate the annual increases of the clinical scores, the difference in the clinical score between baseline and the first follow-up visit was divided by the time interval. Statistical analyses were performed with SAS 9.4 software (SAS Institute, Cary, NC). All tests were 2 sided. Test results were considered significant at the 0.05 level.

Standard protocol approvals, registrations, and patient consents. The study was approved by the local ethics committees. All participants provided written informed consent. This study is registered with ClinicalTrials.gov (NCT02701036).

RESULTS Demographic and clinical data of the study population are given in table 1. In 122, at least one follow-up visit was recorded, resulting in 197 follow-up visits. Flowcharts detailing the number of patients seen in each year following inclusion are given in table e-3.

At baseline, 83 patients met diagnostic criteria of probable MSA-C. Because these criteria have a high predictive value, we classified them as MSA-C. Of

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Table 1 Cohort characteristics at baseline

	SPORTAX	SAOA/non-MSA	MSA-C	*p* Value
No.	249	48	95	
Men	149 (60)	28 (58)	55 (58)	0.9600
Age, y	65.2 ± 8.7	69.5 ± 8.1	63.9 ± 8.5	0.0004
Age at onset, y	56.5 ± 8.7	52.3 ± 8.5	56.9 ± 8.3	0.0013
Disease duration, y	6.4 ± 5.5	14.9 ± 5.7	4.6 ± 3.0	<0.0001
SARA	13.6 ± 5.8	13.6 ± 6.0	16.0 ± 5.8	0.0200
UMSARS-I	13.9 ± 8.1	11.5 ± 6.1	19.3 ± 8.8	<0.0001
UMSARS-II	17.0 ± 7.4	16.5 ± 6.5	20.8 ± 7.6	0.0010
INAS	2.9 ± 1.8	2.7 ± 1.8	3.7 ± 1.8	0.0013
EQ-5D	3.3 ± 1.7	3.0 ± 1.8	3.8 ± 1.7	0.0118
EQ-5D VAS	54 ± 22	60 ± 19	47 ± 20	0.0013
PHQ-9	7.2 ± 5.0	6.6 ± 4.9	7.8 ± 5.0	0.2407
PHQ-9 >9	63 (30)	15 (35)	25 (32)	0.7159

Abbreviations: INAS = Inventory of Non-Ataxia Signs; MSA-C = multiple system atrophy, cerebellar type; PHQ-9 = Patient's Health Questionnaire; SAOA/non-MSA = sporadic adult-onset ataxia of unknown etiology/nonmultiple system atrophy; SARA = Scale for the Assessment and Rating of Ataxia; UMSARS = Unified MSA Rating Scale.
Data are given as mean ± SE or n (%). *p* Values relate to comparison between SAOA/non-MSA and MSA-C.

the remaining 166 patients, 24 met criteria of possible MSA.[6] We assigned these patients to the SAOA group because the criteria for possible MSA have a low predictive value for MSA. During follow-up, 12 SAOA patients developed severe autonomic failure, thus meeting criteria of probable MSA-C. The median latency from onset until conversion to MSA was 4 years (range: 2–12 years). Only 1 of the 12 converters developed severe autonomic failure later than 10 years after ataxia onset. Six of these converters (50%) met criteria of possible MSA at baseline.

To identify factors that determined the severity of ataxia at baseline, we performed an analysis of covariance with the SARA score as the dependent variable and sex, age at onset, disease duration, and positive MSA-C criteria as independent variables. In the final multivariate model, positive MSA-C criteria and disease duration were associated with a higher SARA score (table 2).

The observation that some SAOA patients converted to (probable) MSA-C indicates that SAOA can be subdivided into a group that actually has MSA-C, although diagnostic criteria are not yet fulfilled, and another group that has a disorder that is distinct from MSA-C. Based on the observation that only 1 of 12 converters converted later than 10 years after disease onset, we defined a subgroup of 48 SAOA patients who had a disease duration of at least 10 years and designated them SAOA/non-MSA (table 1). Two of them (4%) met criteria of possible MSA at baseline.

