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## Clinical and genetic keys to cerebellar ataxia due to *FGF14* GAA expansions

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## Summary

**Background:** SCA27B caused by *FGF14* intronic heterozygous GAA expansions with at least 250 repeats accounts for 10–60% of cases with unresolved cerebellar ataxia. We aimed to assess the size and frequency of *FGF14* expanded alleles in individuals with cerebellar ataxia as compared with controls and to characterize genetic and clinical variability.

**Methods:** We sized this repeat in 1876 individuals from France sampled for research purposes in this cross-sectional study: 845 index cases with cerebellar ataxia and 324 affected relatives, 475 controls, as well as 119 cases with spastic paraplegia, and 113 with familial essential tremor.

**Findings:** A higher frequency of expanded allele carriers in index cases with ataxia was significant only above 300 GAA repeats (10·1%,  $n=85$ ) compared with controls (1·1%,  $n=5$ ) ( $p<0\cdot0001$ ) whereas  $GAA_{250-299}$  alleles were detected in 1·7% of both groups. Eight of 14 index cases with  $GAA_{250-299}$  repeats had other causal pathogenic variants (4/14) and/or discordance of co-segregation (5/14), arguing against GAA causality. We compared the clinical signs in 127  $GAA_{\geq 300}$  carriers to cases with non-expanded GAA ataxia resulting in defining a key phenotype triad: onset after 45 years, downbeat nystagmus, episodic ataxic features including diplopia; and a frequent absence of dysarthria. All maternally transmitted alleles above 100 GAA were unstable with a median expansion of +18 repeats per generation ( $r^2=0\cdot44$ ;  $p<0\cdot0001$ ). In comparison, paternally transmitted alleles above 100 GAA mostly decreased in size (-15 GAA ( $r^2=0\cdot63$ ;  $p<0\cdot0001$ )), resulting in the transmission bias observed in SCA27B pedigrees.

**Interpretation:** SCA27B diagnosis must consider both the phenotype and GAA expansion size. In carriers of  $GAA_{250-299}$  repeats, the absence of documented familial transmission and a

presentation deviating from the key SCA27B phenotype, should prompt the search for an alternative cause. Affected fathers have a reduced risk of having affected children, which has potential implications for genetic counseling.

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## **Keywords**

SCA27B; hereditary cerebellar ataxia; GAA expansion; diagnosis

## Introduction

Spinocerebellar ataxias (SCA) are characterized by a lack of coordination, gait imbalance, clumsy voluntary limb movements, dysarthria, dysphagia, and oculomotor abnormalities. There are three major classes of autosomal dominant SCAs according to the underlying mechanisms:<sup>1</sup> polyglutamine SCAs, caused by the expansion of a translated CAG repeat, accounting for 60% of SCAs worldwide;<sup>2,3</sup> SCAs caused by single-nucleotide variants or genomic rearrangements such as micro-deletions, duplications, or insertions;<sup>4</sup> SCAs due to non-coding expansions, such as the recently described SCA27B. This SCA (OMIM: 620174)<sup>5</sup> is caused by one GAA expansion of more than 250 repeats in intron 1 of *FGF14* at chr13:102,161,575–102,161,726 (hg38).<sup>6,7</sup> This expansion has been reported to explain 10–60% of the yet unresolved cases of adult-onset cerebellar ataxia with diverse ancestry.<sup>6–10</sup> *FGF14* is highly expressed in the cerebellum and encodes fibroblast growth factor 14 (FGF14). FGF14 modulates the activity of voltage-dependent channels and exerts an anti-apoptotic activity.<sup>11</sup> The SCA27B phenotype is comprised of a late-onset slowly progressive cerebellar ataxia frequently associated with cerebellar oculomotor signs, such as downbeat nystagmus, and episodic features. GAA expansion size is unstable during transmission with a trend towards maternal expansion and paternal contraction.<sup>6–8,12</sup> We sized the SCA27B GAA repeat in 1876 individuals to assess the frequency of expanded alleles and characterize genetic and clinical variability including instability upon transmission.

## Methods

### Participants



We included 845 index cases with cerebellar ataxia, 324 affected relatives and 197 unaffected blood-related individuals from these families, 119 index cases with spastic paraplegia, 113 with familial essential tremor, and 475 controls.

Index cases were selected with half of the cases having a negative result on a routine diagnostic molecular test for SCAs (consisting of targeted sizing of CAG repeats in *ATXN1*, 2, 3, 7, and *CACNA1A*). Some individuals had undergone video-oculography as previously described.<sup>13</sup> The cohort was from European genetic origin (91%), American (6%), and African (2%).

## **Ethics**

Blood samples were collected between 1990 and 2023 in accordance with local French legislation (approval from local ethics committees SPATAX RBM 01-29 and RBM 03-48 or BIOMOV NCT05034172) respecting the European General Data Protection Regulation (GDPR). All participants gave written informed consent to the research.

## **Exome sequencing**

WES was done in 678 index individuals to detect single nucleotide variants as well as expansions with 100% sensitivity as described previously (paired-end read length of 150 bases and 100x median coverage of the Twist Exome 2.0 capture (Twist Bioscience, San Francisco, USA)).<sup>14</sup> The variants identified in hereditary neurological disorders genes labeled as pathogenic or likely pathogenic based on the American College of Medical Genetics (ACMG) classification were considered causative.<sup>15</sup> The index individuals without WES were clinically selected for SCA27B testing with the presence of downbeat nystagmus or episodic manifestations of cerebellar ataxia.

### ***FGF14* targeted analysis**

The *FGF14* GAA locus was amplified by long-range (LR) and repeat-primed (RP) polymerase chain reactions (PCR) as previously reported.<sup>6,8</sup> We pooled the LR-PCR with the two RP-PCR (3' and 5') to perform a capillary electrophoresis using the ABI3730XL machine (Thermo Fisher Scientific, Waltham, USA). The two RP-PCR were used to confirm the uninterrupted nature of the GAA sequence. The LR-PCR capillary electrophoresis provided very accurate sizing of alleles under 295 GAA. The Fragment Analyzer (Agilent Technologies, Santa Clara, USA) using a DNF-474 HS NGS Fragment Kit with 33 cm array was used to measure the size of larger alleles after purification with AMPure XP beads (Beckman Coulter, Brea, USA) with a 0.7X ratio. The amplicon size measured with both methods was adjusted with a linear and polynomial regression, respectively fitted with nine calibrators sized with targeted Oxford Nanopore long read sequencing, as described previously.<sup>8</sup>

### **Statistics**

We used the R 4.2.3 and ggplot2 packages for statistics.<sup>16,17</sup> Groups were compared using Fisher's test for qualitative variables and Kruskal-Wallis test for quantitative variables, with a conventional two-tailed type I error of 0.05 and p-value adjustment for multiple testing with the Benjamini Hochberg procedure. Proportions were related to the available data. For familial analyses, we inferred the parental transmitted allele by selecting the smallest parent-child size difference upon transmission. We used a linear model to estimate allele size differences, according to the size of the expansion above 100 GAA and the sex of the transmitting parent. Sex/gender was self-reported by study participants without considering it for statistical analyses except for intergenerational instability and parental transmission.

## Role of Funders

The funders had no role in study design, data collection, data analyses, interpretation, or writing of report.

## Results

### Defining a strict threshold for *FGF14* pathogenic expansions

We found 85/845 (10·1%) index cases with cerebellar ataxia carrying at least one *FGF14* GAA expansion ranging from 300 to 495 repeat units (flowchart of the distribution of carriers with  $GAA_{\geq 300}$  in supplementary Figure 1). We tested 232 additional index cases: 119 with spastic paraplegia because of overlapping causal genes, and 113 with familial essential tremor after having observed more frequent tremor in individuals with  $GAA_{\geq 300}$ . None carried a  $GAA_{\geq 300}$  allele.

Previous reports have suggested that  $GAA_{250-299}$  expansions are likely pathogenic albeit with incomplete penetrance, whereas larger expansions appear fully penetrant.<sup>6,7</sup> Indeed, we found the proportion of individuals carrying *FGF14*  $GAA_{250-299}$  alleles to be similar in cases with ataxia and controls (1·7 versus 1·7%;  $p=1$  (Fisher's test); Figure 1). In comparison, the proportion of individuals with  $GAA_{\geq 300}$  was significantly greater in patients (10·1%) than in controls (1·1%) (odds ratio 10.5 with 95% confidence interval [4.3–33.4];  $p<0\cdot0001$  (Fisher's test)). Based on these findings, we proposed a stricter threshold of  $GAA_{\geq 300}$  for further analyses.

Five of 475 controls had GAA-pure alleles ranging from 308 to 380 repeats. Their median age at examination was 37·9 years (IQR=36·6–63·5) [min 27·6–max 69·5] not significantly

different from the other controls examined at 59.7 (IQR=47.4–68) [19.2–87.5] ( $p=0.16$  (Kruskal-Wallis test)) nor from individuals with ataxia (57 years (IQR=45–66) [2–95]). One had compound heterozygous alleles above 250 GAA (250/308) and was unaffected at age 63.5 years.

In addition to GAA-pure expansions, we found four individuals with ataxia with an interrupted expanded allele above 250 repeats in length, ranging from 299 to 339 as well as two controls with 342 and 400 interrupted GAA repeats. They were considered nonpathogenic.<sup>6,7</sup>

### **Detailed phenotypic analysis for 127 individuals with $GAA_{\geq 300}$**

In addition to the 85 index cases, 42 affected relatives also carried  $GAA_{\geq 300}$ . In total, 66 were women and 61 were men. Most exhibited late-onset ataxia with a median age at onset of 55 (IQR=45–60) [6–79] years, starting with episodic symptoms in 47.9% (58/121) (supplementary Table 1 and 2). Only seven individuals had a disease onset prior to 30 years (5.6%), ranging from 6 to 27 with repeat sizes ranging from 305 to 496 GAA. Median SARA scores were 10.5 (IQR=6.5–13.5) [2–28] despite a median disease duration of 10 (IQR=5–18.8) [0–49] years. Median age at death was 81.4 (IQR=73.5–86.1) [48–104] years ( $n=33$ ). Survival was significantly longer compared to polyQ or other non-polyQ ataxias ( $p<0.0001$  (logrank test); supplementary Figure 2).<sup>18</sup>

The absence of dysarthria in 50 of 99 individuals with  $GAA_{\geq 300}$  (50.5%) was unusual compared with other genetic cerebellar ataxias (25.4%).<sup>12,19</sup> This absence of dysarthria was partially explained by a shorter disease duration (8 years (IQR=5–12.5) versus 13 years (IQR=9–20);  $p=0.001$  (Kruskal-Wallis test)), even if there were 31 patients with  $GAA_{\geq 300}$

without dysarthria in the 61 with a disease duration above 10 years. Diplopia was frequent in 58.9% (53/90), as well as nystagmus in 83.3% (80/96), mostly downbeat (66.7% (56/84)). Decreased vibration sense was present in 57.5% (42/73). Reflexes in lower limbs were increased in 30.4% (21/69), extensor plantar reflexes were present in 14.7% (10/68), with overt spasticity in 20.7% (19/92). Postural tremor was present in 26.8% (26/97) and resting tremor in 14.3% (14/98). Extrapyramidal rigidity was found in 21% (13/62) and hypokinesia in 10.8% (7/65). No patient had dysautonomia defined as orthostatic hypotension (20mmHg difference between supine and up wright position). Cognitive impairment was present in only 15.1% (13/86) despite advanced age at examination. We propose the following key feature triad: onset after 45 years, episodic ataxic features including intermittent diplopia and the presence of downbeat nystagmus, and an additional key: the absence of dysarthria.

Eye movement recordings were abnormal in 21/22 (95.5%, supplementary Table 3). Main abnormalities were i) saccadic smooth pursuit in 20/22 (90.9%) mostly vertically; ii) nystagmus in 17/22 (77.3%); iii) downbeat nystagmus in 14/22 (63.6%) and iv) diplopia in 10/22 (45.5%), mainly caused by alternating skew deviation in 8/22 (36.4%). A moderate to important increase of square-wave jerks was present in only 3/22 (13.6%). No hypermetria was noted but horizontal hypometria was measured in 5/22 (22.7%) and vertical hypometria 11/22 (50%) (mainly downward). Antisaccade error rates were abnormal in 16/20 (80%). Saccade latencies were slightly increased in 6/22 (27.3%). A slight decrease of horizontal saccade velocities was noted in only 1/22 patient (4.5%).

Brain MRI showed cerebellar atrophy in 67/76 (88.2%) and sometimes more global cerebral atrophy in 11/27 (40.7%), but without pontine atrophy. All individuals with  $GAA_{\geq 300}$  were European.

### **Phenotype comparison according to GAA size**

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We compared three groups defined by the size of the largest allele:  $<250$  ( $n=1016$ ),  $250-299$  ( $n=22$ ) and  $\geq 300$  GAA ( $n=127$ ) (Figure 2 and supplementary Table 1). The  $GAA_{250-299}$  group was phenotypically similar to  $GAA_{\geq 300}$ . Compared to the  $GAA_{<250}$  group, the  $GAA_{\geq 300}$  group had the latest median age at onset (55 versus 40 years in the  $GAA_{<250}$  group;  $p<0.0001$  (Kruskal-Wallis test)) (Figure 2A). Nystagmus was more frequent in the  $GAA_{\geq 300}$  group (83.3% versus 55.5%;  $p=0.002$ ), especially downbeat nystagmus (66.7% versus 31.4%;  $p=0.002$  (Fisher's test)). Resting tremor also was more frequent in the  $GAA_{\geq 300}$  group (14.3% versus 4.9%;  $p=0.01$  (Fisher's test)). Overt spasticity was less frequent in  $GAA_{\geq 300}$  (20.7% versus 38.3%;  $p=0.02$  (Fisher's test)) as was dysarthria (49.5% versus 74.6%;  $p=0.002$  (Fisher's test)) (Figure 2B).

Overall, 40% of patients with  $GAA_{\geq 300}$  presented the key triad, more frequent than in those with  $GAA_{<250}$  (4%;  $p=0.002$  (Fisher's test)) and similar to those with  $GAA_{250-299}$  (13.3%;  $p=0.13$  (Fisher's test)) (Figure 2C). Considering cases with the key triad, the proportion of SCA27B  $GAA_{\geq 300}$  cases increased to 55.3% and to 75% when associated with the absence of dysarthria.

### **Neither GAA expansion size nor zygosity correlated with clinical severity**

There was no correlation between the age at onset (Kendall tau  $-0.06$ ,  $p=0.3$  (Kendall correlation test)), age at death (Kendall tau  $-0.15$ ,  $p=0.3$  (Kendall correlation test)), SARA score (Kendall tau  $-0.12$ ;  $p=0.3$  (Kendall correlation test)), and the expanded GAA allele size above 300 GAA. Eight cases were compound heterozygous with at least one allele expanded above 300 GAA and the second allele ranging from 265 to 289 GAA in 3/8 (supplementary Table 2ter). There were no significant clinical differences with heterozygous carriers.

### **Intergenerational instability**

Maternal transmission of  $GAA_{\geq 300}$  was more frequent (76.9%,  $n=60$ ) than paternal transmission (23.1%,  $n=18$ ) in familial cases,  $p=0.01$  (Fisher's test). Indeed, including data from the three already described French-Canadian families<sup>6</sup>, mothers had a proportion of affected children of 48.6% (67/138) not significantly different ( $p=0.9$  (Fisher's test)) from the expected 50% for an autosomal dominant disease, whereas only 31.2% (24/77) of children of affected fathers were affected ( $p=0.001$  (Fisher's test)). We studied meiotic instability to see if a bias could account for the deviation from the expected 50% for both parental sexes. The instability of the GAA expansion during parental transmission depended on its size, repeats longer than 84 GAA were all unstable except one ( $n=57/360$ , Figure 3). All the 37 maternally transmitted alleles above 100 GAA were unstable and expanded by a median of +18 (IQR=10–27) [-34 – +63] by generation ( $r^2=0.44$ ;  $p<0.0001$  (Kendall correlation test)). The inverse occurred for the 16 paternally transmitted alleles above 100 GAA which contracted with a median difference of -15 (IQR=-23.5 – -5.75) [-59 – +16] ( $r^2=0.63$ ;  $p<0.0001$  (Kendall correlation test)). Parental alleles above 300 GAA were larger when maternally than paternally transmitted (395.5 (IQR=345.3–454.5) [309–496] vs 334.5 (IQR=318.5–375.8) [301–433] GAA;  $p<0.0001$  (Kruskal-Wallis test)).

### **The significance of pathogenic variants associated to *FGF14* GAA expansions**

In 28.6% (4/14) families with  $GAA_{250-299}$  we found another convincing pathogenic variant in a gene different from *FGF14*, versus only 4.7% (4/85) in those with  $GAA_{\geq 300}$  ( $p=0.03$  (Fisher's test)) since 35.3% (298/845) of the index cases had a previously identified causal gene (supplementary Table 4). Interestingly, 1.3% (4/298) of index cases with another causal gene carried  $GAA_{\geq 300}$  with a frequency similar to that of carriers in controls ( $p=0.8$  (Fisher's test)), whereas 14.8% (81/547) without another identified causal gene had  $GAA_{\geq 300}$ .

In the four individuals with  $GAA_{\geq 300}$ , the additional pathogenic variant was in the following ataxia genes *ITPR1*, *NOP56*, *ATPIA2*, and *CACNA1A* (Table 1). The corresponding individuals presented usually with an earlier onset than in SCA27B and a complex phenotype. This suggested that the additional variant associated with genes is responsible for earlier onset and more severe phenotypes. The possible contribution of *FGF14* to the phenotype may be masked because of late onset and slow progression.

