Research Square

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Very Low Frequency of SCA27B Among Undiagnosed Cerebellar Ataxia Patients in Peru

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Abstract

Background: Spinocerebellar ataxia type 27B (SCA27B) is a recently described autosomal dominant ataxia caused by a pathogenic GAA repeat expansion in the *FGF14* gene. The frequency and the distribution of *FGF14* repeat alleles remain largely unexplored in underrepresented populations, particularly in Latin America.

Objective: To investigate the frequency of SCA27B and characterize the allelic distribution of the GAA-*FGF14* microsatellite locus in a Peruvian cohort of individuals with ataxia of unknown molecular etiology.

Methods: We analysed a cohort of affected individuals evaluated at a referral center for neurogenetic disorders in Peru. All individuals underwent standardized neurological assessment, as well as molecular analysis of the GAA-*FGF14* repeat locus using repeat-primed and long-range PCR-based approaches.

Results: One genetically confirmed case of SCA27B was identified, corresponding to a frequency of 0.59% (1/167) in this cohort. Most alleles (91.61%) were within the non-pathogenic range (<250 repeats), 85.3% of them with less than 30 repeats. Notably, 16.17% of individuals carried non-GAA-pure expanded alleles with a complex $[(GAA)_n(GCA)_m]_z$ repeat structure, currently considered non-pathogenic. These alleles were not associated with a typical SCA27B phenotype.

Conclusions: SCA27B appears to be a rare cause of hereditary ataxia in the Peruvian population. The high prevalence of non-GAA-pure expanded alleles and the distinct *FGF14* allelic distribution suggest population-specific genetic variability, possibly influenced by Native American ancestry. These findings highlight the importance of investigating diverse populations to better understand the genetic mechanisms underlying SCA27B and other repeat expansion-associated ataxias.

Introduction

Spinocerebellar ataxia type 27B (SCA27B) is a recently described form of late-onset dominant ataxia caused by an intronic GAA repeat expansion in the *FGF14* gene [1, 2]. Since its initial description, SCA27B has emerged as a relatively frequent cause of late-onset ataxia in several European [2–5] and Asian [6–8] cohorts, with frequencies similar to other common spinocerebellar ataxias (SCAs), including MJD/SCA3, SCA1, SCA6, and SCA2. The clinical presentation of SCA27B (OMIM: 620174) is characterized by a late-onset, slowly progressive cerebellar syndrome typically presenting with gait and limb ataxia, as well as downbeat nystagmus [5, 9]. More than half of affected individuals also exhibit episodic ataxia and dizziness [10].

The sequence composition of the *FGF14* GAA repeat is an important determinant of repeat stability and pathogenicity. While pathogenic SCA27B repeat expansions are generally composed of pure GAA motifs, complex non-GAA-pure configurations such as $[(GAA)_n(GCA)_m]_z$ repeats have been reported, particularly in some European [2, 5] and more commonly in Asian populations [7, 8]. Interrupted expansions are not associated with the SCA27B phenotype and are currently classified as non-pathogenic or of uncertain

clinical significance [11, 12]. Similar to what has been described with the GAA repeat in *FXN* causing Friedreich's ataxia, repeat interruptions may confer increased stability to the expanded tract, reducing its propensity for further expansion and limiting pathogenicity [13].

SCA27B epidemiological data from South American populations remains extremely limited. The few studies on SCA27B in the Latin American region are mostly limited to a Brazilian [14] and a Chilean cohort [15] with an occurrence of 9% and 16%, respectively. In this study, we aimed to estimate the frequency of SCA27B in a cohort of Peruvian individuals with hereditary ataxia of unknown genetic cause followed at a tertiary referral neurogenetic center. Using a combination of long-range PCR, bidirectional repeat-primed PCR, and Sanger sequencing, we characterized the size and sequence composition of the GAA-*FGF14* repeat region.

Materials and Methods

Subjects and samples

A total of 167 DNA samples and their associated data (clinical and demographic) were obtained from the Neurogenetics - DNA Bank at the *Instituto Nacional de Ciencias Neurologica*s (BADN-INCN). These samples correspond to ataxic individuals followed-up at a national reference ataxic center between 1996 and 2024. Subjects were selected based on the following criteria: i) born in Peru, (ii) with a clinical diagnosis of an ataxic syndrome, (iii) proband and family members lack a definitive molecular diagnosis for the main SCAs including SCA1, SCA2, MJD/SCA3, SCA6 and SCA7, and (iv) availability of both clinical data and DNA aliquot stored in the BADN-INCN. In all included cases, common acquired causes of ataxia were systematically excluded through standardized evaluation, including detailed history, neurological examination, laboratory testing, and neuroimaging when available. Routine screening encompassed basic serum biochemistry, complete blood count, erythrocyte sedimentation rate, thyroid-stimulating hormone, vitamins B12 and E levels, VDRL, HIV serology, qualitative urinalysis, chest radiography, and abdominal ultrasonography depending on suspected diagnosis.