Although the disease duration of the SAOA/non-MSA patients was more than 10 years longer than that of the patients with MSA, their disease phenotype was milder, indicated by lower SARA, UMSARS-I, and UMSARS-II scores and a lower INAS count (table 1). In addition, health-related quality of life was less compromised in SAOA/non-MSA than in MSA-C, as indicated by a lower EQ-5D value and higher EQ-5D VAS values (table 1). By contrast, the PHQ-9 sum score did not differ between SAOA/non-MSA and MSA-C (table 1). Correspondingly, the proportion of patients with clinically relevant depressive symptoms defined by a PHQ-9 sum score >9 was similar in SAOA/non-MSA and MSA-C (table 1).

The frequency of single nonataxia symptoms was similar in SAOA/non-MSA and MSA-C with the exceptions of hyperreflexia, rigidity, and urinary dysfunction, which were less frequent in SAOA/non-MSA than in probable MSA-C (table 3). Urinary dysfunction had a similar distribution between male and female participants (8 SAOA/non-MSA male (29%) vs 9 female (45%) $p < 0.0001$; 46 MSA-C male (84%) vs 35 female (88%), $p = 0.0004$).

Longitudinal data were available for 35 SAOA/non-MSA and 36 MSA-C patients. Annual increases of the SARA, UMSARS-I, and UMSARS-II scores were lower in SAOA/non-MSA than in MSA-C. By

Table 2 Determinants of severity of ataxia at baseline

	Univariate			Multivariate		
	Parameter	95% CI	*p* Value	Parameter	95% CI	*p* Value
Intercept				10.6 ± 0.6	9.47–11.81	
Sex (female)	0.98 ± 0.76	−0.51 to 2.47	0.1973			
MSA-C criteria positive	4.40 ± 0.74	2.95 to 5.85	<0.0001	4.94 ± 0.74	3.49–6.40	<0.0001
Age at onset	−0.03 ± 0.04	−0.12 to 0.05	0.4202			
Disease duration	0.13 ± 0.07	−0.003 to 0.26	0.0562	0.22 ± 0.06	0.09–0.35	0.0007

Abbreviations: CI = confidence interval; MSA-C = multiple system atrophy cerebellar type.
Parameters are given as mean ± SE.

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Table 3 Frequency of nonataxia symptoms

	SAOA/non-MSA (n = 48)	MSA-C (n = 95)	p Value
Hyperreflexia	10 (21)	40 (42)	0.0118
Areflexia	11 (23)	16 (17)	0.3808
Extensor plantar reflex	9 (19)	17 (18)	0.9228
Spasticity	14 (29)	22 (23)	0.4343
Paresis	2 (4)	6 (6)	0.7180
Muscle atrophy	7 (15)	8 (8)	0.2561
Fasciculation[a]	2 (4)	10 (11)	0.3378
Myoclonus[a]	0 (0)	2 (2)	0.5509
Rigidity	3 (6)	27 (28)	0.0021
Chorea/dyskinesia[a]	1 (2)	1 (1)	1.0000
Dystonia[a]	2 (4)	6 (6)	0.7180
Resting tremor	2 (4)	14 (15)	0.0583
Impaired vibration sense	37 (79)	68 (72)	0.3614
Urinary dysfunction	17 (35)	81 (85)	<0.0001
Cognitive impairment	7 (15)	25 (27)	0.1051
Brainstem oculomotor signs[a]	5 (10)	8 (8)	0.7611

Abbreviations: MSA-C = multiple system atrophy, cerebellar type; SAOA/non-MSA = sporadic adult-onset ataxia of unknown etiology/non-multiple system atrophy.
Data are given as n (%). Comparisons were made using the Pearson χ^2 test.
[a] The Fisher exact test was used for small samples.

contrast, there was no difference between the annual changes of the INAS count, EQ-5D value, EQ-5D VAS, and PHQ-9 sum score (table 4).