In individuals with  $GAA_{250-299}$ , disease-causing variants were found in four different genes: *ATXN3*, *SPTLC1*, *RFC1*, and *CACNA1A*. None of them only displayed the key phenotype of SCA27B but rather the phenotype expected given the other pathogenic variants identified (supplementary Table 2bis).



**Table 1. Cases with *FGF14* GAA<sub>≥300</sub> (top) or GAA<sub>250-299</sub> (bottom) and another pathogenic variant**

Familial and Individual ID	<i>FGF14</i> GAA genotype	Other pathogenic gene	Transcript	Other pathogenic variant (c.)	Other pathogenic variant (p.)	ACMG criteria	Age at onset (years)	SCA2 7B key features
AAD-588-011	68/406	<i>ITPR1</i>	NM_001378452.1	c.(?_-350)_(708+1_709-1)del (exon 1_9 del)	p.?	P (Ib): PVS1, PM2, PP3, PP4, PP1	35	no
AAD-588-009	17/393	<i>ITPR1</i>	NM_001378452.1	c.(?_-350)_(708+1_709-1)del (exon 1_9 del)	p.?	P (Ib): PVS1, PM2, PP3, PP4, PP1	48	yes
AAD-1194-001	23/373	<i>NOP56</i>	NM_006392.4	c.3+71_4-62GGCCTG[1000+]	p.?	P (II): PS3, PS4, PM1, PM2, PP3, PP4	49	NA
AAD-1201-001	302/372	<i>ATP1A2</i>	NM_000702.4	c.2999A>G	p.Glu1000Gly	LP (IV): PP3, PM1, PM2, PM5	58	no
-399-498	265/326	<i>CACNA1A</i>	NM_001127222.1	c.889G>A	p.Gly297Arg	P (II): PS1, PM2, PS4, PP3, PP4, PP5	30	no
-SAL-382-069	15/283	<i>ATXN3</i>	NM_004993.6	c.874_915CAG[65]	p.292_305[Gln65]	P (II): PS3, PS4, PM1, PM2, PP3, PP4	50	NA
-SAL-	15/259	<i>ATXN3</i>	NM_004993.6	c.874_915CAG[72]	p.292_305[Gln72]	P (II): PS3, PS4, PM1,	35	no

382-080			3.6			PM2, PP3, PP4		
AAR- 289-003	17/271	<i>SPTLC1</i>	NM_00641 5.4	c.115_117del	p.Leu39del	LP (V): PM4, PM2, PP5, PP4	27	no
-399-966	15/265	<i>RFC1</i>	NM_00120 4747.2	c.132+2864_132+2919TTC CC[1000+] / c.132+2864_132+2919TTC CC[1000+]	p.?	P (II): PS3, PS4, PP3, PP4, PM1, PM3	56	no
AAR- 173-001	15/263	<i>CACNA 1A</i>	NM_00112 7222.1	c.4633C>T	p.Arg1545*	P (Ib): PVS1, PM2, PM5, PP4, PP5, PM6	36	no

NA: Not available; ACMG: American College of Medical Genetics; P: pathogenic; LP: likely pathogenic

## Segregation in families

In two out of 24 families with at least one individual with ataxia who had a  $GAA_{\geq 300}$  expansion, three individuals with ataxia did not carry a  $GAA_{\geq 250}$  expansion (AAD-431 and AAD-900; supplementary Figure 3). In family AAD-431, the age at onset of three affected individuals was under 13 years, only one of the relatives carried an expansion above 300 GAA. This was earlier than usual in the individuals with  $GAA_{\geq 300}$  and could represent an incidental finding. In family AAD-900, one affected individual with a phenotype compatible with SCA27B did not carry a large GAA allele, whereas five other affected cases had  $GAA_{\geq 300}$  expansions. This suggests that the patient without the GAA expansion was a phenocopy.

A discordance of segregation of the  $GAA_{\geq 250}$  expansion with cerebellar ataxia in affected individuals was present in five out of ten families with at least one individual with  $GAA_{250-299}$  expansion (SAL-382, -863, AAD-683, -907, -1328; supplementary Figure 4). In family SAL-382, an *ATXN3* CAG repeat expansion accounted for the phenotype observed in 2/7 patients also carrying a  $GAA_{250-299}$ . In family SAL-863, an allele ranging from 176 to 270 GAA repeat units was found in three patients whereas the fourth had no expansion excluding a causal role of the GAA expansion. In the three remaining families, GAA expansions of 238 and 276 (AAD-683), 245 and 279 (AAD-907) and, 200 and 297 (AAD-1328) co-segregated with the phenotype (late-onset mild episodic ataxia) but they seemed not to be causative on their own alone due to their size. Exome analysis in two of these later families did not reveal additional disease-causing variants. Either these GAA expansions shorter than 250 are not responsible for the disease, or perhaps when associated with yet unknown modifying genetic variants they may become pathogenic.

In sum, more discordances in segregation with cerebellar ataxia were observed in families with  $GAA_{250-299}$  expansions compared to those with  $GAA_{\geq 300}$  (50% versus 8.3%;  $p=0.03$  (Fisher's test)).

## Discussion

We screened a cohort of 1169 patients with ataxia and 475 controls for the recently reported *FGF14* GAA expansion responsible for SCA27B.<sup>6,7</sup> We showed, in contrast with what has previously been reported<sup>6,7,9</sup>, a higher frequency in cases with cerebellar ataxia versus controls was only observed in our cohort for *FGF14*  $GAA_{\geq 300}$  expansions.<sup>6,7</sup> The proportion of *FGF14*  $GAA_{250-299}$  alleles was similar in individuals with ataxia compared to controls (1.7 versus 1.7%;  $p=1$  (Fisher's test)). In controls,  $GAA_{250-299}$  were as rare as in previous control cohorts ranging from 0.2% to 2%.<sup>6,7,20</sup> We had fewer individuals with ataxia carrying  $GAA_{250-299}$  than the first Australian and Canadian studies (5% to 20%) but the percentage was comparable with that of the German cohort (1.7%).<sup>6</sup> Because alleles with  $GAA_{\geq 300}$  were significantly more frequent in patients than in controls ( $p<0.0001$  (Fisher's test)), our data support the use of  $GAA_{\geq 300}$  as the safe pathogenic threshold. The appropriateness of this more conservative threshold is reinforced by two additional findings observed in individuals with  $GAA_{250-299}$  as compared with individuals with  $GAA_{\geq 300}$ : i) the presence of another genetic cause, and ii) the discordant segregation analysis. Indeed, another genetic causal variant was observed in 28.6% of index with  $GAA_{250-299}$  ( $n=14$ ) but only in 4.7% of those with  $GAA_{\geq 300}$  ( $n=85$ ) ( $p=0.03$  (Fisher's test)). Furthermore, the phenotype was compatible with the pathogenic variant observed in this other gene. Segregation analysis was discordant in 50% of families with  $GAA_{250-299}$  versus 8.3% in those with  $GAA_{\geq 300}$  ( $p=0.03$  (Fisher's test)). These data indicate that a significant proportion of cases with  $GAA_{250-299}$  may have an ataxia of different origin

and alleles in this range should be interpreted with care. Some cases with  $GAA_{250-299}$ , particularly those who present with the key phenotype, could still have true *FGF14* ataxia indicating reduced penetrance for these alleles, as previously suggested.<sup>6,7</sup> The size of the GAA could affect the degree of repression of transcription like in Friedreich ataxia GAA.<sup>21</sup> Additional genetic factors or digenism could be involved, as demonstrated for *SCA48/STUB1* where the full phenotype strongly depends on the presence of an intermediate allele at the *SCA17/TBP* locus.<sup>22,23</sup>

The key phenotype of SCA27B includes onset above 45 years, episodic cerebellar signs, and downbeat nystagmus, as previously reported.<sup>6-9</sup> An additional feature was the absence of dysarthria as previously described.<sup>12,19</sup> A recent study also highlighted the absence of dysautonomia, especially of orthostatic hypotension, which could be added as key for isolated cases with  $GAA_{\geq 300}$ .<sup>9</sup>

We recorded eye movement in 22 patients with  $GAA_{\geq 300}$  in favor of involvement of the flocculus with downbeat nystagmus (68%) most frequently and vertical alteration of the pursuit (89%). This is not specific to SCA27B but allows us to distinguish the phenotype from polyQ SCAs.<sup>24,25</sup>

The fact that SCA27B is associated with late-onset and mild progression is well illustrated by the median age at death (81.4 years) close to that of the general French population (82.4 years).<sup>26</sup> The survival of SCA27B patients is preserved when compared with the decreased survival in SCAs with polyQ expansions and even in ataxias with conventional mutations in the most frequent genes.<sup>18</sup> This is supported by the disease-free survival which is longer in SCA27B than in sporadic late-onset ataxia including MSA, *RFC1*, and *SPG7*.<sup>9</sup>

There was no correlation between the size of the GAA repeat and clinical features (age at onset or death, SARA score) contrasting with discovery papers which found inverse correlation with age at onset and GAA size.<sup>6,7</sup> Similarly, there is no evidence for a more severe phenotype in patients carrying SCA27B expansions on both alleles.

Although instability of large alleles was observed in both sexes upon transmission, we confirmed that the rate of contractions and expansions was different according to the sex of the transmitting parent.<sup>6,20</sup> The tendency for maternal expansion is reminiscent of that described for the intronic GAA repeat which causes Friedreich ataxia.<sup>27</sup> Predominantly maternal increased repeat alleles are also observed in *DMPK* CTG expansions or *FRAXA* CGG expansions.<sup>28,29</sup> In contrast, greater paternal instability with a tendency to expand is observed in translated CAG repeat expansions like most polyQ SCAs, particularly SCA1, 2 and 7.<sup>30</sup> The excess of contractions during paternal transmissions may explain why affected fathers had only 31% of affected offspring deviating from the expected 50%. This observation is important for genetic counseling as affected fathers have a reduced risk of having affected children compared to affected mothers. In addition, instability also depends on GAA purity and the presence of a stabilizing sequence before.<sup>6,20</sup>

Our study is limited by the fact that 20% of index cases had not been genetically explored by WES and therefore we may have underestimated the proportion of another genetic cause. In patients with decreased vibration sense at ankle (57.5%), we were not able to distinguish between peripheral neuropathy or isolated posterior cord syndrome due to only few ENMG data (n=16 individuals with  $GAA_{\geq 300}$ ) and absence of sensory evoked potentials measures.<sup>9,12</sup>

Our study confirms that the *FGF14* GAA expansion is a frequent cause of late-onset ataxia but that the threshold for strict diagnosis should be held at 300 repeats. For expansions within the  $GAA_{250-299}$  range where penetrance is reduced, the results should be interpreted with

caution and in consideration of supportive criteria such as: presence of the key triad, absence of dysarthria, familial co-segregation, and whole exome/genome sequencing excluding other genetic forms. Finally, the bias against paternal transmission is important to consider for genetic counseling.

## **Contributors**

1) Conception and design of the study: J.L.M., C.S.D., D.P., M.B., P.J.L., B.B., M.R., A.B., A.D.

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3) Drafting a significant portion of the manuscript or figures: J.L.M., C.S.D., D.P., M.A., G.Co., M.C., A.S., B.G., C.M., J.H., B.D., G.S., P.J.L., B.B., M.R., A.B., A.D.

All authors read and approved the final version of the manuscript. J.L.M. and C.S.D., A.B. and A.D. had full access and verified the data.

## **Data Sharing Statement**

Detailed data was added in the supplementary materials.

## **Declaration of Interests**

MA received consulting fees from Reata pharmaceuticals, Merz, AbbVie, Orkyn, Ever Pharma, Ipsen; honoraria from Reata pharmaceuticals, Merz, AbbVie, Orkyn, Ever Pharma, Ipsen and participated on an advisory board for Reata Pharmaceuticals. ILB received grants from Pfizer, Fondation Plan Alzheimer, JPND/ANR, Alector; consulting fees from Prevail Therapeutics, Alector, JEITO and participated on an advisory board of Prevail Therapeutics. CM received financial support for attending meetings and travel from Nutricia and participated on an advisory board of Medesis Pharma society. BD had public funding contracts for Clinical Research: Contrat de Recherche Clinique (CRC) 2021 (APHP), CRC 2023 (APHP) and Agence Régionale de Santé (ARS); received honoraria from MERZ, IPSEN Pharma, LVL Medical; received support for attending meetings from MERZ Pharma, ADELIA; participated on an advisory board of MERZ, ORION Pharma and received equipment from MERZ. SF received support for participation in national and international meetings from Alnylam. GS received grant from BIOGEN and ASL-HSP association. MB received honoraria for thesis examinations; is member of Australian Academy of Health and Medical Sciences Australian Learned Academies Data Internetworking Network (ALADIN) Project Steering Committee; Australian Academy of Health and Medical Sciences Reports Committee; Clinical Genomics Advisory Committee, Kinghorn Sequencing Center; Gen V Scientific Advisory Committee, Murdoch Children's Research Institute; Viertel Foundation Medical Advisory Board; Australian Academy of Health and Medical Sciences Reports Committee; Present American Epilepsy Society Basic Sciences Committee; Gen V Bioresource Genetics Working Group. AD received grants from Biogen, WAVELIFE, ROCHE, TRIPLET Therapeutics, NIH RO1 (National Institute of Health), National Hospital Clinical Research Program; consulting fees from Wavelife science, ROCHE, TRIPLET



Therapeutics, Pfizer, ASKBIO, Genome Quebec, VICO therapeutics; participated on an advisory board for REATA; is the president of the Société Francophone de Neurogénétique.