From a total of 392 eligible ataxic individuals, 149 were excluded due to prior genetic ataxia diagnosis, and 76 due to not meeting the selection criteria. All samples provided by the BADN-INCN have specific authorization for future research use through appropriate informed consent. This study was approved by the Institutional Review Board at the *Instituto Nacional de Ciencias Neurológicas* (040-2023-CIEI-INCN).

GAA- FGF14 repeat genotyping

All DNA samples (n = 167) were genotyped for the GAA-*FGF14* microsatellite locus following an established diagnostic workflow [16]. Genotyping was initially performed using long-range fluorescent PCR (LR-PCR) and bidirectional repeat-primed PCR (RP-PCR). Sanger sequencing was selectively performed, when required, according to the workflow, to characterize the repeat motif composition (pure GAA versus interrupted repeats).

Alleles were classified according to repeat size at the *FGF14* locus, considering only pure GAA repeat expansions as pathogenic. Alleles containing 249 GAA repeats or fewer were considered within the normal range. Alleles between 250 and 300 pure GAA repeats were classified as likely pathogenic with reduced penetrance, whereas alleles with more than 300 pure GAA repeats were classified as pathogenic and highly penetrant [1–3]. Non-pure repeat expansions, including interrupted motifs such as [(GAA)□(GCA)□], were considered non-pathogenic expansions based on current evidence indicating a lack of disease association [5, 12, 17].

Statistical Analysis

The allelic distribution of the GAA-*FGF14* microsatellite was represented using both vertical bar charts and swarm plots to illustrate allele dispersion, while absolute frequencies of each allele were summarized in table format. Descriptive analyses were performed to summarize allele sizes and frequencies. Comparisons between groups were conducted according to repeat motif composition, distinguishing individuals harboring pure GAA alleles from others with non-pure (interrupted) alleles. Continuous variables were compared using the Wilcoxon rank-sum test, while categorical variables were analyzed using the chi-square test or Fisher's exact test when expected cell counts were fewer than five. All statistical analyses and graphical representations were generated using the open-source R software (version 4.2.2).

Results

Cohort Characteristics

A total of 167 index ataxic participants with a clinical diagnosis of ataxic syndrome without a definitive molecular diagnosis were included in the study. Of the total cohort, 45.5% (76/167) were female. The mean age at onset was 37.4 ± 18.8 years, with a mean disease duration of 6.4 ± 5.7 years. Demographics and clinical description of the population are summarized in Table 1. The study population originated from 17 out of 24 regions of Peru, with 72.22% of cases coming from the Lima/Callao region. The geographic distribution of participants by region of origin is illustrated in Fig. 1.

Table 1
Demographic and clinical characteristics of the cohort

Female sex	**Total (n = 167)**
	76/167 (45.5%)
Age at evaluation	44.2 ± 18.9
Age at onset	37.3 ± 19.6
Disease duration (years)	6.9 ± 6.5
Positive family history	41/141 (29.1%)
Cerebellar clinical features	
Truncal ataxia	131/142 (92.3%)
Limb ataxia	135/141 (95.7%)
Cerebellar dysarthria	111/138 (80.4%)
Ocular motor abnormalities	67/132 (50.8%)
Extracerebellar features	
Hyperreflexia	56/126 (44.4%)
Spasticity	17/123 (13.8%)
MRI features	
Cerebellar atrophy	70/101 (69.3%)
Ataxia Rating scales	
SARA	13.6 ± 7.0
NESSCA	9.8 ± 3.6

Data are reported as mean ± standard deviation for quantitative variables and for qualitative variables are shown as frequencies (percentages). Abbreviations: SARA: Scale for the Assessment and Rating of Ataxia (0–40 points). NESSCA: Neurological Examination Score for the Assessment of Spinocerebellar Ataxias (0–40 points). MRI: magnetic resonance imaging.

Frequency of SCA27B and FGF14 allele subgroups

Molecular analysis of the GAA-*FGF14* repeat identified one individual (0.6%, 1/167) carrying a pathogenic expansion consistent with a diagnosis of SCA27B. This participant carried a 307-repeat allele with a pure GAA motif.

The remaining 166 individuals (99.4%), who tested negative for SCA27B, were subsequently classified into two molecular subgroups based on repeat size and motif composition. Subgroup A comprised 139 participants (83.7%, 139/166) carrying alleles within the normal range (< 250 repeats). Subgroup B

included 27 participants (16.3%, 27/166) carrying expanded alleles exceeding 249 triplets with a non-GAA-pure structure. These alleles exhibited complex [(GAA)□(GCA)□] repeat motifs and were not classified as pathogenic under current SCA27B criteria. Comparative analyses revealed no significant differences in demographic or clinical characteristics between Subgroup A and Subgroup B (Table 2).