DNA for genetic analysis was available in 194 study participants. In 6 (3%), a definitive genetic diagnosis was made. In 3 of them, we found variants in recessive genes (*ATM*, 2x *SPG7*), in the remaining 3, in dominant genes (2x *CACNA1A*, *TRPC3*/*SCA41*). In another 5 (3%), a probable genetic diagnosis was made. In 3 of them, we found variants in recessive genes (*ADCK3*, *POLG*, *SNX14*), in the remaining 2, in dominant genes (*CACNA1A*, *OPA1*). Thus, the total number of definitive or probable genetic diagnoses was 11 (6%). In addition, we found 17 interesting variants in 16 probands, which did not result in a definite or probable genetic diagnosis. Three variants were rated as pathogenic (*GBA* compound heterozygous with a *GBA* VUS, 2x *OPA1*) and 14 as VUS (*ATPB3*, 2x *COQ2*, *ELOVL5*, *GBA*, *OPA1*, 8x *SPTBN2*).

Table 4 Annual increase of the outcome measures

	SAOA/non-MSA	MSA-C	p Value
No.	35	36	
SARA	1.1 ± 2.3	3.3 ± 3.2	0.00133
UMSARS-I	1.0 ± 2.0	4.7 ± 4.0	0.00001
UMSARS-II	1.2 ± 2.9	5.3 ± 4.5	0.00005
INAS	0.1 ± 0.8	0.0 ± 1.4	0.75528
EQ-5D	0.1 ± 0.9	0.2 ± 1.5	0.83675
EQ-5D VAS	−1.1 ± 19.7	4.5 ± 32.4	0.43966
PHQ-9	−0.6 ± 2.6	0.0 ± 6.6	0.63337

Abbreviations: INAS = Inventory of Non-Ataxia Signs; MSA-C = multiple system atrophy, cerebellar type; PHQ-9 = Patient's Health Questionnaire; SAOA/non-MSA = sporadic adult-onset ataxia of unknown etiology/non-multiple system atrophy; SARA = Scale for the Assessment and Rating of Ataxia; UMSARS = Unified MSA Rating Scale.
Data are given as mean ± SD.

Three of the participants with a genetic diagnosis fulfilled MSA-C criteria. The affected genes included *ATM*, *POLG*, and *CACNA1A*. The proportion of patients with a genetic diagnosis was higher in SAOA/non-MSA than in MSA-C, but the difference was not significant (9% vs 4%, $p = 0.2376$). A full account of the clinical and genetic findings of the patients with a genetic diagnosis is given in tables e-4 and e-5.

DISCUSSION This study provides clinical and genetic data from a large multicenter cohort of 249 participants with sporadic adult-onset degenerative ataxia. Strengths of our study include the large number of patients, the use of validated scales, and the systematic genetic testing. Although great efforts were taken to exclude patients with acquired ataxia, we cannot rule out that some of the participants had an immune-mediate ataxia. Limitations of our study are limited follow-up and lack of neuropathologic data. As we have no autopsy confirmation, there remains uncertainty about the final neuropathologic diagnosis. For the diagnosis of MSA, we relied on consensus criteria, which are based on previous clinical-pathologic correlation studies.[6] The accuracy of a clinical diagnosis of MSA is high with positive predictive values ranging from 86% to 100%,[7,16,23] suggesting that most study participants with clinically probable MSA-C indeed had MSA. The neuropathologic substrate of ataxia in participants who did not meet MSA criteria remains unknown.