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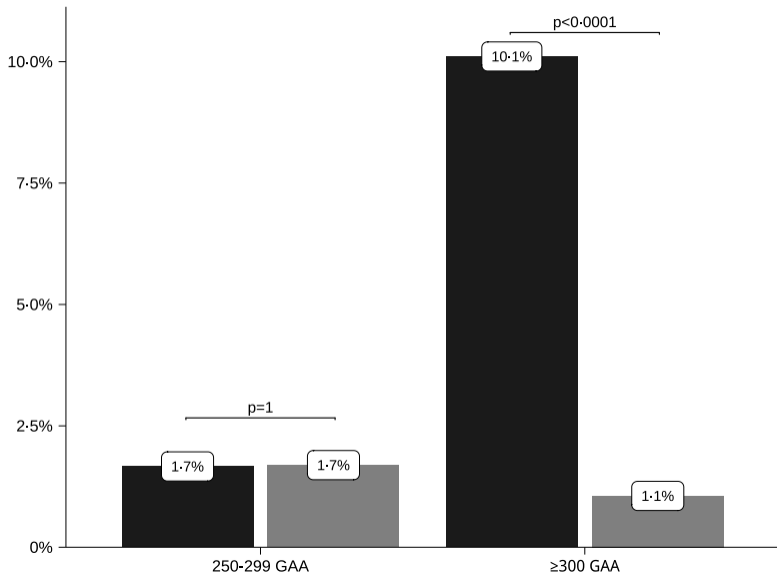
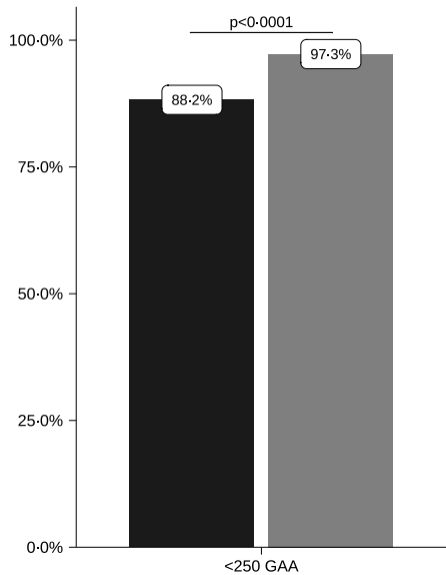
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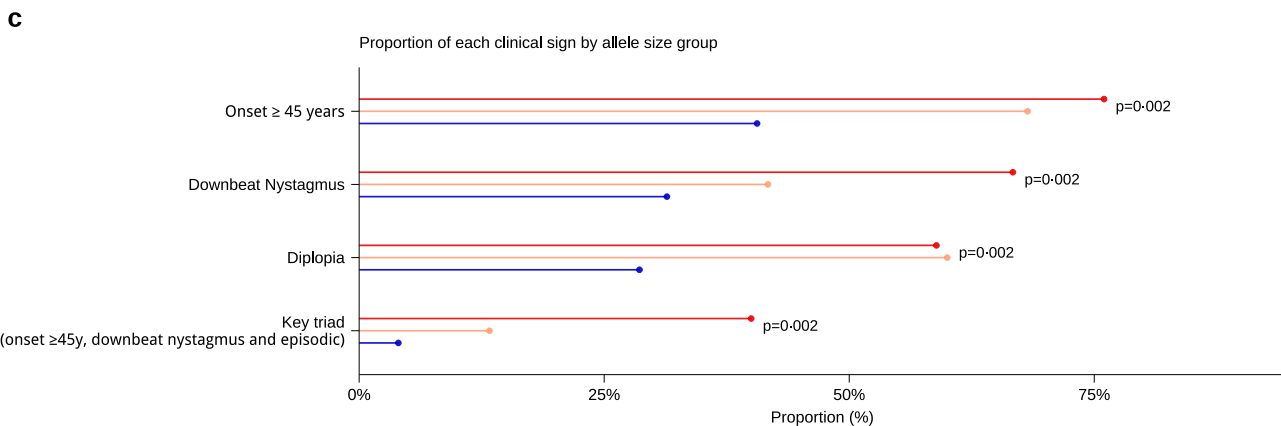
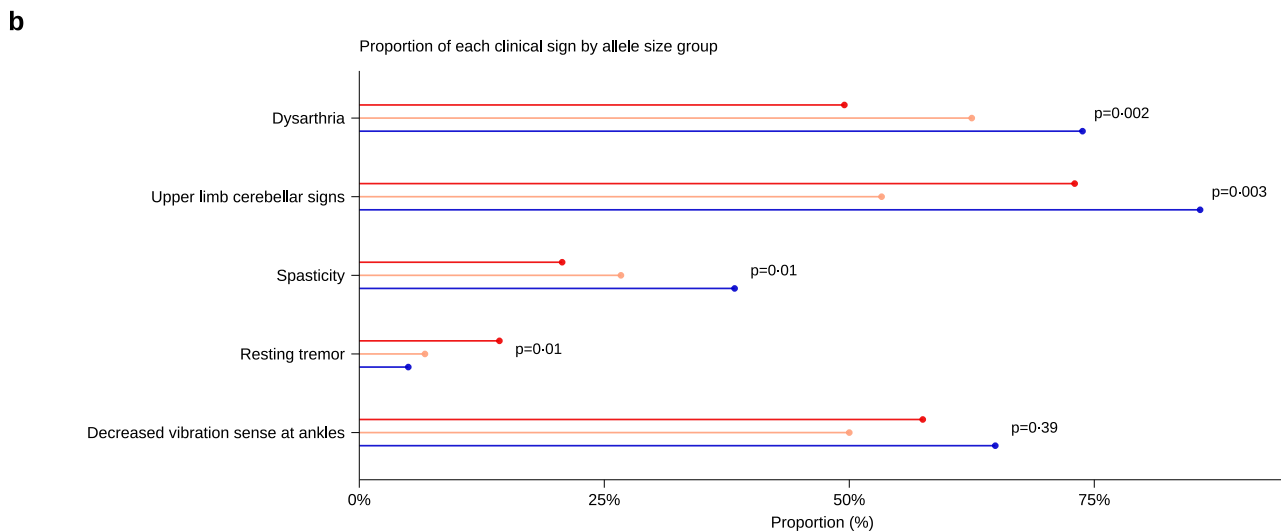
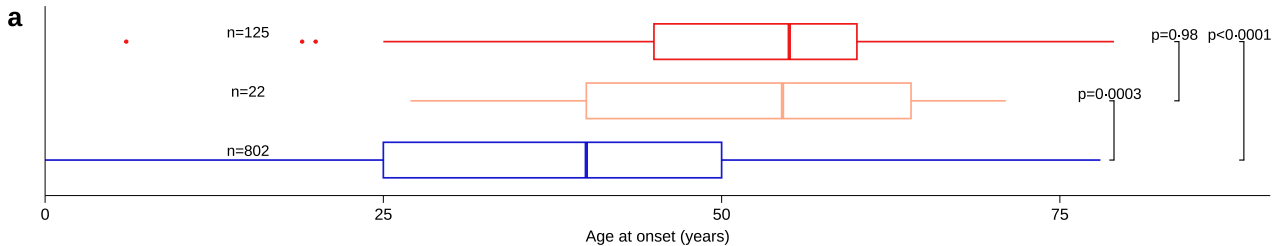
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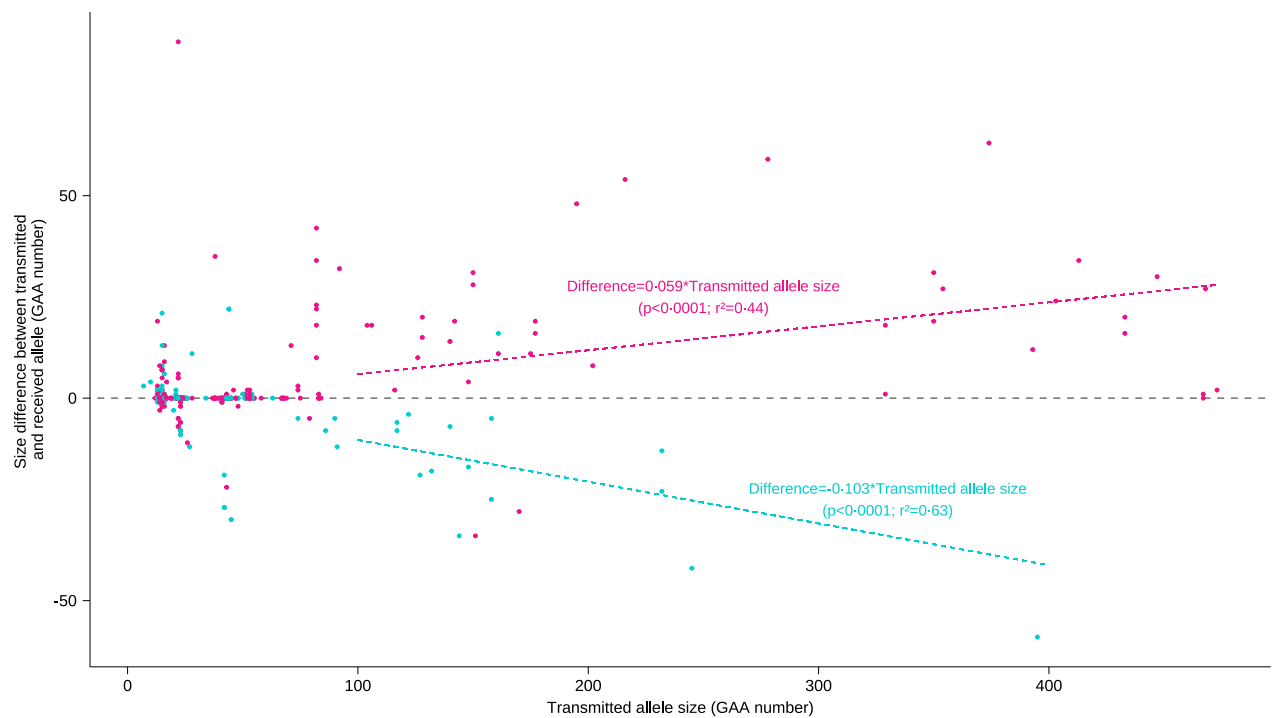
**Figure 1.** Proportion of index patients with ataxia (black) (n=845), and controls (gray) (n=475) according to the size of their largest GAA repeat for *FGF14*. The proportion of carriers differed significantly above 300 GAA in patients (10.1%) compared to controls (1.1%) ( $p<0.001$ ; Fisher's test) as with  $< 250$  GAA whereas it was similar for GAA sizes between 250 and 299 GAA.

**Figure 2.** Clinical features of patients with ataxia according to *FGF14* GAA size groups ( $GAA_{\geq 300}$  in red,  $GAA_{250-299}$  in light orange, and  $GAA_{<250}$  in dark blue). a: boxplot of the age at onset (the ends of the boxes are 25th and 75th percentiles, the middle line is the median, and the whiskers are 1.5 IQR; adjusted p-values after Kruskal-Wallis test). b: clinical features of SCA27B individuals with  $GAA_{\geq 300}$  were similar to those with GAA sizes between 250 and 299 GAA (Fisher's test). c: the three key features of SCA27B which were significantly different in individuals with less than 250 GAA repeats (Fisher's test).

**Figure 3.** Analysis of parent-offspring transmission of *FGF14* GAA alleles according to the size of the expansion and sex of the transmitting parent (375 maternal transmissions in magenta and 255 paternal transmissions in turquoise). Transmission of alleles above 100 GAA showed instability with a maternal propensity to expand ( $p<0.001$ ; Kendall correlation test;  $r^2=0.42$ ) versus a paternal tendency to contract ( $p<0.001$ ; Kendall correlation test;  $r^2=0.61$ ).

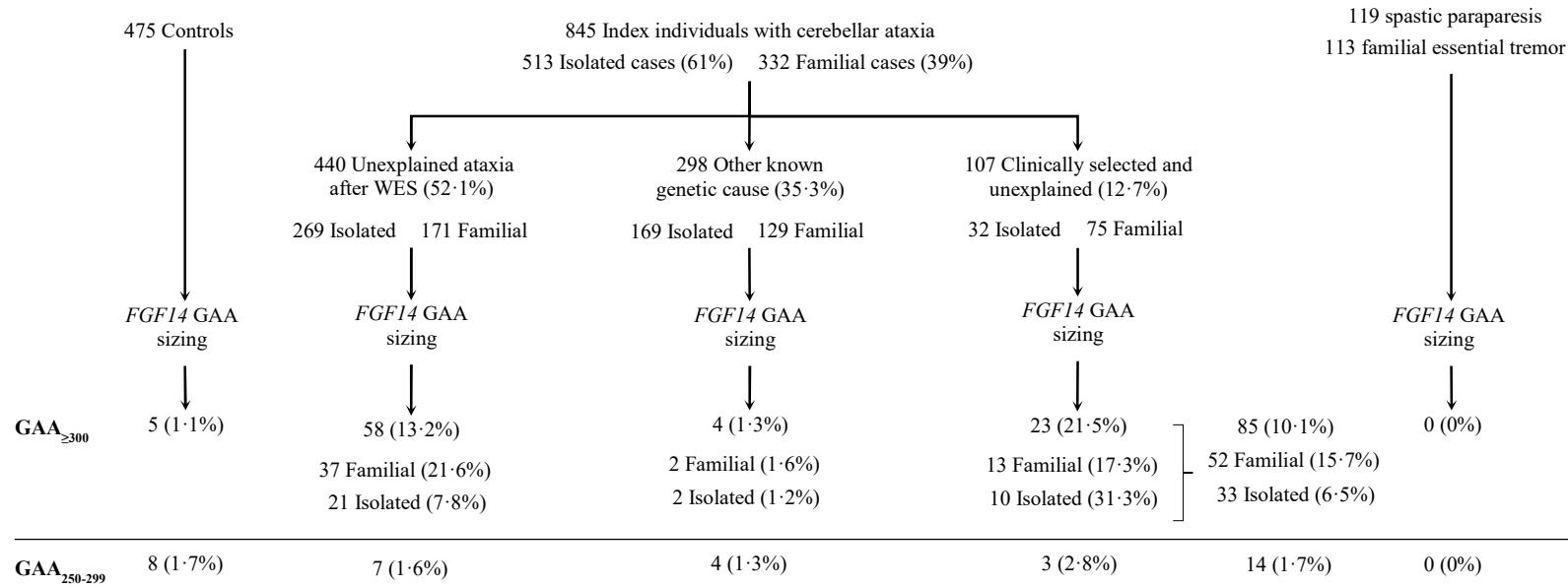






## Supplementary figures

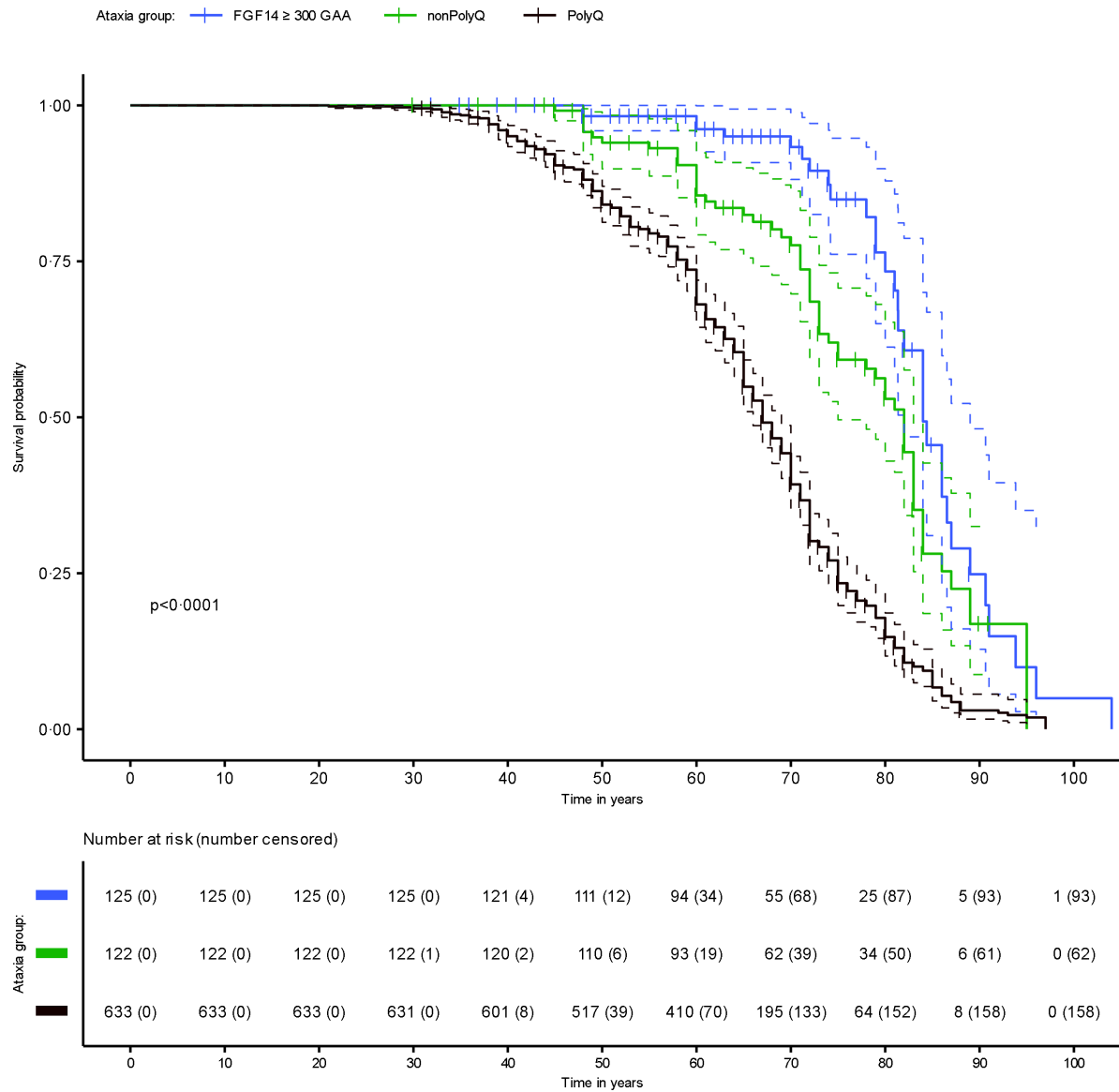
**Supplementary Figure 1. Flowchart indicating the proportion of individuals with  $GAA_{\geq 300}$  and  $GAA_{250-299}$  in 845 index individuals with cerebellar ataxia, 475 controls, 119 with spastic paraparesis, and 113 with familial essential tremor**



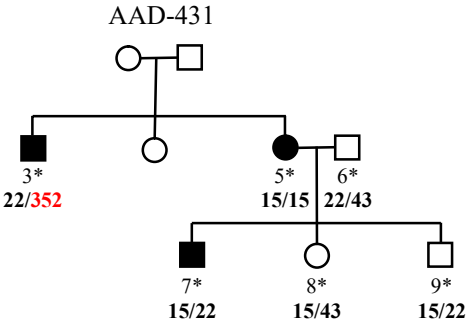
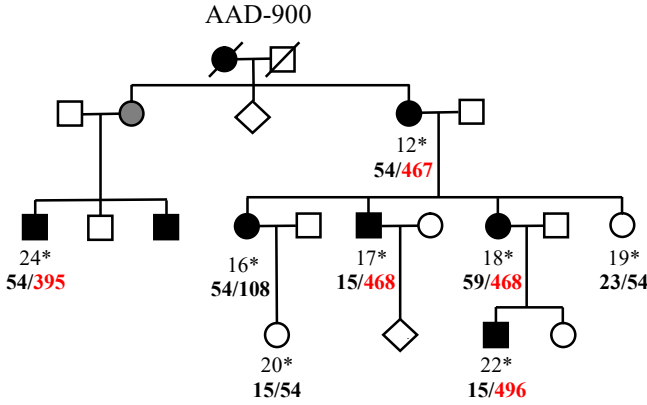
Individuals clinically selected for *FGF14* GAA sizing had downbeat nystagmus or episodic manifestations of cerebellar ataxia