Table 2
Demographic and clinical characteristics of the subgroups A and B

n	**Subgroup A** **< 250 repeats** **n (%)**	**Subgroup B non-GAA-pure structure** **n (%)**	***p* value**
	139	**27**	**-**
Female sex	63/139 (45.3%)	12/27 (44.4%)	0.933
Age at evaluation	44.7 ± 18.6	39.1 ± 19.2	0.257
Age at onset	37.5 ± 19.6	33.8 ± 18.5	0.380
Disease duration (years)	7.2 ± 6.8	5.3 ± 4.8	0.290
Positive family history	35/119 (29.4%)	6/21 (28.6%)	0.938
Cerebellar clinical features			
Truncal ataxia	109/120 (90.8%)	21/21 (100.0%)	0.148
Limb ataxia	113/119 (95.0%)	21/21 (100.0%)	0.293
Cerebellar dysarthria	93/117 (79.5%)	17/20 (85.0%)	0.567
Ocular motor abnormalities	56/111 (50.5%)	10/20 (50.0%)	0.976
Extracerebellar features			
Hyperreflexia	47/105 (44.8%)	8/20 (40.0%)	0.694
Spasticity	14/105 (13.3%)	3/17 (17.6%)	0.634
MRI features			
Cerebellar atrophy	60/85 (70.6%)	9/15 (60%)	0.669
Rating scales			
SARA	13.6 ± 6.7	13.7 ± 8.3	0.652
NESSCA	9.8 ± 3.5	9.6 ± 3.8	0.699

Data are reported as mean ± standard deviation for quantitative variables and for qualitative variables are shown as frequencies (percentages). Abbreviations: SARA: Scale for the Assessment and Rating of Ataxia (0–40 points). NESSCA: Neurological Examination Score for the Assessment of Spinocerebellar Ataxias (0–40 points). MRI: magnetic resonance imaging.

GAA- FGF14 Allelic Distribution

A total of 334 alleles were analyzed. We identified 306 normal-range alleles (< 250 repeats) with repeats ranging from 7 to 139 repeats, with 285 alleles (85.33%) being < 30 repeats. The most frequent allele was the 8-repeat allele, accounting for 25.1% (84/334) of the total, followed by the 9-repeat allele (18.9%, 63/334) and the 15-repeat allele (7.5%, 25/334), as shown in Fig. 2A.

We also identified 28 expanded alleles (> 250 repeats) ranging from 307 to 332 repeat units. The pathogenic SCA27B allele was composed of a pure GAA expansion (0.3%, 1/334), whereas all other 27 expanded alleles carried the non-GAA-pure [(GAA)(GCA)] repeat motif (8.1/%, 27/334) **(**Fig. 2B**)**.

One SCA27B case in this Peruvian cohort

An 84-year-old right-handed Peruvian retired professor, with no known family history of ataxia (both parents born in Europe; Fig. 3), presented with late-onset progressive imbalance. Her medical history was notable for hypertension, seborrheic dermatitis, colon resection for premalignant villous adenoma (age 65), and left nephrectomy for urothelial carcinoma (age 80).

Gait instability began at age 78 and progressed gradually. By age 80, she reported visual difficulties while reading. At age 82, recurrent falls required walker assistance, and bilateral hearing loss necessitated hearing aids. At age 83, she developed exertional fatigue, and by 84 years, handwriting deteriorated. She also described episodic dizziness and fluctuating dysarthria lasting several hours.

Neurological examination at age 84 revealed preserved cognition and ambulation with walker support. Strength and primary sensory modalities were normal. Lower-limb hyperreflexia was present and plantar reflexes were downgoing. Oculomotor evaluation showed increased saccadic latency and primary gaze downbeat nystagmus. Mild axial and appendicular ataxia with upper-limb dysmetria was observed, without clear cerebellar dysarthria. The total SARA score was 12.5/40 and NESSCA score was 13/40, reflecting gait impairment, ocular findings, mild sensory involvement, and urinary urgency.

Extensive autoimmune and paraneoplastic testing was negative, however β2-microglobulin was mildly elevated (2.8 mg/L). Tumor markers were unremarkable aside from marginal CYFRA 21 − 1 elevation considered age-related. Video-oculography confirmed downbeat nystagmus and bilateral vestibular involvement. EMG was normal. Audiovestibular testing demonstrated symmetric sensorineural hearing loss consistent with presbycusis and normal caloric responses. Brain MRI revealed predominant cerebellar hemispheric atrophy with hyperintense signals in superior cerebellar peduncles (SCPs), alongside periventricular white matter hyperintensities compatible with chronic microvascular disease **(**Fig. 4**)**. Ataxia panel for SCA2, MJD/SCA3 and SCA6 were negative. Genetic testing identified a heterozygous *FGF14* GAA repeat expansion (307/139 repeats), with a pure GAA configuration on the expanded allele.

