Reduced Age-Dependent Penetrance of a Large *FGF14* GAA Repeat Expansion in a 74-Year-Old Woman from a German Family with SCA27B

Spinocerebellar ataxia 27B (SCA27B) is a recently described autosomal dominant cerebellar ataxia caused by an intronic GAA repeat expansion in the *FGF14* gene.[1] Since SCA27B is one of the most common genetic ataxias worldwide,[2,3] a better understanding of disease penetrance is essential for improving genetic counseling and management of at-risk individuals, as well as for guiding eligibility assessment for future clinical trials.

Initial reports have suggested a pathogenic threshold of $(GAA)_{\geq 250}$ repeat units, albeit with reduced penetrance for $(GAA)_{250–300}$ alleles, since they were observed in ~1.5%–2% of controls.[1,2] A subsequent study identified expansions ranging from 308 to 380 GAA repeat units in 5 of 475 controls, raising the possibility that $(GAA)_{>300}$ expansions may also show incomplete penetrance.[4] Notwithstanding, direct evidence for the reduced penetrance of *FGF14* GAA repeat expansions remains limited. Here, we provide an in-depth, multimodal assessment of an asymptomatic 74-year-old woman carrying a $(GAA)_{483}$ expansion from a family with SCA27B, thus providing further direct evidence for the reduced age-dependent penetrance even of large *FGF14* GAA repeat expansions.

A 74-year-old woman of German descent presented to the Ataxia Clinic in Tübingen for evaluation of her genetic risk following the diagnosis of SCA27B in two of her relatives (Fig. 1A). She reported no symptoms suggestive of SCA27B,[2] such as episodic or progressive imbalance, visual disturbances, vertigo and/or dizziness, and alcohol sensitivity. Neurological examination by two independent SCA27B experts (M.S., A.T.) was unremarkable (including absence of downbeat nystagmus), except for questionable mild dysdiadochokinesia of the right upper extremity and mild reduction of vibration sense at the ankles bilaterally. The total score on the Scale for the Assessment and Rating of Ataxia (SARA) was 0.5/40 points (threshold for ataxia: ≥3 points[5]). Furthermore, the score on the Friedreich Ataxia Rating Scale (FARS) Part E, a gait and balance assessment tool with even higher senstivity,[6] was 0. We next performed quantitative gait analysis using body-worn sensors (see Supporting Information), which is able to detect even subtle gait and balance changes in the very early stages of cerebellar disease.[7-9] Her gait performance, as assessed by the ataxic-sensitive measures "lateral step deviation" and "stride length variability"[7] lay outside the 90% confidence intervals for aged-matched ataxic patients, but within the 90% confidence interval for age-matched healthy controls (Fig. 1B,C). Following a standardized protocol employing long-range polymerase chain reaction (PCR) and bidirectional repeat-primed PCRs,[10] genetic testing revealed that her *FGF14* genotype was 483 and 9 GAA repeat units, without evidence of interruptions within the expanded allele. This result was confirmed with two independent blood samples. In comparison, the subject's brother and cousin, who respectively carried a $(GAA)_{488}$ and $(GAA)_{496}$ expansion, developed slowly progressive cerebellar ataxia at the age of 55 and 63 years, respectively (Table S1).

Key Words: SCA27B, GAA-*FGF14* ataxia, repeat expansion disorder, penetrance

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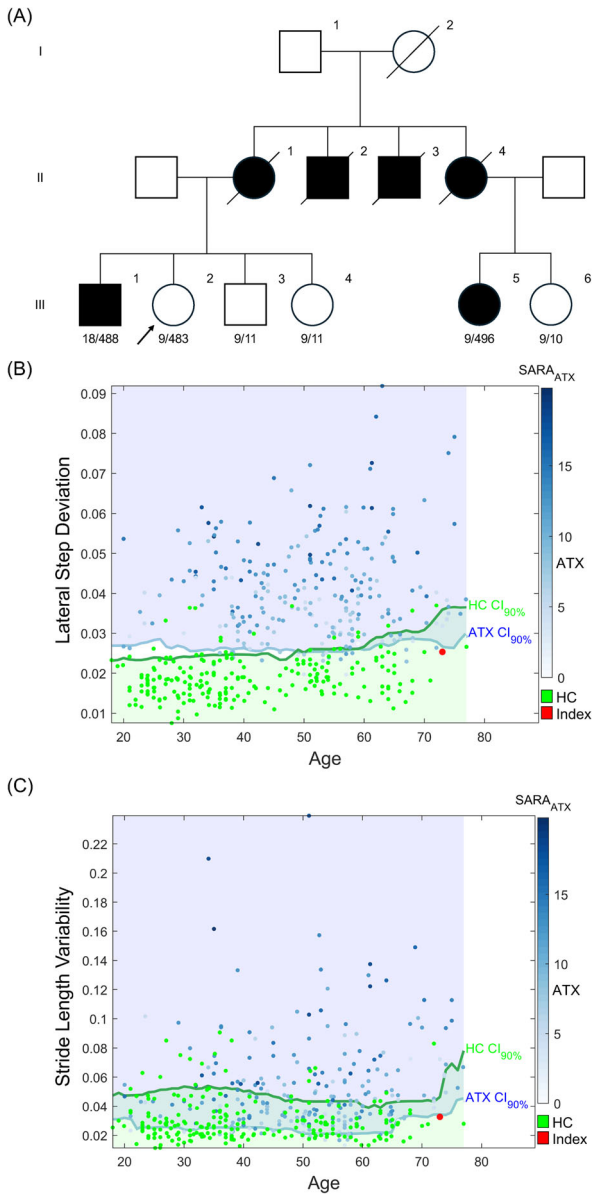