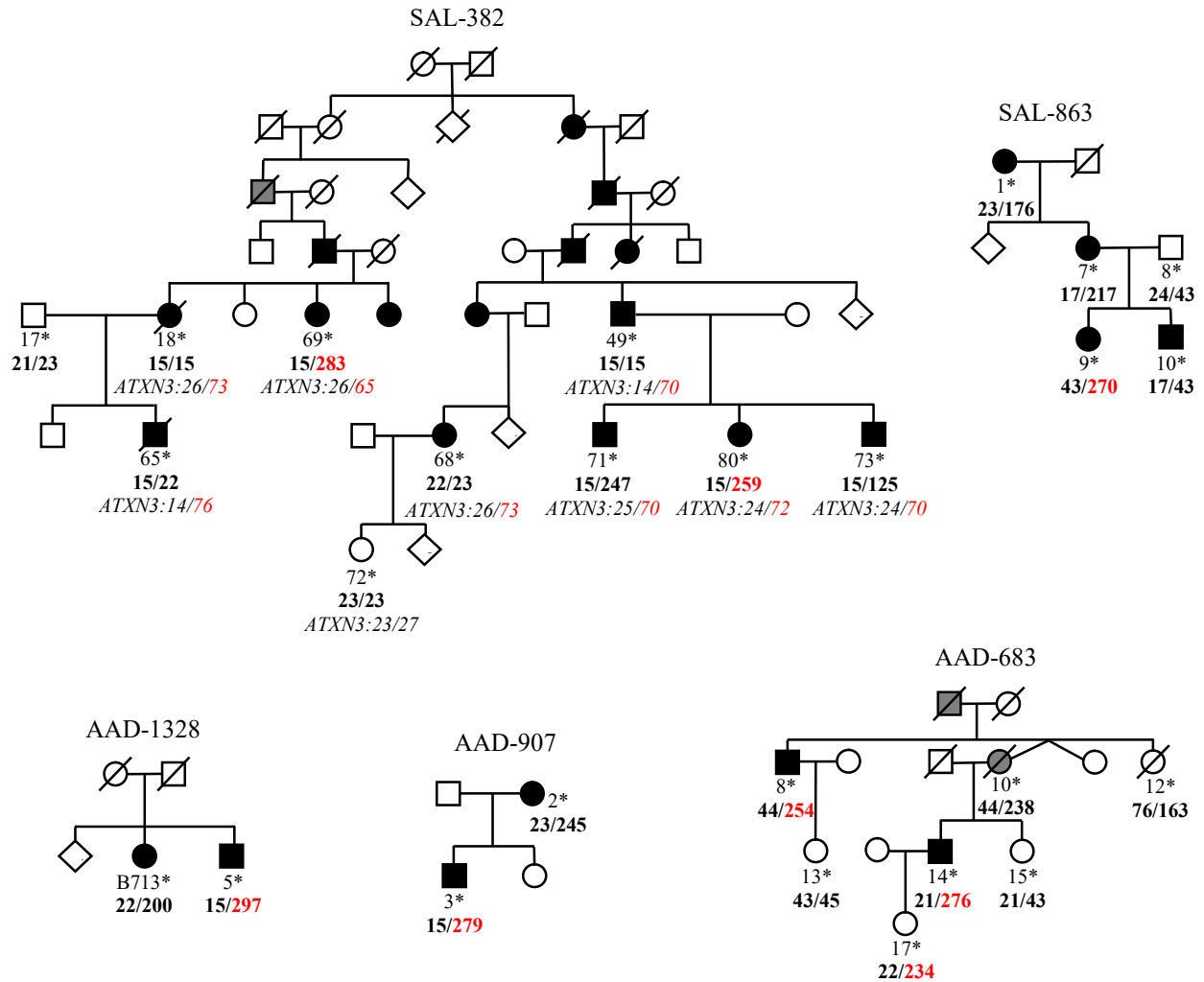
**Supplementary Figure 2. Survival curves of *FGF14* expansion carriers (blue curve) compared to patients with other autosomal dominant genetic causes of ataxia (black: polyglutamine expansions (PolyQ) and green: other variants in 14 genes (nonPolyQ)<sup>15</sup>. The non polyQ group included patients with variants in the seven most frequent dominant ataxia genes (*PRKCG*, *AFG3L2*, *NOP65*, *SPTBN2*, *KCNC3*, *ITPR1*, *KCND3*) (logrank test)**



**Supplementary Figure 3. Pedigrees showing partial cosegregation of GAA expansion and ataxia in two families with  $GAA_{\geq 300}$ . Squares represent males and circles females. Blackened symbols represent affected individuals. Asterisks indicate sampled individuals with *FGF14* GAA length below and individual code with  $GAA_{\geq 300}$  alleles in red.**



**Supplementary Figure 4. Pedigrees showing partial cosegregation of GAA expansion and ataxia in five families with  $GAA_{250-299}$ . Squares represent males and circles females. Blackened symbols represent affected individuals. Asterisks indicate sampled individuals with *FGF14* GAA length below and individual code with  $GAA_{\geq 250}$  alleles in red. In family SAL-382, the *ATXN3* genotype is indicated below with the pathologically expanded allele in red.**



## Supplementary Tables

**Supplementary Table 1. Clinical characteristics and comparison of SCA27B phenotypes according to *FGF14* GAA expansion size**

<i>FGF14</i> GAA size of the largest allele	<250 (n=1016)	250-299 (n=22)	≥300 (n=127)	p value <sup>a</sup>	Proportion of <i>FGF14</i> ≥300 GAA
Median Small Allele Size (IQR=Q1-Q3) [MIN-MAX]	15 (IQR=15-22) [8-179]	17 (IQR=15-42.2) [15-127]	23 (IQR=16-64) [12-448]		
Median Large Allele Size (IQR=Q1-Q3) [MIN-MAX]	32 (IQR=22-71) [9-247]	272 (IQR=261.5-278.8) [250-297]	384 (IQR=335.5-428) [301-496]		
Familial cases	546/1016 (53.7%)	16/22 (72.7%)	94/127 (74%)	<b>0.002</b>	14.3%
Maternal origin	170/301 (56.5%)	4/9 (44.4%)	60/78 (76.9%)	<b>0.01</b>	25.6%
Men	525/1016 (51.7%)	14/22 (63.6%)	61/127 (48%)	0.56	11.7%
Women	491/1016 (48.3%)	8/22 (36.4%)	66/127 (52%)	0.56	11.7%
Median age at onset (years)	40 (IQR=25-50) [0-78]	54.5 (IQR=40-64) [27-71]	55 (IQR=45-60) [6-79]	<b>&lt;0.0001</b>	
Onset ≥ 45 years	326/802 (40.6%)	15/22 (68.2%)	95/125 (76%)	<b>0.002</b>	21.8%
Median age at examination (years)	54 (IQR=42-64) [2-95]	66 (IQR=58-74) [30-93]	66 (IQR=57-74) [32-90]	<b>&lt;0.0001</b>	
Median disease duration (years)	12 (IQR=6-23) [0-70]	8 (IQR=5-14) [1-53]	10 (IQR=5-18.8) [0-49]	0.21	
Median disability score <sup>b</sup> (max severity at 7)	3 (IQR=3-4) [0-7]	3 (IQR=2-4) [1-6]	3 (IQR=2-4) [1-7]	0.16	
Median disability score adjusted to disease duration	0.3 (IQR=0.2-0.6) [0-4]	0.3 (IQR=0.2-0.6) [0.1-4]	0.3 (IQR=0.2-0.5) [0.1-3]	0.57	
SARA (Scale for the Assessment and Rating of Ataxia, max severity at 40)	13 (IQR=8-17.5) [0.5-39]	8.5 (IQR=6.5-12.5) [3-30]	10.5 (IQR=6.5-13.5) [2-28]	<b>0.003</b>	
Median SARA adjusted to disease duration	1.1 (IQR=0.6-2) [0-15]	1.2 (IQR=0.8-1.9) [0.1-5]	1 (IQR=0.5-1.8) [0.1-13]	0.7	
CCFS (Composite Cerebellar Functional Score)	1 (IQR=0.9-1.1) [0.2-1.6]	0.8 (IQR=0.8-0.8) [0.8-0.8]	0.9 (IQR=0.8-1) [0.8-1.1]	0.04	
Median age at death (years)	67.7 (IQR=57.8-76.3) [29.9-96.2]	83 (IQR=78-85) [73-87]	81.4 (IQR=73.5-86.1) [48-104]	<b>0.002</b>	
Episodic manifestations at onset	8/15 (53.3%)	11/17 (64.7%)	58/121 (47.9%)	0.72	75.3%
Key triad (onset ≥45y, vertical nystagmus and episodic)	27/676 (4%)	2/15 (13.3%)	34/85 (40%)	<b>0.002</b>	54.0%
Cerebellar Ataxia	638/667 (95.7%)	12/12 (100%)	69/74 (93.2%)	0.69	9.6%
Ataxic gait	596/636 (93.7%)	15/15 (100%)	70/74 (94.6%)	0.92	10.3%
Upper limb cerebellar signs	533/621 (85.8%)	8/15 (53.3%)	54/74 (73%)	<b>0.003</b>	9.1%
Lower limb cerebellar signs	553/614 (90.1%)	12/15 (80%)	58/72 (80.6%)	0.04	9.3%
Dysarthria	515/698 (73.8%)	10/16 (62.5%)	49/99 (49.5%)	<b>0.002</b>	8.5%
Dysphagia	189/559 (33.8%)	2/9 (22.2%)	20/67 (29.9%)	0.73	9.5%
Diplopia	179/625 (28.6%)	9/15 (60%)	53/90 (58.9%)	<b>0.002</b>	22.0%
Ptosis	63/503 (12.5%)	1/13 (7.7%)	5/64 (7.8%)	0.72	7.2%
Nystagmus	371/668 (55.5%)	9/13 (69.2%)	80/96 (83.3%)	<b>0.002</b>	17.4%
Downbeat Nystagmus	168/535 (31.4%)	5/12 (41.7%)	56/84 (66.7%)	<b>0.002</b>	36.4%
Spasticity	259/677 (38.3%)	4/15 (26.7%)	19/92 (20.7%)	<b>0.01</b>	6.7%
Spasticity at rest of the lower limbs	177/563 (31.4%)	3/15 (20%)	8/72 (11.1%)	<b>0.002</b>	4.3%
Spastic gait	168/591 (28.4%)	2/15 (13.3%)	9/73 (12.3%)	<b>0.01</b>	5.0%
Increased patellar reflexes	347/665 (52.2%)	2/14 (14.3%)	21/69 (30.4%)	<b>0.002</b>	5.7%
Extensor plantar reflex	258/659 (39.2%)	5/14 (35.7%)	10/68 (14.7%)	<b>0.003</b>	3.7%
Resting tremor	33/662 (5%)	1/15 (6.7%)	14/98 (14.3%)	<b>0.01</b>	29.2%
Postural tremor	157/624 (25.2%)	6/16 (37.5%)	26/97 (26.8%)	0.62	13.8%
Hypokinesia	143/578 (24.7%)	3/13 (23.1%)	7/65 (10.8%)	<b>0.04</b>	4.6%

<sup>a</sup>adjusted *p* value between the different groups with Fisher's test for qualitative variables and Kruskal-Wallis test for quantitative variables.

<sup>b</sup>Functional impairment was rated by the SPATAX disability score: 0 (no functional handicap), 1 (no functional handicap but signs at examination), 2 (mild, able to run, unlimited walking), 3 (moderate, unable to run, limited walking without aid), 4 (severe, walking with one stick), 5 (walking with two sticks), 6 (unable to walk, requiring a wheelchair), 7 (confined to a bed).

For all quantitative variables median followed by IQR: interquartile range; MIN: minimum; MAX: maximum

<i>FGF14</i> GAA size of the largest allele	<250 (n=1016)	250-299 (n=22)	≥300 (n=127)	p value <sup>a</sup>	Proportion of <i>FGF14</i> ≥300 GAA
<b>Rigidity</b>	129/618 (20.9%)	1/14 (7.1%)	13/62 (21%)	0.7	9.1%
<b>Cognitive impairment</b>	169/655 (25.8%)	1/16 (6.2%)	13/86 (15.1%)	0.04	7.1%
<b>Psychiatric signs</b>	91/633 (14.4%)	5/15 (33.3%)	12/93 (12.9%)	0.19	11.1%
<b>Hearing impairment</b>	108/626 (17.3%)	4/14 (28.6%)	12/68 (17.6%)	0.65	9.7%
<b>Superficial sensory loss</b>	35/816 (4.3%)	0/18 (0%)	3/97 (3.1%)	0.92	7.9%
<b>Decreased vibration sense at ankles</b>	393/606 (64.9%)	7/14 (50%)	42/73 (57.5%)	0.39	9.5%
<b>Abnormal Cerebral MRI</b>	352/411 (85.6%)	11/13 (84.6%)	75/85 (88.2%)	0.92	15.6%
<b>Cerebral atrophy</b>	80/250 (32%)	3/5 (60%)	11/27 (40.7%)	0.39	11.7%
<b>Cerebellar atrophy</b>	301/319 (94.4%)	10/11 (90.9%)	67/76 (88.2%)	0.19	17.7%
<b>Abnormal medullar MRI (spinal cord atrophy)</b>	6/94 (6.4%)	0/2 (0%)	1/9 (11.1%)	0.7	14.3%
<b>Abnormal ENMG (peripheral neuropathy)</b>	57/189 (30.2%)	1/4 (25%)	4/16 (25%)	0.92	6.5%

<sup>a</sup>adjusted *p* value between the different groups with Fisher's test for qualitative variables and Kruskal-Wallis test for quantitative variables.

<sup>b</sup>Functional impairment was rated by the SPATAX disability score: 0 (no functional handicap), 1 (no functional handicap but signs at examination), 2 (mild, able to run, unlimited walking), 3 (moderate, unable to run, limited walking without aid), 4 (severe, walking with one stick), 5 (walking with two sticks), 6 (unable to walk, requiring a wheelchair), 7 (confined to a bed).

For all quantitative variables median followed by IQR: interquartile range; MIN: minimum; MAX: maximum

**Supplementary Table 2. Clinical characteristics of 122 affected individuals with *FGF14* GAA<sub>≥300</sub> followed by 22 affected individuals with *FGF14* GAA<sub>250-299</sub>**

ID/Sex	<i>FGF14</i> GAA sizes	Key features <sup>a</sup>   Dysarthria	Age at onset (y), E/P	Disease duration (y) / age at examination / death	SARA (max value 40)	Disability stage <sup>b</sup> (max value 7)	Eye movement anomalies	Pyramidal (reflexes ++ and/or EPR +)	Extra-Pyramidal signs	Cognitive / psychiatric manifestations	Brain MRI atrophy	Comments	Segregation   Exome <sup>c</sup>	Supportive criteria score <sup>d</sup>
AAD-900-022/M	15/496	--+   -	25 (P)	10/35/NA	2	2	SAC	++ (Hoffmann)	no	no	NA		- (5/6)   + (NA)	3
AAD-900-017/M	15/468	+++   -	52 (P)	4/56/NA	5.5	2	SAC	normal	postural tremor	dysexecutive disorders	NA	urinary incontinence	- (5/6)   + (NA)	3
AAD-900-018/W	59/468	-+ -   -	20 (P)	31/51/NA	8	3	Nys H/V	++	no	no	vermian	dysphagia	- (5/6)   + (NA)	3
AAD-900-012/W	54/467	--+   +	40 (P)	35/75/NA	11	3	Nys H, LVG	normal	no	no	NA		- (5/6)   + (NA)	2
AAD-900-024/M	54/395	--+   -	42 (E, diplopia)	17/59/NA	5.5	2	Nys, saccadic intrusions	++	no	prefrontal	global		- (5/6)   + (NA)	3
AAR-101-003/M	89/495	---   NA	37 (P)	2/39/NA	mild	2	Nys	++ left EPR+	upper limbs tremor	NA	NA		+ (2/2)   + (NA)	3
AAR-101-005/M	46/305	-++   NA	25	14/39/48	severe	4	Nys H/V	normal	NA	memory difficulties	cerebellar	visual vertigo	+ (2/2)   + (NA)	3
AAD-546-009/M	44/482	+- -   +	46 (P)	9/55/72	mild	3	Nys, SAC	normal	NA	NA	NA	intermittent dysarthria	+ (2/2)   + (NA)	3
AAD-074-027/W	15/477	+- -   -	57, Tremor	0/57/NA	0	1	normal	++	postural and	no	NA	tremor increased	+ (6/6)	4

<sup>a</sup>Key features are age onset ≥ 45 years, vertical nystagmus and episodic features. +: if sign is present and -: absent

<sup>b</sup>Functional impairment rated by the SPATAX disability score: 0 (no functional handicap), 1 (no functional handicap but signs at examination), 2 (mild, able to run, unlimited walking), 3 (moderate, unable to run, limited walking without aid), 4 (severe, walking with one stick), 5 (walking with two sticks), 6 (unable to walk, requiring a wheelchair), 7 (confined to a bed).

<sup>c</sup>Segregation in the family (concordance in affected individual samples) | Exome done (gene with pathogenic variant)

<sup>d</sup>Each of the five supportive criteria fulfilled counts one point: expansion size above 299 GAA, presence of the key triad, absence of dysarthria, co-segregation, and exome done without other causal variant found

Abbreviations. DBN: downbeat nystagmus; EPR: extensor plantar reflex (Babinski sign); E: episodic onset; F: Female; FIX: fixation instability; H: horizontal; LL: lower limbs; LVG: Limited vertical gaze; M: Male; NA: not available; Nys: nystagmus; P: permanent ataxia onset; RBD: REM behavioral disorder; SAC: saccadic pursuit; SARA: Scale for the Assessment and Rating of Ataxia; UL: upper limbs; V: vertical; ++: increased reflexes.

ID/Sex	FGF14 GAA sizes	Key features <sup>a</sup>   Dysarthria	Age at onset (y), E/P	Disease duration (y) / age at examination / death	SARA (max value 40)	Disability stage <sup>b</sup> (max value 7)	Eye movement anomalies	Pyramidal (reflexes ++ and/or EPR +)	Extra-Pyramidal signs	Cognitive / psychiatric manifestations	Brain MRI atrophy	Comments	Segregation   Exome <sup>c</sup>	Supportive criteria score <sup>d</sup>
									resting tremor			by emotional stress	+ (NA)	
AAD-074-025/W	23/433	- + +   -	41 (E, vertigo)	16/57/NA	4	2	Nys H/V	+	head tremor	Mild depression	vermian		+ (6/6)   + (NA)	4
AAD-074-010/W	75/428	+ - +   NA	58 (E)	20/78/81	mild	3	SAC	++	no	NA	NA	crisis with falls	+ (6/6)   + (NA)	3
AAD-074-016/W	122/448	+ + +   -	60 (E)	30/90/104	moderate	5	Nys H/V, LVG	++	parkinsonism	dementia	NA		+ (6/6)   + (NA)	5
AAD-074-023/M	245/390	- + +   +	40 (E, vertigo)	25/65/NA	mild	2	Nys H/V	normal (no ankle reflex)	no	no	hemispheres, pontine	crisis (dysarthria, gait, diplopia)	+ (6/6)   + (NA)	3
FPD-1051-025/M	17/476	- - -   +	42 (P)	9/51/54	9-5	2	Nys H	normal	postural tremor UL	depression, suicide	NA	mild swallowing difficulties	+ (5/5)   - (NA)	2
BMV-0543/W	17/476	+ + -   -	60	0/60/NA	0	1	DBN	normal	no	depression	NA		+ (5/5)   + (NA)	4
FPD-1051-022/M	21/462	+ + +   +	46 (E, diplopia)	11/57/NA	6-5	2	Nys V, H, SAC	decreased	no	depression	NA	mild swallowing	+ (5/5)   +	4

<sup>a</sup>Key features are age onset  $\geq$  45 years, vertical nystagmus and episodic features. +: if sign is present and -: absent

<sup>b</sup>Functional impairment rated by the SPATAX disability score: 0 (no functional handicap), 1 (no functional handicap but signs at examination), 2 (mild, able to run, unlimited walking), 3 (moderate, unable to run, limited walking without aid), 4 (severe, walking with one stick), 5 (walking with two sticks), 6 (unable to walk, requiring a wheelchair), 7 (confined to a bed).