Treatment with 4-aminopyridine (20 mg/day) was initiated upon SCA27B diagnosis. After five weeks, she showed marked clinical improvement, with SARA improving to 8/40 and NESSCA to 8/40, despite reported diurnal fluctuation. Due to reduced renal function (30% residual function), the dose was reduced to 10 mg/day, after which partial attenuation of benefit was noted, though improvement in gait and speech persisted.

Discussion

We report the first genetically confirmed case of SCA27B in the Peruvian population and estimate its frequency in a cohort of participants with ataxic syndrome without a definitive molecular diagnosis. Since SCA27B was identified in only one individual - corresponding to a frequency of 0.6%- it suggests that this condition is very rare in the Peruvian population. The cohort in this study presented a relatively high proportion of individuals carrying expanded non-GAA-pure repeats which are currently considered non-pathogenic. This finding contrasts with reports from European populations, in which non-GAA-pure expansions appear relatively less common, and supports the presence of population-specific variability at the *FGF14* locus that may influence repeat stability and disease susceptibility. In contrast, more comparable frequencies of non-pure expansions have been reported in certain Asian cohorts [7, 8].

The frequency of SCA27B in the Peruvian cohort was rarer than that reported in other populations. When compared with reports from European and Asian cohorts, as well as the limited data available from Latin America [2, 4, 5, 14, 18], the frequency observed in our Peruvian cohort is below the 1.2–61% range observed in late-onset cerebellar ataxia cohorts from diverse ethnic backgrounds [19]. To date, SCA27B has been investigated in two Latin American countries. The Brazilian ataxic cohort reports a SCA27B relative frequency of 9%, predominantly in individuals with substantial European ancestry [2, 4, 14, 20, 16]. More recently, a Chilean multicenter cohort identified 9/56 (16.1%) cases of SCA27B [15].

Variable ancestry-related genetic markers and environmental factors may cause the low frequency of SCA27B observed in the Peruvian cohort. The Peruvian population may harbor a reduced prevalence of permissive haplotypes predisposing to GAA repeat expansion, and a higher proportion of non-GAA-pure alleles, which seems to prevent long expansions. [17]. The occurrence of sequence interruptions may limit the propensity of the GAA tract to undergo pathogenic expansion and reduce disease expression, as has been reported in other genetic ataxias like Friedreich's ataxia [13]. These findings show the importance of analyzing global populations when assessing the epidemiology of recently identified repeat expansion disorders.

The allelic distribution of the *FGF14*-GAA repeat in our cohort shows a distinct pattern compared with previously studied populations. The allelic distribution of the *FGF14* GAA microsatellite in this Peruvian cohort differs markedly from that reported in European populations. Most alleles fell within the lower repeat range, with a predominance of short alleles, and a comparatively small proportion of long pure expansions. This allelic profile contrasts with that reported in European cohorts, where longer alleles and pathogenic pure GAA expansions are more frequently observed [11, 1]. These differences suggest that

population-specific factors, including ancestry-related genetic backgrounds, may influence repeat stability, expansion propensity, and motif composition at the *FGF14* locus. The predominantly Native American ancestry of the Peruvian population, in contrast to the higher European ancestry observed in cohorts with higher SCA27B frequencies, may partly account for the low prevalence of pathogenic GAA-pure expansions observed in this study. Furthermore, our population may have a distinct allelic distribution pattern, with a higher frequency of alleles under 30 repeats (85.3%) compared with global Caucasian populations (71.2%) [17].

A high proportion of individuals in this cohort carried expanded non-GAA-pure alleles at the *FGF14* locus. In our cohort, the *FGF14* repeat expansions range from 7 to 139 repeats, which is different from the distribution observed in European cohorts. However, a significant proportion (16.17%) of individuals carried non-GAA-pure expanded alleles, a feature not previously reported in other populations. These non-GAA expansions are not associated with the SCA27B phenotype and may reflect a specific structural variation of the *FGF14* locus within the Peruvian population. Although these complex [(GAA)□(GCA)□] expansions exceeded the pathogenic repeat length threshold, they lacked the pure GAA motif currently regarded as necessary for pathogenicity, and current classification schemes consider them non-pathogenic or of uncertain clinical significance [17]. The relatively high frequency of these complex expansions in the Peruvian cohort represents a notable finding and contrasts with reports from other populations, where such alleles have been described only sporadically [2, 6, 14].