Approximately 40% of the cohort met MSA-C diagnostic criteria. For the inclusion in SPORTAX, we adopted an age at onset of 40 years, which is higher than that in previously published criteria for SAOA.[3] Inclusion of patients with an earlier onset than 40 years had presumably decreased the percentage of MSA-C. In the 12 participants who converted to MSA-C, the median latency from onset to occurrence of severe autonomic failure was 4 years. These data are in good agreement with 2 previous studies.[10,15] Occurrence of autonomic failure in MSA more than 10 years after onset of motor symptoms is extremely rare.[24] To select SAOA patients who were unlikely to convert to MSA-C, we defined a cutoff of

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10 years after onset and designated them as SAOA/non-MSA.

Compared with MSA-C, SAOA/non-MSA patients had a less severe phenotype and slower progression. A milder phenotype was proven by lower SARA and UMSARS scores, a lower INAS count and a higher estimate of health-related quality of life despite the longer disease duration. Although longitudinal data are limited so far, they showed a smaller annual increase of the SARA and UMSARS scores in SAOA/non-MSA compared with MSA-C. The increase of the total UMSARS score in the MSA-C patients (10.0/12 months) is in good agreement with that of a prospective study of 141 patients with MSA (21.9/24 months).[25] The serious nature of MSA-C is further underlined by the finding that positive diagnostic criteria for MSA-C were a major determinant of ataxia severity. These findings are in line with studies of smaller cohorts that reported significantly better survival in SAOA/non-MSA than in MSA-C.[10,15,16]

Although ataxia was the prominent symptom in all participants, the majority had additional neurologic symptoms. Among the 16 assessed symptoms, hyperreflexia, rigidity, and urinary dysfunction were more frequent in MSA-C. Similarly, autonomic symptoms including urinary urgency and incontinence were more frequently encountered in a study that compared 53 MSA-C with 12 SAOA patients.[16] However, the higher prevalence of urinary dysfunction and rigidity in MSA-C is explained by the applied diagnostic criteria.[6] Thus, hyperreflexia was the only phenotypic difference between MSA-C and SAOA/non-MSA that we identified a posteriori.

As MSA-C and SAOA/non-MSA have a different prognosis, it would be useful to identify indicators that allow to predict whether an individual SAOA patient will convert to MSA-C or remain permanently free of severe autonomic failure resulting in a diagnosis of SAOA/non-MSA. To date, the number of follow-up visits in the SPORTAX cohort is limited so that the statistical power to identify such indicators is insufficient. However, we noted that 50% of the converters met criteria of possible MSA at baseline, whereas this proportion was only 4% in the participants with SAOA/non-MSA.[6]

Using a gene panel that included 201 genes associated with ataxia, we were able to make a definitive or probable genetic diagnosis in 11 of 194 (6%) tested participants. This is by far the largest group of patients with adult-onset sporadic ataxia that underwent systematic genetic testing. To reduce the likelihood of including patients with unrecognized familial forms of ataxia, we used strict inclusion criteria. In addition, all study participants were negatively tested for the common repeat mutations causing ataxia. Previous studies that looked for repeat mutations in patients with adult-onset sporadic ataxia reported prevalence rates ranging from 10% to 19%.[1–3] Combining these results with those of the present study, one can conclude that a 2-stage genetic diagnostic approach including search for common repeat mutations followed by an ataxia-specific gene panel will result in a genetic diagnosis in 15%–24% of patients with sporadic adult-onset ataxia. We did not screen for mitochondrial mutations, so we cannot rule out that single patients had mitochondrial disorders.

The genes that we identified by gene panel diagnostics included both recessive and dominant genes. A late onset of disease has been described for many recessive ataxias. Dominant mutations in sporadic disease can be explained by a new mutation, reduced penetrance, or misattributed paternity. As studies of family members were not possible in SPORTAX, the mechanisms underlying the occurrence of dominant mutations in our cohort remain unresolved. A relatively high number of VUS with damaging in silico prediction was observed, especially in the *OPA1* and the *SPTBN2* genes. Because we could not initiate further family investigations, this observation remains remarkable, but needs to be addressed systematically in follow-up studies.