<sup>c</sup>Segregation in the family (concordance in affected individual samples) | Exome done (gene with pathogenic variant)

<sup>d</sup>Each of the five supportive criteria fulfilled counts one point: expansion size above 299 GAA, presence of the key triad, absence of dysarthria, co-segregation, and exome done without other causal variant found

Abbreviations. DBN: downbeat nystagmus; EPR: extensor plantar reflex (Babinski sign); E: episodic onset; F: Female; FIX: fixation instability; H: horizontal; LL: lower limbs; LVG: Limited vertical gaze; M: Male; NA: not available; Nys: nystagmus; P: permanent ataxia onset; RBD: REM behavioral disorder; SAC: saccadic pursuit; SARA: Scale for the Assessment and Rating of Ataxia; UL: upper limbs; V: vertical; ++: increased reflexes.

ID/Sex	FGF14 GAA sizes	Key features <sup>a</sup>   Dysarthria	Age at onset (y), E/P	Disease duration (y) / age at examination / death	SARA (max value 40)	Disability stage <sup>b</sup> (max value 7)	Eye movement anomalies	Pyramidal (reflexes ++ and/or EPR +)	Extra-Pyramidal signs	Cognitive / psychiatric manifestations	Brain MRI atrophy	Comments	Segregation   Exome <sup>c</sup>	Supportive criteria score <sup>d</sup>
												difficulties	(NA)	
FPD-1051-024/BMV-733/M	15/461	---   -	40 (P)	23/63/NA	mild	2	Nys H	normal	no	NA	NA	mild dysphagia and mildly decreased vibration at ankles	+ (5/5)   + (NA)	4
BMV-0623/M	61/451	+++   NA	75 (P)	7/82/NA	NA	4	Nys H, SAC	normal	no	NA	NA		+ (5/5)   + (NA)	3
AAD-734-010 BMV-080/M	12/475	+++   NA	45 (P)	4/52/63	10.5	2	Nys H	normal	distal tremor hands; head	NA	vermian	fasciculations	+ (3/3)   + (NA)	3
AAD-743-005/W	23/473	+++   +	55 (P)	18/73/NA	moderate	3	Nys H	++, EPR+	no	no	vermian		+ (3/3)   + (NA)	3
AAD-743-007/W	22/472	+++   -	67 (P)	3/70/NA	mild	2	LVG	normal (no ankle reflex)	tremor hands and head rigidity	NA	vermian	Intermittent diplopia	+ (3/3)   + (NA)	4
AAD-834-001/M	23/458	+++   +	79 (E, dysarthria)	4/83/93	mild	2	Nys H, LVG	normal	no	no	vermian	1h dysarthria 3 times a year, sensory and motor demyelinating	NA   + (NA)	2

<sup>a</sup>Key features are age onset  $\geq$  45 years, vertical nystagmus and episodic features. +: if sign is present and -: absent

<sup>b</sup>Functional impairment rated by the SPATAX disability score: 0 (no functional handicap), 1 (no functional handicap but signs at examination), 2 (mild, able to run, unlimited walking), 3 (moderate, unable to run, limited walking without aid), 4 (severe, walking with one stick), 5 (walking with two sticks), 6 (unable to walk, requiring a wheelchair), 7 (confined to a bed).

<sup>c</sup>Segregation in the family (concordance in affected individual samples) | Exome done (gene with pathogenic variant)

<sup>d</sup>Each of the five supportive criteria fulfilled counts one point: expansion size above 299 GAA, presence of the key triad, absence of dysarthria, co-segregation, and exome done without other causal variant found

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ID/Sex	FGF14 GAA sizes	Key features <sup>a</sup>   Dysarthria	Age at onset (y), E/P	Disease duration (y) / age at examination / death	SARA (max value 40)	Disability stage <sup>b</sup> (max value 7)	Eye movement anomalies	Pyramidal (reflexes ++ and/or EPR +)	Extra-Pyramidal signs	Cognitive / psychiatric manifestations	Brain MRI atrophy	Comments	Segregation   Exome <sup>c</sup>	Supportive criteria score <sup>d</sup>
												polyneuropathy		
AAD-1103-001/M	15/451	++-   +	58 (P)	10/68/NA	9	3	Nys H, V, LVG	++, EPR+	rigidity, hypokinesia	no	global : cerebellar and cortex	fasciculations, myokymias, pes cavus	NA   + (NA)	2
AAD-059-008/W	16/448	+-+   +	60 (P)	9/69/79	NA	2	Nys H	normal	Froment sign	no	no atrophy	urinary urgency	+ (2/2)   + (NA)	3
AAD-059-010/M	49/438	+-+   +	50 (P)	16/66/78	mild	2	SAC	EPR+	parkinsonism	no	global		+ (2/2)   + (NA)	3
AAD-1149-001/W	448/448	-++   +	27 (E)	5/32/NA	12.5	3	SAC, DBN*	normal	no	no	vermian	urinary urgency, ptosis	+ (2/2)   - (NA)	2
AAD-1149-002/W	15/413	+-+   +	56 (P)	4/60/NA	6	2	SAC, Nys H	++ LL	head and UL tremor	cognitive impairment	vermian		+ (2/2)   - (NA)	2
AAD-1313-002/W	17/440	+-+   +	45	17/62/NA	7	3	Nys H, square waves	decreased	chorea	no	NA		+ (2/2)   + (NA)	3
AAD-1313-001/W	26/426	+++   -	59 (E)	12/71/NA	4	3	DBN	Absent LL	mild truncal dystonia	NA	global, Schelt	worse in the morning	+ (2/2)   +	5

<sup>a</sup>Key features are age onset  $\geq 45$  years, vertical nystagmus and episodic features. +: if sign is present and -: absent

<sup>b</sup>Functional impairment rated by the SPATAX disability score: 0 (no functional handicap), 1 (no functional handicap but signs at examination), 2 (mild, able to run, unlimited walking), 3 (moderate, unable to run, limited walking without aid), 4 (severe, walking with one stick), 5 (walking with two sticks), 6 (unable to walk, requiring a wheelchair), 7 (confined to a bed).

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Abbreviations. DBN: downbeat nystagmus; EPR: extensor plantar reflex (Babinski sign); E: episodic onset; F: Female; FIX: fixation instability; H: horizontal; LL: lower limbs; LVG: Limited vertical gaze; M: Male; NA: not available; Nys: nystagmus; P: permanent ataxia onset; RBD: REM behavioral disorder; SAC: saccadic pursuit; SARA: Scale for the Assessment and Rating of Ataxia; UL: upper limbs; V: vertical; ++: increased reflexes.

ID/Sex	FGF14 GAA sizes	Key features <sup>a</sup>   Dysarthria	Age at onset (y), E/P	Disease duration (y) / age at examination / death	SARA (max value 40)	Disability stage <sup>b</sup> (max value 7)	Eye movement anomalies	Pyramidal (reflexes ++ and/or EPR +)	Extra-Pyramidal signs	Cognitive / psychiatric manifestations	Brain MRI atrophy	Comments	Segregation   Exome <sup>c</sup>	Supportive criteria score <sup>d</sup>
											ens 2		(NA)	
AAD-1036-001/M	15/438	---   -	31 (tremor)	6/37/NA	0	1	NA	normal	tremor only left>right	no	NA		+ (4/4)   + (NA)	4
AAD-1036-004/W	25/312	+++   +	45 (P)	23/68/NA	28	6	Nys H	normal	NA	no	global		+ (4/4)   + (NA)	3
AAD-1036-002/W	301/301	+++   +	48 (P)	13/61/NA	severe	5	normal	normal	postural tremor	no	NA		+ (4/4)   + (NA)	3
399-214/W	329/432	+++   +	56 (E)	27/73/74	NA	7	DBN	++, unilateral	resting and postural tremor	cognitive impairment	NA	dysphagia	NA   - (NA)	2
399-1013/M	190/428	+++   +	75 (P)	7/82/89	11	3	Nys, SAC	normal	no	no	global	dysphagia	NA   + (NA)	2
BMV-0695/M	22/427	+++   -	64 (P)	0/64/NA	4	1	Nys	normal	NA	NA	NA		+ (2/2)   + (NA)	4
AAR-895/W	45/405	+++   +	60 (tremor)	25/85/NA	23	6 (wheelchair at age 81)	Nys, FIX	normal	postural, orthostatic tremor	no	no atrophy	absent vibration sense at ankles	+ (2/2)   + (NA)	3
AAD-1352-003/W	63/426	+++   -	75 (P)	6/81/NA	9	4	Nys H/V	+	rigidity	no	cerebellar	decreased vibration sense at	+ (2/2)   +	4

<sup>a</sup>Key features are age onset  $\geq 45$  years, vertical nystagmus and episodic features. +: if sign is present and -: absent

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ID/Sex	FGF14 GAA sizes	Key features <sup>a</sup>   Dysarthria	Age at onset (y), E/P	Disease duration (y) / age at examination / death	SARA (max value 40)	Disability stage <sup>b</sup> (max value 7)	Eye movement anomalies	Pyramidal (reflexes ++ and/or EPR +)	Extra-Pyramidal signs	Cognitive / psychiatric manifestations	Brain MRI atrophy	Comments	Segregation   Exome <sup>c</sup>	Supportive criteria score <sup>d</sup>
												ankles, CCFS 0.776	(NA)	
AAD-1352-007/M	63/401	+++   +	55	15/70/NA	10.5	4	DBN	+	no	no	cerebellar		+	4
AAD-369-009/W	17/425	+++   -	50 (diplopia)	2/52/NA	mild	1	DBN	++	no	no	NA		NA   + (NA)	4
AAD-852-008/W	41/407	+ - +   -	52 (E)	8/60/NA	1	1	SAC	normal	no	no	no atrophy		NA   - (NA)	2
AAD-588-011/M	68/406	- - +   +	35	10/45/NA	NA	NA	Nys	++	no	no	cerebellar	<i>ITPR1</i>	+	2
AAD-588-009/W	17/393	+++   +	48	16/64/81	NA	5	DBN	normal	no	mood disorder	NA	<i>ITPR1</i>	+	3
AAD-1337-004/M	25/397	+ + -   -	60 (subacute onset)	8/68/NA	6.5	3	DBN	++, indifferent EPR	no	no	NA	visual vertigo, CCFS 0.849	NA   - (NA)	2
AAD-373-011/M	160/396	+ - -   +	40 (tremor)	19/59/NA	11.5	2	SAC	normal	no	no	NA	55 y for ataxia onset, CCFS	+	3

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ID/Sex	FGF14 GAA sizes	Key features <sup>a</sup>   Dysarthria	Age at onset (y), E/P	Disease duration (y) / age at examination / death	SARA (max value 40)	Disability stage <sup>b</sup> (max value 7)	Eye movement anomalies	Pyramidal (reflexes ++ and/or EPR +)	Extra-Pyramidal signs	Cognitive / psychiatric manifestations	Brain MRI atrophy	Comments	Segregation   Exome <sup>c</sup>	Supportive criteria score <sup>d</sup>
												0-941		
AAD-373-010/W	74/348	---   +	30 (P)	21/51/NA	moderate	3	Nys	++, Hoffman++, flex	NA	no	cerebellar	worse in the morning, no vertigo	+ (4/4)   + (NA)	3
AAD-373-008/M	75/331	- + +   +	38 (E) (dysarthria in the morning)	15/63/NA	11	3	NysH/V	normal	head tremor	no	cerebellar	subacute onset while playing tennis, intermittent diplopia	+ (4/4)   + (NA)	3
AAD-373-005/W	289/330	---   NA	33 (E)	40/73/NA	severe	5	Nys	normal	NA	depression	Important cerebellar atrophy, normal pontine	qualified as hysteric, falls, intermittent	+ (4/4)   + (NA)	3
AAD-430-029/M	25/387	---   NA	39 (P)	4/43/NA	mild	1	Nys H	++, EPR+	myoclonus	NA	NA		+ (7/7)   + (NA)	3
AAD-430-027/M	29/386	+ + -   NA	50 (P)	2/52/NA	mild	4	Nys H/V	++	NA	memory impairment	NA		+ (7/7)   + (NA)	3
AAD-430-	13/355	+ + -	67 (P)	10/77/86	16-5	4	Nys H/V	normal	NA	NA	NA	urinary	+	3

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023/W		NA										incontinence	(7/7)   + (NA)	
AAD-430-020/W	16/354	++ -   NA	72 (P)	4/76/NA	mild	3	Nys H/V	normal (no ankle reflex)	NA	NA	NA		+ (7/7)   + (NA)	3
AAD-430-016/W	15/351	+ - -   NA	65 (P)	16/81/96	moderate	4	no	normal (no ankle reflex)	dystonia LL	no	global	cataract	+ (7/7)   + (NA)	3
AAD-430-018/W	16/333	+ - +   NA	75 (P)	4/79/82	severe	5	Nys H	++	NA	NA	NA		+ (7/7)   + (NA)	3
AAD-430-015/M	15/328	+ - -   NA	55 (P)	19/74/79	moderate	4	Nys	++, EPR+	no	no	vermian, pontine		+ (7/7)   + (NA)	3
AAD-565-012/M	52/395	+++   NA	55 (diplopia)	9/64/NA	moderate	3	DBN	normal	NA	NA	vermian	triggered by food	NA   - (NA)	2
AAD-1064-001/M	15/336	+ - -   -	54 (P)	11/65/NA	12.5	4	slow saccades, DBN, LVG	spastic gait, upper limb reflexes ++	rigidity	no	vermian		+ (2/2)   + (NA)	4
AAD-1064-002/M	22/395	NA   -	60	23/83/86	NA	NA	NA	NA	NA	NA	NA		+ (2/2)   + (NA)	4
TEF-070-	44/393	- - -	30	23/53/NA	mild	2	slow	Increased, no ankle	severe	NA	no	diabetes,	NA   -	1

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001/W		NA	(tremor UL)				saccades	reflex	postural tremor (head, voice) rest tremor trunk		atrophy	fragile X excluded	(NA)	
AAD-1035-001/W	15/384	+-+   +	55	20/75/NA	9	3	SAC, Nys gaze evoked	normal	Froment sign	no	mild cerebellar	1h attacks triggered by alcohol, fatigue, coffee, good response to fampridine neuropathy (sensory, axonal), hypoacusia (otospongiosis)	NA   + (NA)	2
AAD-139-010/W	17/380	+-+   NA	54 (P)	18/72/80	moderate	3	Nys	++, unilateral EPR+	NA	NA	NA		NA   + (NA)	2
AAD-816-013/W	179/377	+++   -	51 (E)	13/64/NA	4-5	1	Nys, DBN	++	postural tremor	NA	NA	Intermittent diplopia	NA   - (NA)	3
399-283/M	24/376	+++   +	50 (E)	15/65/NA	12-5 (18 at	2	Nys H/V, LVG	++, calf fasciculations	no	no	vermian	dysphagia, exacerbati	NA   - (NA)	2

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					age 70)							on after general anesthesia		
AAD-1047-001/M	22/374	+++   +	63	12/75/NA	14	4	Nys H, V, DBN	normal	bradykinesia	frontal syndrome	NA	intermittent diplopia, sphincter disturbances	NA   + (NA)	3
AAD-1194-001/W	23/373	+ - +   NA	49 (P)	4/53/NA	12.5	3	SAC, Nys H	++, EPR+ bilat	NA	NA	vermian	NOP56	NA   + (NOP56)	1
AAD-1061-001/M	17/367	++ -   +	66 (sudden onset)	6/67/NA	13	3	DBN, SAC	normal	no	no	mild cerebellar		NA   + (NA)	2
AAD-1111/W	21/369	+ - +   -	68 (P)	2/70/NA	7	3	Nys H, DBN, SAC, FIX	normal	normal	normal	mild cerebellar		NA   + (NA)	3
BMV-0655/M	64/365	- + +   -	43 (diplopia)	0/43/NA	4	1	Nys DBN, H	normal (decreased ankle reflex)	no	NA	NA		NA   - (NA)	2
AAD-245-17/W	22/361	+ - +   -	70 (E)	7/77/NA	mild	2	NA	absent	NA	NA	mild cerebellar	vibration at ankles absent, intermittent diplopia, worse in the morning	+ (2/2)   + (NA)	4
AAD-245-	22/338	++ -	65 (P)	13/78/84	severe	5	Nys H/V	decreased	NA	NA	NA	possible	+	3

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12/M		+										optic atrophy and hypoaousia	(2/2)   + (NA)	
AAD-1184-001/M	64/353	+ - +   -	67 (P)	8/75/81	8.5	4	Nys	++, indifferent EPR	head tremor	no	cerebellar		NA   + (NA)	3
AAD-431-003/M	22/352	- - -   +	6 (P)	38/44/NA	moderate	2	SAC	++, EPR+ left, spastic legs	NA	NA	NA		- (1/3)   - (NA)	1
AAD-1096-001/W	15/346	+ - +   -	55 (E)	10/65/NA	2.5	2	SAC	normal, EPR+	no	no	cerebellar		NA   + (NA)	3
AAD-1112-001/W	15/343	+++   -	70 (vertigo)	7/77/NA	6	3	DBN, LVG	normal	postural tremor	no	cerebellar		+ (2/2)   + (NA)	5
AAD-1112-002/W	15/315	+ - -   NA	60 (P)	12/82/NA	NA	NA	NA	normal	NA	NA	NA		+ (2/2)   + (NA)	3
AAD-1349-004/W	116/338	- + +   +	42 (diplopia)	21/63/NA	5 (CCFS 0-76)	2	DBN	++, EPR+	head tremor, Froment sign	NA	mild cerebellar		+ (2/2)   + (NA)	3
AAD-1148-004/W	46/329	- - +   -	41 (diplopia)	5/46/NA	0	1	no	++, unilateral EPR+	no	no	normal		+ (2/2)   + (NA)	4
AAD-1148-	123/318	+++	47	8/55/NA	14/763	4	Nys, DBN,	normal	Froment	no	vermi	sense	+	5