The late disease onset observed in the only SCA27B case identified in our cohort is highly consistent with previous studies. Reported French Canadian patients have shown onsets of episodic symptoms as late as 87 years of age [2]. Despite being born in Peru, the patient has a strong European ancestral background, which should be considered when interpreting the genetic results in the context of population-specific allele frequencies. There is no strong correlation with the repeat length of GAA and the age of onset, and no reliable repeat-length threshold predicts clinical presentation in SCA27B [19]. The main clinical features of this case are concordant with prior reports of SCA27B, with a slow disease progression and the presence of oculomotor abnormalities such as downbeat nystagmus [1, 2, 10]. The absence of episodic symptoms in this patient is also in line with the known phenotypic variability of SCA27B, in which episodic manifestations are reported in roughly half of cases [10, 20]. Brain MRI showed cerebellar atrophy predominantly affecting the cerebellar hemispheres, supporting the diagnosis and aligning with imaging patterns reported in other SCA27B cohorts [2, 20, 16, 21]. A subtle hyperintense signal suggestive of SCPs involvement was also observed **(**Fig. 4B**)**. This finding is consistent with prior reports describing frequent SCPs abnormalities in SCA27B [22, 23].

Our study acknowledges many limitations that might be considered when interpreting the results. The cohort was derived from a single national referral center, which, although it receives patients from different regions of the country, may not fully capture the genetic and clinical diversity of hereditary ataxias across the entire Peruvian population. Second, the retrospective nature of part of the clinical data limited the availability of detailed information on certain features classically associated with SCA27B, such as episodic symptoms, which may therefore be underreported. Third, despite the relatively

large sample size for a rare disease cohort, the identification of only one pathogenic SCA27B case cannot confer robust genotype-phenotype correlations or meaningful statistical comparisons with non-SCA27B cases. In addition, functional studies assessing the biological impact of non-GAA-pure expanded alleles were not performed, limiting our ability to directly evaluate their potential protective or modifying effects. Finally, ancestry was inferred at the population level rather than assessed individually using genetic markers, which restricts more precise analyses of the relationship between genetic background and *FGF14* repeat architecture.

Conclusion

This study reports the first genetically confirmed case of SCA27B in Peru, corresponding to a frequency of 0.6% in a cohort of patients with hereditary ataxia without a definitive diagnosis. Although SCA27B appears to be a rare cause of ataxia in the Peruvian population, the findings suggest that the Peruvian population may exhibit unique genetic variability that differentiates it from other cohorts, particularly in terms of allelic distribution of the *FGF14* gene. In populations with a high frequency of interrupted or complex expansions, additional repeat motif characterization may be required to fully capture allelic diversity and to support accurate molecular and clinical interpretation.

Declarations

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Ethical Approval

The study was approved by the Ethics Committee at INCN, the *Comite Institucional de Etica en Investigación del Instituto Nacional de Ciencias Neurologicas* (IRB number 040-2023-CIEI-INCN). This research was conducted in accordance with the Declaration of Helsinki. The identified DNA samples and associated clinical data were obtained through the Neurogenetics DNA Bank, and therefore, no direct contact with study participants occurred. All sample donors had previously provided written informed consent authorizing the use of their genetic and clinical data for anonymized ongoing and future research studies. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Competing interests

The authors declare that they have no conflicts of interest to report.

Author Contribution

A.SM, D.P., and M.CO conceptualized the study; C.BC contributed to the study design; A.SM, E.S, and M.CO contributed to material preparation; A.SM, MJ.D., E.SC, E.S., and M.CO contributed to data collection; A.SM and M.GC performed data analysis; A.SM, D.P., M.CO, E.SC, C.BC, M.GC, E.S., MJ.D, M.D., S.Z., A.A., and B.B. were responsible for drafting and editing the manuscript. All authors read and approved the final manuscript.

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Data Availability

Raw data were generated at the Neurogenetics Research Center - INCN. The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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Figures