In 4% of the patients who fulfilled clinical diagnostic criteria of MSA-C, the gene panel analysis led to a genetic diagnosis. Rare families with definitive MSA have been reported, and presumably causative mutations of the *COQ2* gene have been identified in 2 Japanese MSA families.[26] *COQ2* was included in our gene panel, but variants with suspected pathogenicity were not found. Variants were rather found in *ATM*, *POLG*, and *CACNA1A*. Because the MSA diagnoses were not confirmed by autopsy, there is no proof that the participants fulfilling clinical MSA-C criteria had MSA. It is more likely that they represent MSA phenocopies.

Systematic genetic testing of patients with adult-onset sporadic ataxia has been previously performed in 2 smaller studies that used whole-exome sequencing (WES). Among 25 patients with sporadic ataxia with onset after age 20, 3 (12%) had pathogenic variants and 8 (32%) variants of uncertain significance or potential pathogenicity.[27] In a study of 12 patients with sporadic ataxia with onset after age 30, 4 (33%) had pathogenic mutations.[28] The higher proportion of genetic diagnosis in these studies may be due to the inclusion of patients with lower age at onset, and by less restrictive criteria for pathogenicity. In one of these studies, 6 rare homozygous mutations in recessive genes typically seen in consanguineous populations were identified, which have not been enriched in our central European cohort.[27] A general sensitivity issue in our approach compared with the published

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WES studies is not likely because all disease genes identified in these studies were included and sequenced at high quality. In all 3 studies, there was a high degree of heterogeneity of the genetic findings, and many genes were found only in single patients. Those that appear to be most frequently associated with adult-onset sporadic ataxia are CACNA1A and SPG7.

Our analysis of baseline and longitudinal data of the SPORTAX cohort provide a detailed quantitative account of the clinical phenotype and natural history of sporadic ataxias with adult onset. Our results give useful information for the counseling of patients. The finding that application of an ataxia-specific gene panel established a genetic diagnosis in 6% of the cohort has important implications for the diagnostic approach in patients with sporadic ataxia.

AUTHOR CONTRIBUTIONS

Dr. Giordano: research project organization, research project execution, data monitoring, statistical analysis design, statistical analysis review and critique, genetic results review and critique, and writing of the first draft of the manuscript. Mr. Harmuth: genetic testing, genetic analysis review and critique, and manuscript review and critique. Dr. Jacobi: research project organization, research project execution, statistical analysis review and critique, and manuscript review and critique. Dr. Paap: interpretation of genetic testing results and manuscript review and critique. Dr. Vielhaber: research project execution, statistical analysis review and critique, and manuscript review and critique. Mrs. Machts: research project execution and manuscript review and critique. Dr. Schöls: research project execution, statistical analysis review and critique, and manuscript review and critique. Dr. Synofzik: research project execution, interpretation genetic results, and manuscript review and critique. Dr. Sturm: genetic testing and manuscript review and critique. Dr. Tallaksen, Dr. Wedding, and Dr. Boesch: research project execution, statistical analysis review and critique, and manuscript review and critique. Dr. Eigentler: research project execution and manuscript review and critique. Dr. van de Warrenburg: research project execution, statistical analysis review and critique, and manuscript review and critique. Dr. van Gaalen, Dr. Kamm, Dr. Dudesek, and Dr. Kang: research project execution and manuscript review and critique. Dr. Timmann: research project execution, statistical analysis design, statistical analysis review and critique, and manuscript review and critique. Dr. Silvestri, Dr. Masciullo, Dr. Klopstock, Dr. Neuhofer, Dr. Ganos, and Dr. Filla: research project execution and manuscript review and critique. Dr. Bauer: genetic testing, genetic analysis review and critique, and manuscript review and critique. Dr. Tezenas du Montcel: statistical analysis design and execution and manuscript review and critique. Dr. Klockgether: research project conception, research project organization, research project execution, statistical analysis design, statistical analysis review and critique, genetic results review and comment, and review and critique of the first draft.

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