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002/M		-	(diplopia)				alternate skew deviation		left		an	decreased vibration sense at ankles	(2/2)   + (NA)	
AAR-248-003/W	15/336	+ - -   +	55 (P)	17/75/90	severe	6	LVG	decreased	tremor	depression MMS28/30	cerebellar	cataract, only mild dysarthria	NA   + (NA)	2
AAD-1418-008/M	74/336	+ - +   NA	55 (E)	18/73/NA	mild	3	hypometric saccades	no ankle reflex	NA	NA	vermian	sensory-motor polyneuropathy	NA   - (NA)	1
AAD-1161/M	41/335	+ - +   +	45 (P)	23/68/NA	14	4	Nys, SAC, FIX	absent	NA	cognitive impairment	cerebellar and unspecific white matter changes		NA   + (NA)	2
AAD-945-001/M	15/335	+ - +   -	50 (E)	22/72/84	8	2	Nys, SAC, vertical ophthalmoplegia	normal	no	no	cerebellar	lip myokimias	NA   - (NA)	2
BMV-0252/M	22/333	+ - +   +	65 (E)	7/72/NA	9	3	Nys H	normal	normal	no	NA		NA   - (NA)	1
AAD-967-008/M	15/331	+ - -   -	60 (P, tremor at age 18)	17/77/87	mild	2	Nys H, Sacc	absent	tremor head, voice, UL	NA	no atrophy	hearing loss at age 50, bilateral cataract	+ (2/2)   + (NA)	4

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AAD-967-006/W	21/315	+ - -   +	60 (P)	19/79/86	27	6	SAC	decreased	no	frontal	global	weakness, wasting, vibration abolished, visual loss at age 60, axonal neuropathy	+ (2/2)   + (NA)	3
AAD-1304-002/W	15/330	+ - +   -	49 (E, diplopia)	15/64/NA	5	2	Nys H	normal	mild rigidity	no	no atrophy		+ (2/2)   + (NA)	4
AAD-922-008/W	22/320	+++   -	59 (E)	2/61/NA	9	2	Nys H/V	normal (no ankle reflex)	postural tremor	no	vermian		+ (3/3)   + (NA)	5
AAD-922-013/W	22/308	+ - +   -	50 (P)	5/55/NA	3-5	1	congenital Nys	++	NA	NA	NA	epilepsy	+ (3/3)   + (NA)	4
AAD-922-006/W	22/304	+++   -	66 (P)	2/68/NA	7	2	Nys H/V	++	postural tremor, Froment	no	no atrophy	presbycusis	+ (3/3)   + (NA)	4
AAD-1425/W	45/318	+++   +	60 (falls)	11/71/NA	17	5	DBN, slow saccades, LVG	normal	no	mild cognitive impairment	cerebellar	urinary symptoms, swallowing difficulties	NA   - (NA)	2
AAD-1019-	14/318	+ - +	77 (E)	4/81/91	9 (15 at	4	Nys H	decreased,	no	no	vermi	fasciculati	NA	3

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001/W		-			age 85)			indifferent EPR			an	ons	+ (NA)	
AAD-1320-002/M	14/484	+-+   +	53 (P)	18/71/NA	13.5	4	NysH, SAC	no ankle reflex	no	no	vermian	ptosis	NA   + (NA)	2
AAR-875-003/M	22/446	+-+   +	51 (P)	8/58/60	15 (at 54.7)	5	Nys, slow sacc	no ankle reflex	no	no	vermian	worsening with crisis	NA   + (NA)	2
AAR-740-001/M	15/441	+++   +	55 (P)	10/65/NA	11.5	4	Nys H, V	decreased	no	memory decline at age 55	cerebellar	dysphagia	NA   + (NA)	2
AAD-1044/W	120/430	+-+   NA	68 (P)	2/70/NA	mild	NA	NA	absent	NA	NA	NA	decreased vibration at ankles (ENMG normal)	NA   + (NA)	2
399-845/M	23/419	+++   NA	58/E (fever triggers ataxia)	7/65/71	7	NA	SAC	++	no	no	no atrophy		NA   - (NA)	1
399-654/M	14/417	+++   -	45 (P)	5/49/NA	mild	3	DBN	normal	no	NA	no atrophy		NA   + (NA)	3
AAD-1379-001/M	15/417	+++   -	55 (E)	6/61/NA	9.5	4	Square waves, LVG, SAC	decreased, unilateral	orthostatic tremor	no	global	dysphagia and hearing difficulties, CCFS 0.914	NA   + (NA)	3
399-660/W	21/415	--+   NA	42 (E, visual)	9/51/NA	4	3	Nys, SAC, LVG	++, left EPR+	head tremor	NA	vermian	maculopathy,	NA   +	2

<sup>a</sup>Key features are age onset  $\geq 45$  years, vertical nystagmus and episodic features. +: if sign is present and -: absent

<sup>b</sup>Functional impairment rated by the SPATAX disability score: 0 (no functional handicap), 1 (no functional handicap but signs at examination), 2 (mild, able to run, unlimited walking), 3 (moderate, unable to run, limited walking without aid), 4 (severe, walking with one stick), 5 (walking with two sticks), 6 (unable to walk, requiring a wheelchair), 7 (confined to a bed).

<sup>c</sup>Segregation in the family (concordance in affected individual samples) | Exome done (gene with pathogenic variant)

<sup>d</sup>Each of the five supportive criteria fulfilled counts one point: expansion size above 299 GAA, presence of the key triad, absence of dysarthria, co-segregation, and exome done without other causal variant found

Abbreviations. DBN: downbeat nystagmus; EPR: extensor plantar reflex (Babinski sign); E: episodic onset; F: Female; FIX: fixation instability; H: horizontal; LL: lower limbs; LVG: Limited vertical gaze; M: Male; NA: not available; Nys: nystagmus; P: permanent ataxia onset; RBD: REM behavioral disorder; SAC: saccadic pursuit; SARA: Scale for the Assessment and Rating of Ataxia; UL: upper limbs; V: vertical; ++: increased reflexes.

ID/Sex	FGF14 GAA sizes	Key features <sup>a</sup>   Dysarthria	Age at onset (y), E/P	Disease duration (y) / age at examination / death	SARA (max value 40)	Disability stage <sup>b</sup> (max value 7)	Eye movement anomalies	Pyramidal (reflexes ++ and/or EPR +)	Extra-Pyramidal signs	Cognitive / psychiatric manifestations	Brain MRI atrophy	Comments	Segregation   Exome <sup>c</sup>	Supportive criteria score <sup>d</sup>
			loss at 36)									intermittent leg weakness, gait spasticity	(NA)	
AAD-1240-001/W	15/409	+ - +   -	57 (E)	5/62/NA	7	2	SAC	normal	no	no	mild cerebellar	vibration diminished 2-5/8	NA   - (NA)	2
AAR-887-003/W	15/405	+ + -   -	58 (P)	10/68/NA	5.5	2	SAC, DBN	decreased LL	rigidity and hypokinetic	NA	cerebellar and pontine	optic atrophy	NA   + (NA)	3
399-707/M	17/402	+ - +   +	60 (E)	12/72/NA	21	4	Nys	Decreased, EPR+ right	parkinsonism rigidity, rest tremor, micrographia	no	cerebellar	dysphagia, vibration sense decreased, urinary troubles, no dysautonomia, CCFS 1·117	NA   - (NA)	1
AAD-1296-003/M	395/395	+ - +   +	47	9/56/NA	12	4	SAC	abolished	myokymias	no	cerebellar		NA   + (NA)	2
AAD-1288-003/M	187/395	+ - +   +	60	12/72/74	13	3	SAC	++	no	no	cerebellar		NA   + (NA)	2
399-795/W	14/393	+++	50 (E)	4/54/NA	modera	4	gaze evoked	normal	NA	NA	NA	hypoacusis	NA   -	2

<sup>a</sup>Key features are age onset  $\geq 45$  years, vertical nystagmus and episodic features. +: if sign is present and -: absent

<sup>b</sup>Functional impairment rated by the SPATAX disability score: 0 (no functional handicap), 1 (no functional handicap but signs at examination), 2 (mild, able to run, unlimited walking), 3 (moderate, unable to run, limited walking without aid), 4 (severe, walking with one stick), 5 (walking with two sticks), 6 (unable to walk, requiring a wheelchair), 7 (confined to a bed).

<sup>c</sup>Segregation in the family (concordance in affected individual samples) | Exome done (gene with pathogenic variant)

<sup>d</sup>Each of the five supportive criteria fulfilled counts one point: expansion size above 299 GAA, presence of the key triad, absence of dysarthria, co-segregation, and exome done without other causal variant found

Abbreviations. DBN: downbeat nystagmus; EPR: extensor plantar reflex (Babinski sign); E: episodic onset; F: Female; FIX: fixation instability; H: horizontal; LL: lower limbs; LVG: Limited vertical gaze; M: Male; NA: not available; Nys: nystagmus; P: permanent ataxia onset; RBD: REM behavioral disorder; SAC: saccadic pursuit; SARA: Scale for the Assessment and Rating of Ataxia; UL: upper limbs; V: vertical; ++: increased reflexes.

ID/Sex	FGF14 GAA sizes	Key features <sup>a</sup>   Dysarthria	Age at onset (y), E/P	Disease duration (y) / age at examination / death	SARA (max value 40)	Disability stage <sup>b</sup> (max value 7)	Eye movement anomalies	Pyramidal (reflexes ++ and/or EPR +)	Extra-Pyramidal signs	Cognitive / psychiatric manifestations	Brain MRI atrophy	Comments	Segregation   Exome <sup>c</sup>	Supportive criteria score <sup>d</sup>
		NA	diplopia)		te		Nys, DBN					ia, vertigo	(NA)	
AAD-958-001/W	84/386	+- -   +	60 (P)	5/65/69	13	3 (wheelchair at age 66)	SAC, LVG	++, EPR+	slight rigidity	NA	no atrophy		NA   + (NA)	2
BMV-0539/M	24/377	+- +   +	51 (E)	6/57/NA	6.5	2	SAC	++	no	no	cerebellar	dysphagia	NA   - (NA)	1
AAD-1201-001/M	302/372	+- +   +	54 (P)	6/62/NA	18	3	SAC	++	no	no	cerebellar	left ptosis, paroxysmic episodes of ataxia with acrocyanosis and facial flushes passing with bed rest, <i>ATP1A2</i>	NA   + (ATP1A2)	1
399-1053/W	75/356	+++   -	60	8/68	14	3	DBN	normal (no ankle reflex)	slight parkinsonism	depression at age 30	vermian		NA   + (NA)	3
AAD-1303-001/M	69/342	+- +   -	52 (E, diplopia)	6/58/NA	12	3	SAC	+, indifferent EPR	no	no	global	past history of alcohol and drugs, decreased vibration sense at	NA   + (NA)	3

<sup>a</sup>Key features are age onset  $\geq 45$  years, vertical nystagmus and episodic features. +: if sign is present and -: absent

<sup>b</sup>Functional impairment rated by the SPATAX disability score: 0 (no functional handicap), 1 (no functional handicap but signs at examination), 2 (mild, able to run, unlimited walking), 3 (moderate, unable to run, limited walking without aid), 4 (severe, walking with one stick), 5 (walking with two sticks), 6 (unable to walk, requiring a wheelchair), 7 (confined to a bed).

<sup>c</sup>Segregation in the family (concordance in affected individual samples) | Exome done (gene with pathogenic variant)

<sup>d</sup>Each of the five supportive criteria fulfilled counts one point: expansion size above 299 GAA, presence of the key triad, absence of dysarthria, co-segregation, and exome done without other causal variant found

Abbreviations. DBN: downbeat nystagmus; EPR: extensor plantar reflex (Babinski sign); E: episodic onset; F: Female; FIX: fixation instability; H: horizontal; LL: lower limbs; LVG: Limited vertical gaze; M: Male; NA: not available; Nys: nystagmus; P: permanent ataxia onset; RBD: REM behavioral disorder; SAC: saccadic pursuit; SARA: Scale for the Assessment and Rating of Ataxia; UL: upper limbs; V: vertical; ++: increased reflexes.

ID/Sex	FGF14 GAA sizes	Key features <sup>a</sup>   Dysarthria	Age at onset (y), E/P	Disease duration (y) / age at examination / death	SARA (max value 40)	Disability stage <sup>b</sup> (max value 7)	Eye movement anomalies	Pyramidal (reflexes ++ and/or EPR +)	Extra-Pyramidal signs	Cognitive / psychiatric manifestations	Brain MRI atrophy	Comments	Segregation   Exome <sup>c</sup>	Supportive criteria score <sup>d</sup>
												ankles		
AAD-1421-002/M	44/341	+++   -	60 (strabismus)	14/74/NA	7.5	2	DBN, skew deviation	normal	no	NA	vermian	diplopia, intermittent gait instability	NA   + (NA)	4
AAD-1411-002/M	23/340	+++   -	65 (E)	65/68/NA	11.5	4	DBN	normal	no	dysexecutive	no atrophy	hypoacusia at 58, vertigo, orthostatic hypotension, episodic ataxia episodes of 30 min triggered by movement : ataxia, diplopia, headache, nausea, vomiting	NA   - (NA)	3
399-1042/M	22/333	- ++   -	40 (visual)	10/50/NA	3.5	2	Nys H/V LVG	normal	no	no	flocculus		NA   + (NA)	3
AAD-1285-004/W	41/333	+++   -	60 (P)	12/72/NA	6	2	Nys H/V	++	rigidity and hypokinetic	no	NA		NA   + (NA)	4
AAD-1239-008/W	195/331	+ - +   -	57 (E)	10/67/NA	8	2	Nys	++, EPR+	rigidity and	no	vermian		NA   - (NA)	2

<sup>a</sup>Key features are age onset  $\geq 45$  years, vertical nystagmus and episodic features. +: if sign is present and -: absent

<sup>b</sup>Functional impairment rated by the SPATAX disability score: 0 (no functional handicap), 1 (no functional handicap but signs at examination), 2 (mild, able to run, unlimited walking), 3 (moderate, unable to run, limited walking without aid), 4 (severe, walking with one stick), 5 (walking with two sticks), 6 (unable to walk, requiring a wheelchair), 7 (confined to a bed).

<sup>c</sup>Segregation in the family (concordance in affected individual samples) | Exome done (gene with pathogenic variant)

<sup>d</sup>Each of the five supportive criteria fulfilled counts one point: expansion size above 299 GAA, presence of the key triad, absence of dysarthria, co-segregation, and exome done without other causal variant found

Abbreviations. DBN: downbeat nystagmus; EPR: extensor plantar reflex (Babinski sign); E: episodic onset; F: Female; FIX: fixation instability; H: horizontal; LL: lower limbs; LVG: Limited vertical gaze; M: Male; NA: not available; Nys: nystagmus; P: permanent ataxia onset; RBD: REM behavioral disorder; SAC: saccadic pursuit; SARA: Scale for the Assessment and Rating of Ataxia; UL: upper limbs; V: vertical; ++: increased reflexes.

ID/Sex	<i>FGF14</i> GAA sizes	Key features <sup>a</sup>   Dysarthria	Age at onset (y), E/P	Disease duration (y) / age at examination / death	SARA (max value 40)	Disability stage <sup>b</sup> (max value 7)	Eye movement anomalies	Pyramidal (reflexes ++ and/or EPR +)	Extra-Pyramidal signs	Cognitive / psychiatric manifestations	Brain MRI atrophy	Comments	Segregation   Exome <sup>c</sup>	Supportive criteria score <sup>d</sup>
									hypokinetic					
AAR-876-001/W	15/329	++-   -	74 (P)	6/80/NA	4-5	2	SAC, DBN	normal	no	no	NA	vertigo	NA   - (NA)	2
399-498/M	265/326	---   +	30 (P)	15/55/NA	13	4	Nys, slow	++	no	low performance at school	cerebellar	maculopathy, ptosis, <i>CACNA1A</i>	NA   + (CACNA1A)	1
AAR-880-003/W	15/324	+++   +	56 (P)	12/68/NA	10	4	DBN, LVG	decreased LL	Froment bilateral	no	vermian		NA   + (NA)	3
AAD-1360-005/W	17/322	+++   -	75 (E)	3/78/NA	6-5	2	SAC, DBN	normal	no	no	vermian		NA   + (NA)	4
399-995/M	26/322	+-   -	57 (P)	26/83/NA	17	4	SAC, LVG	normal	postural head tremor	normal	mild cerebellar	bulging eyes	NA   + (NA)	3
MHU-2444/W	15/319	---   NA	40 (vertigo)	12/44/48	mild	2	LVG	decreased, EPR+	chorea, dystonia	normal	vermian	<i>JPH3</i> , <i>HTT</i> , <i>TBP</i> (37/38) neg, sensitive neuronopathy	NA   + (NA)	2
AAR-159-016/W	22/317	--   +	38 (E)	5/43/NA	moderate	4	no	++, no ankle reflex	NA	NA	cerebellar and of corpus callos	urinary problems, fluctuating diplopia, dysphagia, diffuse	NA   + (NA)	3

<sup>a</sup>Key features are age onset  $\geq 45$  years, vertical nystagmus and episodic features. +: if sign is present and -: absent

<sup>b</sup>Functional impairment rated by the SPATAX disability score: 0 (no functional handicap), 1 (no functional handicap but signs at examination), 2 (mild, able to run, unlimited walking), 3 (moderate, unable to run, limited walking without aid), 4 (severe, walking with one stick), 5 (walking with two sticks), 6 (unable to walk, requiring a wheelchair), 7 (confined to a bed).