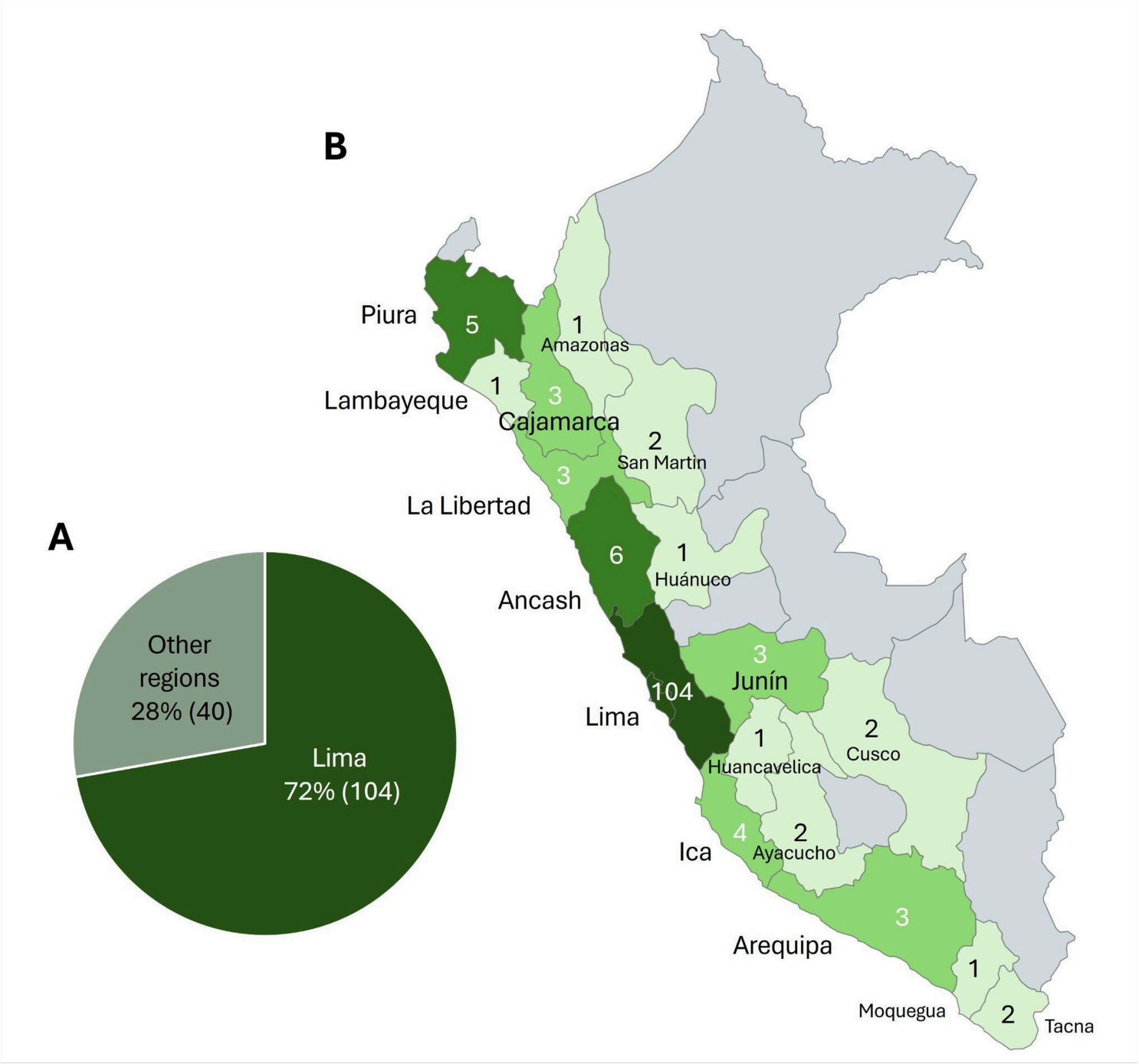


Figure 1

Geographic distribution of the participant's region of origin (A) Proportion of participants from Lima (72%, n=104) and other regions (28%, n=40)**. (B)** Map of Peru showing the number of participants per region. Values are indicated within each region.