<sup>c</sup>Segregation in the family (concordance in affected individual samples) | Exome done (gene with pathogenic variant)

<sup>d</sup>Each of the five supportive criteria fulfilled counts one point: expansion size above 299 GAA, presence of the key triad, absence of dysarthria, co-segregation, and exome done without other causal variant found

Abbreviations. DBN: downbeat nystagmus; EPR: extensor plantar reflex (Babinski sign); E: episodic onset; F: Female; FIX: fixation instability; H: horizontal; LL: lower limbs; LVG: Limited vertical gaze; M: Male; NA: not available; Nys: nystagmus; P: permanent ataxia onset; RBD: REM behavioral disorder; SAC: saccadic pursuit; SARA: Scale for the Assessment and Rating of Ataxia; UL: upper limbs; V: vertical; ++: increased reflexes.

ID/Sex	FGF14 GAA sizes	Key features <sup>a</sup>   Dysarthria	Age at onset (y), E/P	Disease duration (y) / age at examination / death	SARA (max value 40)	Disability stage <sup>b</sup> (max value 7)	Eye movement anomalies	Pyramidal (reflexes ++ and/or EPR +)	Extra-Pyramidal signs	Cognitive / psychiatric manifestations	Brain MRI atrophy	Comments	Segregation   Exome <sup>c</sup>	Supportive criteria score <sup>d</sup>
											um	pain		
AAR-588-001/W	17/314	- + +   NA	19 (diplopia)	17/48/NA	8·5	2	Nys H/V	++, unilateral	toe dystonia	depression	cerebellar	onset in the context of anorexia, deafness since age 40	NA   + (NA)	2
AAR-901/M	64/314	+ + -   -	76 (asthenia)	6/82/84	7·5	3	DBN	normal	no	normal	mild cerebellar	decreased vibration sense at ankles	NA   - (NA)	2
AAD-1036-003/W	289/289	- - -   +	25 (tremor)	39/65/NA	16	6	Nys H	normal	postural tremor	no	NA	dysphagia	+ (4/4)   + (NA)	2
AAD-1349-003/W	15/278	- + +   +	40 (E)	23/63/NA	5	3	Nys V, DBN	normal reflexes, bilateral EPR+	postural tremor	NA	cerebellar	diplopia	+ (2/2)   + (NA)	2
AAD-1304-001/W	15/289	+ - +   -	65 (E, diplopia)	1/66/NA	5	NA	SAC	normal reflexes, unilateral EPR+	no	no	no atrophy		+ (2/2)   + (NA)	3
AAD-1328-005/M	15/297	+ - +   +	55 (P)	17/72/NA	7	3	gaze evoked Nys, SAC	normal	postural tremor	no	vermian	neuropathy (axonal, sensory), bipallidal calcifications, diplopia	- (1/2)   + (NA)	1

<sup>a</sup>Key features are age onset  $\geq 45$  years, vertical nystagmus and episodic features. +: if sign is present and -: absent

<sup>b</sup>Functional impairment rated by the SPATAX disability score: 0 (no functional handicap), 1 (no functional handicap but signs at examination), 2 (mild, able to run, unlimited walking), 3 (moderate, unable to run, limited walking without aid), 4 (severe, walking with one stick), 5 (walking with two sticks), 6 (unable to walk, requiring a wheelchair), 7 (confined to a bed).

<sup>c</sup>Segregation in the family (concordance in affected individual samples) | Exome done (gene with pathogenic variant)

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Abbreviations. DBN: downbeat nystagmus; EPR: extensor plantar reflex (Babinski sign); E: episodic onset; F: Female; FIX: fixation instability; H: horizontal; LL: lower limbs; LVG: Limited vertical gaze; M: Male; NA: not available; Nys: nystagmus; P: permanent ataxia onset; RBD: REM behavioral disorder; SAC: saccadic pursuit; SARA: Scale for the Assessment and Rating of Ataxia; UL: upper limbs; V: vertical; ++: increased reflexes.



ID/Sex	FGF14 GAA sizes	Key features <sup>a</sup>   Dysarthria	Age at onset (y), E/P	Disease duration (y) / age at examination / death	SARA (max value 40)	Disability stage <sup>b</sup> (max value 7)	Eye movement anomalies	Pyramidal (reflexes ++ and/or EPR +)	Extra-Pyramidal signs	Cognitive / psychiatric manifestations	Brain MRI atrophy	Comments	Segregation   Exome <sup>c</sup>	Supportive criteria score <sup>d</sup>
AAR-291-005/W	103/296	+- -   NA	64	NA/NA/87	NA	NA	NA	NA	NA	NA	NA		+ (2/2)   + (NA)	2
AAR-291-004/M	22/271	+- +   -	64 (E)	1/65/83	mild	NA	gaze evoked Nys	normal	no	depression	NA	episodes of diplopia, deafness	+ (2/2)   + (NA)	3
AAD-968-007/M	40/291	- - -   -	36 (tremor)	30/66/NA	8·5	2	SAC	normal reflexes, mild spasticity	tremor, rigidity	depression	mild cerebellar	fasciculations	+ (2/2)   + (NA)	3
AAD-968-001/M	17/277	+- -   +	50 (acute dysarthria)	4/54/NA	10	3	SAC	++, EPR+	bradykinesia, head tremor	no	mild cerebellar	increased emotivity, CCFS 0·970	+ (2/2)   + (NA)	2
-SAL-382-69/W	15/283	+- +   +	50 (P)	26/76/NA	30	6	Nys	bilateral EPR+	hypokinesia	no	NA	hypopallesia, diplopia, ptosis, diminished visual acuity, dysphagia, ATXN3	- (2/8)   - (ATXN3)	0
-SAL-382-80/W	15/259	- - +   -	35 (P)	5/40/NA	5·5	2	Nys	normal	no	no	NA	diplopia, ATXN3	- (2/8)   - (ATXN3)	1
AAD-907-003/M	15/279	- + +   NA	40 (E, diplopi)	5/45/NA	8·5	3	Nys H/V	absent reflexes at ankles	no	no	vermian		- (1/2)   -	0

<sup>a</sup>Key features are age onset  $\geq 45$  years, vertical nystagmus and episodic features. +: if sign is present and -: absent

<sup>b</sup>Functional impairment rated by the SPATAX disability score: 0 (no functional handicap), 1 (no functional handicap but signs at examination), 2 (mild, able to run, unlimited walking), 3 (moderate, unable to run, limited walking without aid), 4 (severe, walking with one stick), 5 (walking with two sticks), 6 (unable to walk, requiring a wheelchair), 7 (confined to a bed).

<sup>c</sup>Segregation in the family (concordance in affected individual samples) | Exome done (gene with pathogenic variant)

<sup>d</sup>Each of the five supportive criteria fulfilled counts one point: expansion size above 299 GAA, presence of the key triad, absence of dysarthria, co-segregation, and exome done without other causal variant found

Abbreviations. DBN: downbeat nystagmus; EPR: extensor plantar reflex (Babinski sign); E: episodic onset; F: Female; FIX: fixation instability; H: horizontal; LL: lower limbs; LVG: Limited vertical gaze; M: Male; NA: not available; Nys: nystagmus; P: permanent ataxia onset; RBD: REM behavioral disorder; SAC: saccadic pursuit; SARA: Scale for the Assessment and Rating of Ataxia; UL: upper limbs; V: vertical; ++: increased reflexes.

ID/Sex	FGF14 GAA sizes	Key features <sup>a</sup>   Dysarthria	Age at onset (y), E/P	Disease duration (y) / age at examination / death	SARA (max value 40)	Disability stage <sup>b</sup> (max value 7)	Eye movement anomalies	Pyramidal (reflexes ++ and/or EPR +)	Extra-Pyramidal signs	Cognitive / psychiatric manifestations	Brain MRI atrophy	Comments	Segregation   Exome <sup>c</sup>	Supportive criteria score <sup>d</sup>
			a)										(NA)	
AAD-683-014/M	21/276	--+   -	30 (E)	30/60/NA	3	2	Nys	normal	hypokinesia, dystonia	no	NA		-(2/3)   + (NA)	2
AAD-683-008/M	44/254	++ +   +	54 (E)	9/63/NA	NA	3	Nys	normal	no	no	no atrophy		-(2/3)   + (NA)	1
BMV-0165/W	127/261	+++   NA	70	3/73/NA	NA	1	normal	++	NA	no	global cerebellar and cortex		+(3/3)   + (NA)	2
AAD-1262-001/M	15/250	++ +   +	68 (subacute onset)	16/84/NA	14	4	Nys H, LVG	absent reflexes at ankles	hypokinesia	no	NA	diplopia, mild dysphagia, hearing loss vibration sensation absent at ankles, weaned alcoholism	+(3/3)   + (NA)	2
AAD-1262-002=399-932/M	15/250	+++   +	65 (P)	6/73/NA	11.5	4	Nys H, LVG	decreased	NA	depression	NA		+(3/3)   + (NA)	2
AAD-1329-002/M	22/273	+++   +	60 (dysarthria)	9/69/NA	7.5 (CCFS 0.847)	3	DBN	absent reflexes	no	NA	global mild	diplopia	NA   + (NA)	2
AAD-1160/M	64/273	+++   -	48 (P)	10/58/NA	14	3	normal	++, bilateral EPR+	postural	cognitive	cereb	spasticity	NA	1

<sup>a</sup>Key features are age onset  $\geq 45$  years, vertical nystagmus and episodic features. +: if sign is present and -: absent

<sup>b</sup>Functional impairment rated by the SPATAX disability score: 0 (no functional handicap), 1 (no functional handicap but signs at examination), 2 (mild, able to run, unlimited walking), 3 (moderate, unable to run, limited walking without aid), 4 (severe, walking with one stick), 5 (walking with two sticks), 6 (unable to walk, requiring a wheelchair), 7 (confined to a bed).

<sup>c</sup>Segregation in the family (concordance in affected individual samples) | Exome done (gene with pathogenic variant)

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Abbreviations. DBN: downbeat nystagmus; EPR: extensor plantar reflex (Babinski sign); E: episodic onset; F: Female; FIX: fixation instability; H: horizontal; LL: lower limbs; LVG: Limited vertical gaze; M: Male; NA: not available; Nys: nystagmus; P: permanent ataxia onset; RBD: REM behavioral disorder; SAC: saccadic pursuit; SARA: Scale for the Assessment and Rating of Ataxia; UL: upper limbs; V: vertical; ++: increased reflexes.

ID/Sex	<i>FGF14</i> GAA sizes	Key features <sup>a</sup>   Dysar- thria	Age at onset (y), E/P	Disease duration (y) / age at examination / death	SARA (max value 40)	Disabili- ty stage <sup>b</sup> (max value 7)	Eye movement anomalies	Pyramidal (reflexes ++ and/or EPR +)	Extra- Pyramid- al signs	Cognitive / psychiatric manifestations	Brain MRI atrophy	Comments	Segrega- tion   Exome <sup>c</sup>	Supportive criteria score <sup>d</sup>
		+							tremor	impairment	ellar	of the four limbs	+ (NA)	
AAR-289- 003/W	17/271	---   NA	27	3/70/NA	NA	NA	NA	NA	NA	NA	NA	<i>SPTLC1</i>	NA   + ( <i>SPTLC1</i> )	0
399-966/M	15/265	++-    -	56 (P)	9/64/73	8	3	SAC, DBN	absent reflexes	postural tremor UL	depression	cerebellar atrophy vermian predominant	sensory neuropathy, diffuse motor neuropathy, <i>RFC1</i>	NA   + ( <i>RFC1</i> )	1
AAR-173/M	15/263	--+   NA	36 (E)	8/44/NA	mild	2	Nys	NA	no	normal	NA	2 to 3 crises and drowsiness, <i>CACNA1A</i>	NA   + ( <i>CACNA1A</i> )	0
BMV- 0444/M	71/258	+++    +	71 (E)	6/77/NA	8	3	DBN	++ LL	no	depression	cerebellar	decreased vibration sense at ankles, diplopia	NA   - (NA)	1

<sup>a</sup>Key features are age onset  $\geq 45$  years, vertical nystagmus and episodic features. +: if sign is present and -: absent

<sup>b</sup>Functional impairment rated by the SPATAX disability score: 0 (no functional handicap), 1 (no functional handicap but signs at examination), 2 (mild, able to run, unlimited walking), 3 (moderate, unable to run, limited walking without aid), 4 (severe, walking with one stick), 5 (walking with two sticks), 6 (unable to walk, requiring a wheelchair), 7 (confined to a bed).

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Abbreviations. DBN: downbeat nystagmus; EPR: extensor plantar reflex (Babinski sign); E: episodic onset; F: Female; FIX: fixation instability; H: horizontal; LL: lower limbs; LVG: Limited vertical gaze; M: Male; NA: not available; Nys: nystagmus; P: permanent ataxia onset; RBD: REM behavioral disorder; SAC: saccadic pursuit; SARA: Scale for the Assessment and Rating of Ataxia; UL: upper limbs; V: vertical; ++: increased reflexes.

**Supplementary Table 2bis. Clinical characteristics of the individuals in families with GAA expansion in *FGF14* and pathogenic variant in another gene selected from supplementary Table 2.**

ID/Sex	<i>FGF14</i> GAA sizes	Additional gene	Key features <sup>a</sup>   Dysarthria	Age at onset (y), E/P	Disease duration (y) / age at examination / death	SARA (max value 40)	Disability stage <sup>b</sup> (max value 7)	Eye movement anomalies	Pyramidal (reflexes ++ and/or EPR +)	Extra-Pyramidal signs	Cognitive / psychiatric manifestations	Brain MRI atrophy	Additional signs
AAD-588-011/M	68/406	<i>ITPR1</i>	--+ +	35	10/45/NA	NA	NA	Nys	++	no	no	cerebellar	
AAD-588-009/W	17/393	<i>ITPR1</i>	+++ +	48	16/64/81	NA	5	DBN	normal	no	mood disorder	NA	
AAD-1194-001/W	23/373	<i>NOP56</i>	+ - +   NA	49 (P)	4/53/NA	12.5	3	SAC, Nys H	++, EPR+ bilat	NA	NA	vermian	
AAD-1201-001/M	302/372	<i>ATP1A2</i>	+ - +   +	54 (P)	6/62/NA	18	3	SAC	++	no	no	cerebellar	left ptosis, paroxysmic episodes of ataxia with acrocyanosis and facial flushes passing with bed rest
399-498/M	265/326	<i>CACNA1A</i>	--- +	30 (P)	15/55/NA	13	4	Nys, slow	++	no	low performance at school	cerebellar	maculopathy, ptosis
-SAL-382-69/W	15/283	<i>ATXN3</i>	+ - +   +	50 (P)	26/76/NA	30	6	Nys	bilateral EPR+	hypokinesia	no	NA	hypopallesthesia, diplopia, ptosis, diminished visual acuity, dysphagia
-SAL-382-80/W	15/259	<i>ATXN3</i>	--+ -	35 (P)	5/40/NA	5.5	2	Nys	normal	no	no	NA	diplopia
AAR-289-	17/271	<i>SPTLC1</i>	--- NA	27	3/70/NA	NA	NA	NA	NA	NA	NA	NA	NA

<sup>a</sup>Key features are age onset  $\geq 45$  years, vertical nystagmus and episodic features. +: if sign is present and -: absent

<sup>b</sup>Functional impairment rated by the SPATAX disability score: 0 (no functional handicap), 1 (no functional handicap but signs at examination), 2 (mild, able to run, unlimited walking), 3 (moderate, unable to run, limited walking without aid), 4 (severe, walking with one stick), 5 (walking with two sticks), 6 (unable to walk, requiring a wheelchair), 7 (confined to a bed).

<sup>c</sup>Segregation in the family (concordance in affected individual samples) | Exome done (gene with pathogenic variant)

<sup>d</sup>Each of the five supportive criteria fulfilled counts one point: expansion size above 299 GAA, presence of the key triad, absence of dysarthria, co-segregation, and exome done without other causal variant found

Abbreviations. DBN: downbeat nystagmus; EPR: extensor plantar reflex (Babinski sign); E: episodic onset; F: Female; FIX: fixation instability; H: horizontal; LL: lower limbs; LVG: Limited vertical gaze; M: Male; NA: not available; Nys: nystagmus; P: permanent ataxia onset; RBD: REM behavioral disorder; SAC: saccadic pursuit; SARA: Scale for the Assessment and Rating of Ataxia; UL: upper limbs; V: vertical; ++: increased reflexes.

ID/Sex	<i>FGF14</i> GAA sizes	Additional gene	Key features <sup>a</sup>   Dysarthria	Age at onset (y), E/P	Disease duration (y) / age at examination / death	SARA (max value 40)	Disability stage <sup>b</sup> (max value 7)	Eye movement anomalies	Pyramidal (reflexes ++ and/or EPR +)	Extra-Pyramidal signs	Cognitive / psychiatric manifestations	Brain MRI atrophy	Additional signs
003/W													
399-966/M	15/265	<i>RFC1</i>	++ -   -	56 (P)	9/64/73	8	3	SAC, DBN	absent reflexes	postural tremor UL	depression	cerebellar atrophy vermian predominant	sensory neuropathy, diffuse motor neuropathy
AAR-173/M	15/263	<i>CACNA1A</i>	-- +   NA	36 (E)	8/44/NA	mild	2	Nys	NA	no	normal	NA	2 to 3 crises and drowsiness

<sup>a</sup>Key features are age onset  $\geq 45$  years, vertical nystagmus and episodic features. +: if sign is present and -: absent

<sup>b</sup>Functional impairment rated by the SPATAX disability score: 0 (no functional handicap), 1 (no functional handicap but signs at examination), 2 (mild, able to run, unlimited walking), 3 (moderate, unable to run, limited walking without aid), 4 (severe, walking with one stick), 5 (walking with two sticks), 6 (unable to walk, requiring a wheelchair), 7 (confined to a bed).