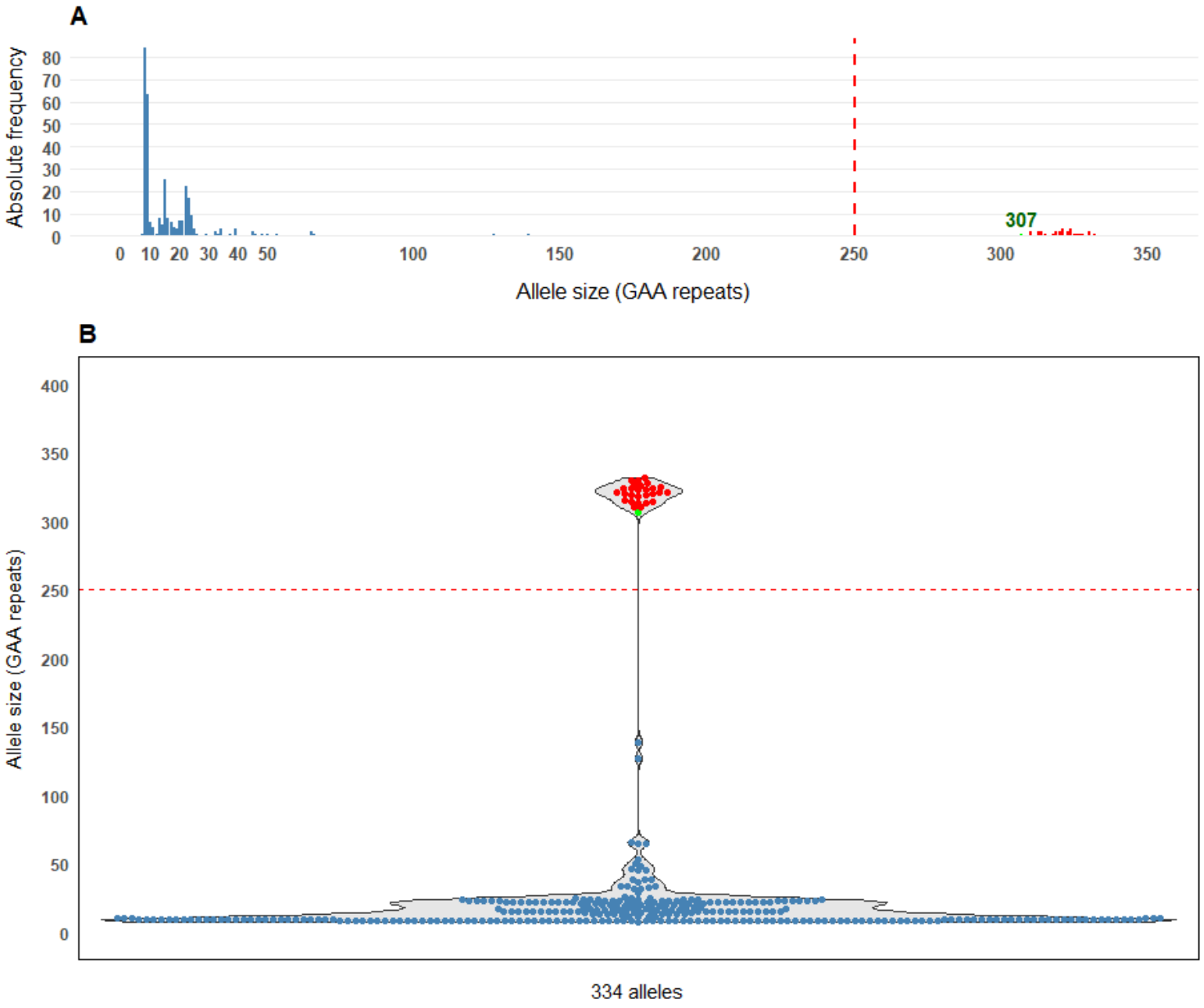


Figure 2

Allelic distribution of the *FGF14*repeat locus in 167 Peruvian individuals with undiagnosed hereditary ataxia. (A) Bar plot, indicating the absolute frequency of alleles in the total population. **(B)** Swarm plot, showing the dispersion of individual *FGF14* alleles. Alleles belonging to subpopulation A (pure GAA repeats) are shown in blue, whereas alleles from subpopulation B (non-pure GAA repeats) are shown in red. The only pathogenic allele (307 GAA repeats) is highlighted in green. The dashed red line indicates the pathogenic threshold (≥250 GAA repeat units).

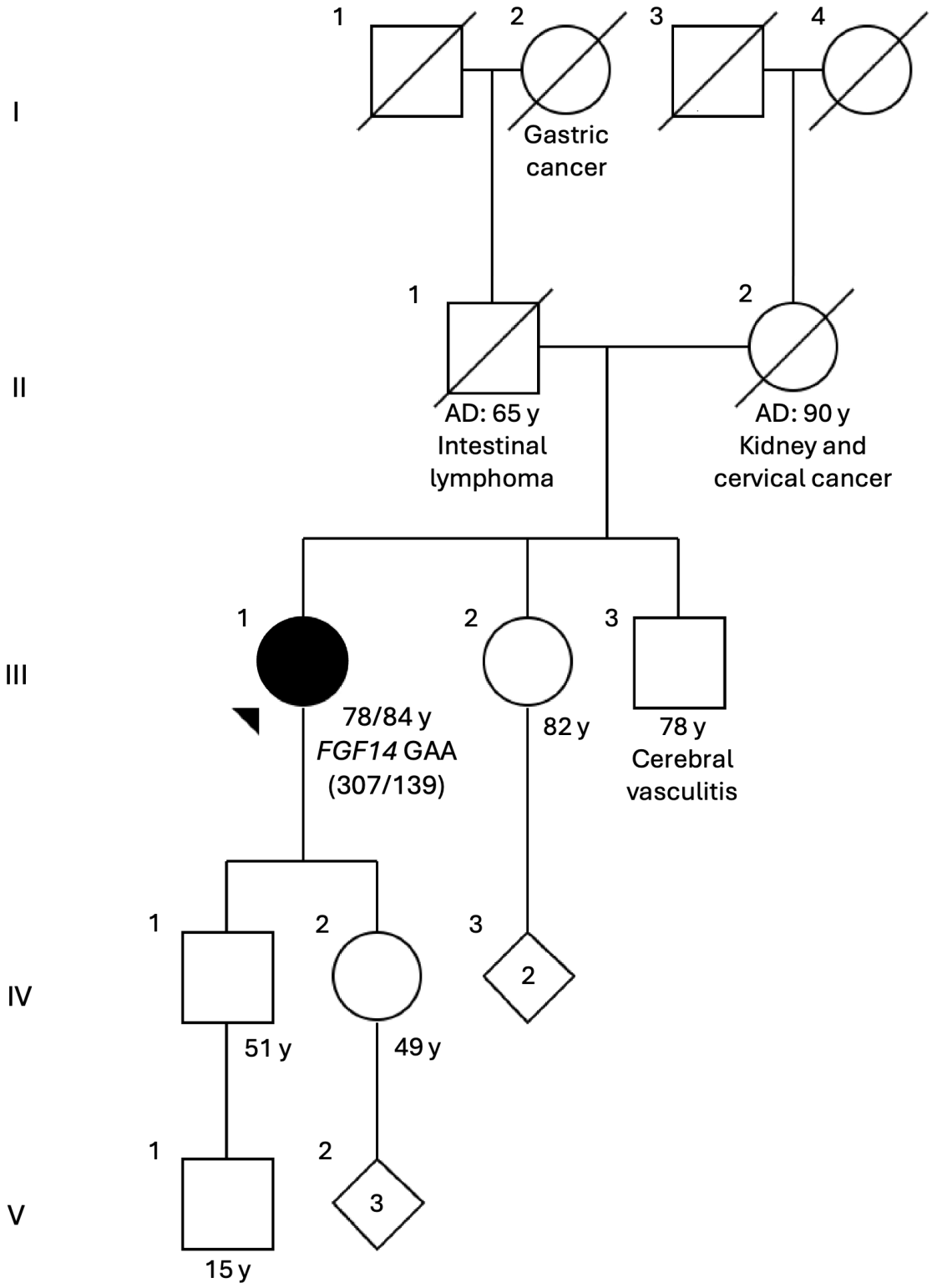


Figure 3

SCA27B case pedigree Ages are shown below each symbol; AD indicates age at death. The affected individual carries expanded 307 *FGF14*GAA repeats (age at onset 78 years/age at last evaluation 84 years). Squares denote males and circles females; slashed symbols indicate deceased individuals. Diamonds represent multiple individuals. The proband is indicated by an arrow.

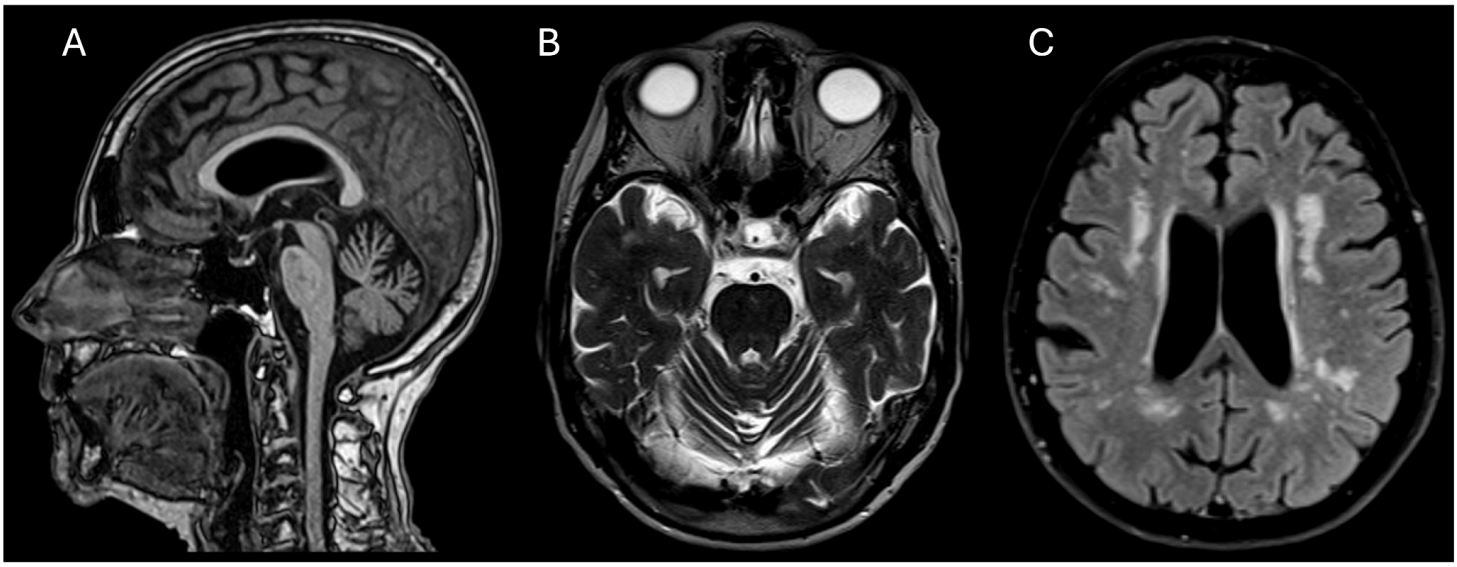


Figure 4

Brain MRI of the SCA27B case (A) Sagittal FLAIR image demonstrating cerebellar atrophy. **(B)** Axial T2-weighted image suggesting subtle hyperintensity of the superior cerebellar peduncles (SCPs), with associated vermian atrophy. **(C)** Axial FLAIR image showing white matter hyperintensities, likely reflecting microvascular changes.