<sup>c</sup>Segregation in the family (concordance in affected individual samples) | Exome done (gene with pathogenic variant)

<sup>d</sup>Each of the five supportive criteria fulfilled counts one point: expansion size above 299 GAA, presence of the key triad, absence of dysarthria, co-segregation, and exome done without other causal variant found

Abbreviations. DBN: downbeat nystagmus; EPR: extensor plantar reflex (Babinski sign); E: episodic onset; F: Female; FIX: fixation instability; H: horizontal; LL: lower limbs; LVG: Limited vertical gaze; M: Male; NA: not available; Nys: nystagmus; P: permanent ataxia onset; RBD: REM behavioral disorder; SAC: saccadic pursuit; SARA: Scale for the Assessment and Rating of Ataxia; UL: upper limbs; V: vertical; ++: increased reflexes.

**Supplementary Table 2ter. Clinical characteristics of the individuals with GAA compound heterozygous expansion in *FGF14* selected from supplementary Table 2.**

ID/Sex	<i>FGF14</i> GAA sizes	Key features <sup>a</sup>   Dysarthria	Age at onset (y), E/P	Disease duration (y) / age at examination / death	SARA (max value 40)	Disability stage <sup>b</sup> (max value 7)	Eye movement anomalies	Pyramidal (reflexes ++ and/or EPR +)	Extra-Pyramidal signs	Cognitive / psychiatric manifestations	Brain MRI atrophy	Comments
AAD-1149-001/W	448/448	- ++   +	27 (E)	5/32/NA	12.5	3	SAC, DBN*	normal	no	no	vermian	urinary urgency, ptosis
399-214/W	329/432	+++   +	56 (E)	27/73/74	NA	7	DBN	++, unilateral	resting and postural tremor	cognitive impairment	NA	dysphagia
AAD-1296-003/M	395/395	+ - +   +	47	9/56/NA	12	4	SAC	abolished	myokymias	no	cerebellar	
AAD-1036-003/W	289/289	- - -   +	25 (tremor)	39/65/NA	16	6	Nys H	normal	postural tremor	no	NA	dysphagia
AAD-1201-001/M	302/372	+ - +   +	54 (P)	6/62/NA	18	3	SAC	++	no	no	cerebellar	left ptosis, paroxysmic episodes of ataxia with acrocyanosis and facial flushes passing with bed rest, <i>ATPIA2</i>
AAD-373-005/W	289/330	- - +   NA	33 (E)	40/73/NA	severe	5	Nys	normal	NA	depression	Important cerebellar atrophy, normal pontine	qualified as hysteric, falls, intermittent
399-498/M	265/326	- - -   +	30 (P)	15/55/NA	13	4	Nys, slow	++	no	low performance at school	cerebellar	maculopathy, ptosis, <i>CACNA1A</i>
AAD-1036-002/W	301/301	+ - -   +	48 (P)	13/61/NA	severe	5	normal	normal	postural tremor	no	NA	

<sup>a</sup>Key features are age onset  $\geq 45$  years, vertical nystagmus and episodic features. +: if sign is present and -: absent

<sup>b</sup>Functional impairment rated by the SPATAX disability score: 0 (no functional handicap), 1 (no functional handicap but signs at examination), 2 (mild, able to run, unlimited walking), 3 (moderate, unable to run, limited walking without aid), 4 (severe, walking with one stick), 5 (walking with two sticks), 6 (unable to walk, requiring a wheelchair), 7 (confined to a bed).

<sup>c</sup>Segregation in the family (concordance in affected individual samples) | Exome done (gene with pathogenic variant)

<sup>d</sup>Each of the five supportive criteria fulfilled counts one point: expansion size above 299 GAA, presence of the key triad, absence of dysarthria, co-segregation, and exome done without other causal variant found

Abbreviations. DBN: downbeat nystagmus; EPR: extensor plantar reflex (Babinski sign); E: episodic onset; F: Female; FIX: fixation instability; H: horizontal; LL: lower limbs; LVG: Limited vertical gaze; M: Male; NA: not available; Nys: nystagmus; P: permanent ataxia onset; RBD: REM behavioral disorder; SAC: saccadic pursuit; SARA: Scale for the Assessment and Rating of Ataxia; UL: upper limbs; V: vertical; ++: increased reflexes.

**Supplementary Table 3. Eye-movement study with video-oculography in 27 *FGF14* carriers above 240 GAA**

ID	Largest GAA number	Age (years)	H Sac lat	H Sac vel	H Sac gain	V Sac vel	Up Sac gain	Down Sac gain	AS	H pursuit	Up-Down pursuit	SWJ	DBN score	GEN	Diplopia
AAD-1149-001	448	31	N	N	N (V+)	N-	N	Hypo	1	2	NA	1	1	0	ASD, Eso
AAD-1240-001	409	63	N	N	N	N	N	N	NA	0	0	1	0	0	0
AAR-887-003	405	67	N	N	N	N	Hypo	Hypo	2	2	2-3	1	2	0	0
AAD-1337-004	397	69	N	N	Hypo (V+)	N	N	N	1	2	2-3	1	2	1	0
AAD-1288-003	395	66	N	N	N (V+)	N	N	N	1	2	1-1	1	0	0	0
AAD-900-024	395	59	N	N	N	N	N	Hypo	1	3	2-2	2	0	1	Exo
-399-795	393	54	I	N	Hypo	N	NA	NA	0	3	3-3	1	1	1	ASD
AAD-958-001	386	69	I	N	N	N	N	Hypo (V+)	3	3	NA	1	0	0	0
AAD-1111-001	369	74	N	N	Hypo (V+)	N	N	Hypo (V+)	1	3	3-3	1	2	1+RN	ASD, Eso
BMV-0655	365	34	N	N	N (V+)	N	Hypo	N	1	2	0-3	2	3	1	0
AAD-1096-001	346	62	N	N	Hypo	N	NA	NA	0	0	0	1	0	0	0
AAD-1421-002	341	72	N	N	N	N	N	N	1	1	1-2	2	1	0	ASD
AAD-1411-002	340	67	N	N	N	N	N	Hypo	2	2	2-3	1	2	0	0
AAD-1349-004	338	60	N	N	N	N	Hypo	Hypo (V+)	0	2	2-3	1	2	1+RN	ASD
AAD-1418-008	336	73	N	N	N	N	Hypo	Hypo	0	2	NA	1	0	0	0
AAD-1285-004	333	72	N	N	N	N	N	N	1	3	3-3	1	1	1+RN	Eso
-399-1042	333	49	N	N	N (V+)	N	N	Hypo	NA	3	3-3	1	0	1+RN	0
AAD-967-008	331	78	I	N	N	N	N	N	3	3	NA	1	0	1	0
AAR-876-001	329	79	N	N	N	N	N	N (V+)	1	2	2-3	1	2	1	0
AAR-880-003	324	64	N	N	N	N	N	N	2	3	3-3	1	3	1	ASD
AAD-1360-005	322	78	I	N	N	N	Hypo	N (V+)	1	2	2-3	1	2	0	ASD
AAD-1148-002	318	54	N	N	Hypo	N	N	N	1	3	2-3	1	2	1+RN	ASD, Exo
AAD-683-014	276	61	N	N	N	N	N	Hypo	1	1	1-2	2	2	0	0
AAD-1329-002	273	70	N	N	Hypo (V+)	N	N	N	0	1	1-NA	1	1	0	ASD
-399-1079	247	64	N	N	N	N	N	N (V+)	0	1	NA	1	0	0	H
AAD-1378-001	244	74	I	N	N	N	N	N	NA	2	2-3	1	1	1	ASD, Eso
AAD-1316-004	243	71	I	S	Hypo (V+)	N-	N	N	1	1	1-1	1	0	1	Hypertropia RE
	<b>Large Allele Size</b>	<b>Age</b>	<b>H Sac lat</b>	<b>H Sac vel</b>	<b>H Sac gain</b>	<b>V Sac vel</b>	<b>Up Sac gain</b>	<b>Down Sac gain</b>	<b>AS</b>	<b>H pursuit</b>	<b>Up: Down pursuit</b>	<b>SWJ</b>	<b>DBN</b>	<b>GEN</b>	<b>Diplopia</b>
	<b>Summary (median or proportion)</b>	338 (IQR: 323–389.5)	67 (IQR: 60.5–72)	<b>I:</b> 6/27 (22%) <b>S:</b> 1/27 (4%)	<b>N (V+):</b> 4/27 (15%) <b>Hypo:</b> 7/27 (26%)	<b>S:</b> 0/27 (0%)	<b>Hypo:</b> 5/25 (20%)	<b>N (V+):</b> 3/25 (12%) <b>Hypo:</b> 5/24 (21%) <b>Hypo:</b> 10/25 (40%)	<b>1:</b> 13/24 (54%) <b>2:</b> 11/27 (41%) <b>3:</b> 9/27 (33%)	<b>1:</b> 5/27 (19%) <b>2:</b> 3/22 (14%) <b>2/3:</b> 4/27 (15%) <b>3:</b> 9/27 (33%)	<b>1:</b> 23/27 (85%) <b>2:</b> 9/27 (33%) <b>2/3:</b> 17/22 (77%)	<b>1:</b> 6/27 (22%) <b>2:</b> 9/27 (33%) <b>3:</b> 2/27 (7%)	14/27 (52%)	14/27 (52%)	
	<b>Summary (median or proportion) in ≥ 300 GAA carriers</b>	343.5 (IQR: 333–394.5)	66.5 (IQR: 59.3–72)	<b>I:</b> 4/22 (18%) <b>S:</b> 0/22 (0%)	<b>N (V+):</b> 4/22 (18%) <b>Hypo:</b> 5/22	<b>S:</b> 0/22 (0%)	<b>Hypo:</b> 5/20 (25%)	<b>N (V+):</b> 2/20 (10%) <b>Hypo:</b> 9/20	<b>1:</b> 11/20 (55%) <b>2:</b> 5/20	<b>1:</b> 1/22 (5%) <b>2:</b> 10/22 (45%)	<b>1:</b> 1/18 (6%) <b>2:</b> 15/18	<b>1:</b> 19/22 (86%) <b>2:</b> 3/22	<b>1:</b> 4/22 (18%) <b>2:</b> 8/22	12/22 (55%)	10/22 (45%)

Horizontal (H) saccade (Sac) latency (lat) scored as normal (N): [130-220ms], increased (I): [220-250ms]; Horizontal saccade gain scored as N: [0.82-1.06], hypometria (Hypo): < 0.82, V+ (increased variability): sd > 0.11; Up saccade gain scored as N: [0.69-1.02], hypometria: < 0.69, V+ (increased variability): sd > 0.21; Down saccade gain scored as N: [0.85-1.16], hypometria: < 0.85, V+ (increased variability): sd > 0.20; Antisaccades (AS) scored as 0: normal (< 25%), 1: slightly increased (25-50%), 2: moderately increased: (50-75%), greatly increased (> 75%); Pursuit scored as 0: normal, 1: slightly saccadic, 2: clearly saccadic, 3: very saccadic or absent; Square-wave jerks (SWJ) scored as 1: few or absent, 2: increased; Downbeat nystagmus (DBN) severity score was 0: absent, 1: moderate or with activation maneuver, 2: spontaneous and marked, 3: symptomatic; For others signs: 0: absent and 1: present

Abbreviations: AS: antisaccades; ASD: alternate skew deviation; DBN: downbeat nystagmus; Eso: esotropia, Exo: exotropia, GEN: gaze-evoked nystagmus; H: horizontal; IQR: interquartile range; N: normal (N- for inferior limit); NA: not available; RE: right eye; +RN: with rebound nystagmus; S: slow velocity; Sac: saccade; SWJ: square-wave jerks; V: vertical; vel: velocity

					(23%)			(45%)	(25%)	3: 9/22 (41%)	(83%)	(14%)	(36%) 3: 2/22 (9%)		
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Eye movement recordings were abnormal in 21/22 (95.5%, supplementary Table 3). Main abnormalities were saccadic smooth pursuit 20/22 (90.9%) more pronounced in the vertical downward direction and nystagmus in 17/22 (77.3%). Downbeat nystagmus was present in 14/22 (63.6%) and symptomatic in only 2/22 (9.1%). Gaze evoked nystagmus was present in 12/22 (54.5%) associated with a rebound nystagmus in 5/22 (22.7%). Diplopia was present in 10/22 (45.5%) mainly caused by alternating skew deviation in 8/22 (36.4%). A moderate to important increase of square-wave jerks was present in only 3/22 (13.6%). No hypermetria was noted but horizontal hypometria was measured in 5/22 (22.7%) and vertical hypometria 11/22 (50%) (mainly downward). Antisaccade error rates were abnormal in 16/20 (80%) (slight increase in 11/20 (55%), moderate to severe increase in 5/20 (25%)). Saccade latencies were slightly increased in 6/22 (27.3%). A slight decrease of horizontal saccade velocities was noted in only 1/22 patient (4.5%).

Horizontal (H) saccade (Sac) latency (lat) scored as normal (N): [130-220ms], increased (I): [220-250ms]; Horizontal saccade gain scored as N: [0.82-1.06], hypometria (Hypo): < 0.82, V+ (increased variability): sd > 0.11; Up saccade gain scored as N: [0.69-1.02], hypometria: < 0.69, V+ (increased variability): sd > 0.21; Down saccade gain scored as N: [0.85-1.16], hypometria: < 0.85, V+ (increased variability): sd > 0.20; Antisaccades (AS) scored as 0: normal (< 25%), 1: slightly increased (25-50%), 2: moderately increased: (50-75%), greatly increased (> 75%); Pursuit scored as 0: normal, 1: slightly saccadic, 2: clearly saccadic, 3: very saccadic or absent; Square-wave jerks (SWJ) scored as 1: few or absent, 2: increased; Downbeat nystagmus (DBN) severity score was 0: absent, 1: moderate or with activation maneuver, 2: spontaneous and marked, 3: symptomatic; For others signs: 0: absent and 1: present  
Abbreviations: AS: antisaccades; ASD: alternate skew deviation; DBN: downbeat nystagmus; Eso: esotropia, Exo: exotropia, GEN: gaze-evoked nystagmus; H: horizontal; IQR: interquartile range; N: normal (N- for inferior limit); NA: not available; RE: right eye; +RN: with rebound nystagmus; S: slow velocity; Sac: saccade; SWJ: square-wave jerks; V: vertical; vel: velocity



**Supplementary Table 4. Genes with another causal variant than FGF14 in 298 index individuals with cerebellar ataxia**

<b>Gene</b>	<b>Individuals with another known genetic cause (298/845)</b>
<i>ATXN3</i>	30
<i>SPG7</i>	28
<i>PRKCG</i>	17
<i>STUB1</i>	16
<i>CACNA1A</i>	15
<i>SACS</i>	12
<i>ATXN2</i>	11
<i>RFC1</i>	11
<i>AFG3L2</i>	10
<i>FXN</i>	9
<i>SYNE1</i>	9
<i>ATXN1</i>	8
<i>ITPR1</i>	8
<i>SETX</i>	8
<i>ANO10</i>	6
<i>NOP56</i>	6
<i>ADCK3</i>	4
<i>ATM</i>	4
<i>ATXN7</i>	4
<i>CYP7B1</i>	3
<i>KCND3</i>	3
<i>PNPT1</i>	3
<i>POLG</i>	3
<i>SPTAN1</i>	3
<i>SPTBN2</i>	3
<i>ALDH18A1</i>	2
<i>APTX</i>	2
<i>CAPN1</i>	2
<i>HEXA</i>	2
<i>KCNC3</i>	2
<i>KIF1C</i>	2
<i>NPTX1</i>	2
<i>PLA2G6</i>	2
<i>PNPLA6</i>	2
<i>PRDX3</i>	2
<i>ALS2</i>	1
<i>ANO3</i>	1
<i>ATPIA2</i>	1
<i>ATPIA3</i>	1
<i>ATP5MK</i>	1
<i>CACNA1G</i>	1
<i>CEP290</i>	1
<i>CHCHD10</i>	1
<i>CLN5</i>	1
<i>COG1</i>	1
<i>DNAJC6</i>	1
<i>DNMT1</i>	1
<i>EIF2B2</i>	1
<i>ERCC5</i>	1
<i>GBA2</i>	1
<i>GRN</i>	1
<i>HSD17B4</i>	1
<i>IRF2BPL</i>	1
<i>KCNA1</i>	1
<i>KIF1A</i>	1
<i>KIF5A</i>	1
<i>LMNB2</i>	1
<i>MT-ATP6</i>	1
<i>MT-CO3</i>	1
<i>MT-TL1</i>	1
<i>NDRG1</i>	1
<i>NPC1</i>	1
<i>PNKP</i>	1
<i>RNF216</i>	1
<i>SAMD9L</i>	1
<i>SLC1A3</i>	1
<i>SLC25A46</i>	1

<i>SNX14</i>	1
<i>SPAST</i>	1
<i>SPG11</i>	1
<i>SPTLC1</i>	1
<i>TRPC3</i>	1
<i>TTBK2</i>	1
<i>TTPA</i>	1
<i>TWNK</i>	1
<i>UBQLN2</i>	1
<i>USH2A</i>	1
<i>VPS13A</i>	1
<i>VPS41</i>	1