FIG. 1. Pedigree of the German family with SCA27B and quantitative gait analysis. (A) Pedigree of the German family with spinocerebellar ataxia 27B (SCA27B). The allele sizes, expressed as numbers of GAA repeat units, are provided for the family members who underwent genotyping of the *FGF14* repeat locus. Squares represent male family members and circles female family members. Solid black shapes indicate affected persons. Slashed symbols indicate deceased persons. The pedigree has been abbreviated and family members randomly rearranged to preserve privacy. The subject of this study is indicated by a black arrow. Comparison of (B) lateral step deviation and (C) stride length variability by quantitative gait analysis using APDM wearable sensors between the index subject (red dot), healthy controls (HC, green), and patients with degenerative cerebellar ataxia (ATX, blue), according to their age at time of assessment. The green line indicates the upper bound of the 90% confidence interval around the average gait performance of healthy controls. The blue line indicates the lower bound of the 90% confidence interval around the average gait performance of ataxic patients. The color of the data points for the ataxic individuals is a function of the severity of ataxia as measured by the Scale for the Assessment and Rating of Ataxia (SARA) score, with dark blue indicating more severe ataxia (a hue scale is shown on the right *y*-axes). [Color figure can be viewed at wileyonlinelibrary.com]

Through in-depth, multimodal assessment that included highly sensitive standardized clinical scoring (FARS-E) and quantitative digital-motor gait analysis, this study provides first direct evidence for reduced age-dependent penetrance of a large *FGF14* $(GAA)_{483}$ repeat expansion in an otherwise still asymptomatic 74-year-old woman from a German family with SCA27B. Quantitative analysis of gait parameters shown to be highly sensitive to mild gait and balance deficits, namely lateral step deviation and stride length variability,[7] showed that the subject had a performance within the range of age-matched healthy controls, but outside the range of ataxic individuals. Our findings extend previous evidence of reduced penetrance of *FGF14* GAA repeat expansions, as supported by their observation in non-ataxic controls and inferred from the frequent sporadic presentation of SCA27B (15%–50%),[2] where an asymptomatic parent must have been an obligate expansion carrier. Although it is not clear how thoroughly the relatives of sporadic cases reported in previous series were assessed, they were likely not assessed using highly sensitive clinical scales like the FARS-E and quantitative gait assessment.

While most patients with SCA27B develop ataxia in their 50s and 60s,[2] some occasionally manifest ataxia in their 80s,[1] thus not ruling out that the subject reported here may develop SCA27B later in life. While longitudinal follow-up is warranted to investigate this, our results support the reduced age-dependent penetrance of large *FGF14* repeat expansions past the age of 70 years. They also further corroborate the observed intrafamilial variability in the age at onset associated even with *FGF14* GAA repeat expansions of same size.[2] The reduced penetrance of *FGF14* expansions may be the result of modifying genetic factors and/or somatic mosaicism in the central nervous system, similar to what has previously been shown in Friedreich ataxia.[11]

In conclusion, our findings show that reduced age-dependent penetrance may also be observed with large *FGF14* repeat expansions past the age of 70 years, which is of importance for genetic counseling and future trial planning. In addition, they highlight the need to comprehensively study factors that modulate age of onset and age-dependent penetrance of SCA27B, given its high frequency.

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Ethical Compliance Statement

The study was approved by the Institutional Review Board of the University of Tübingen (AZ 598/2011BO1).

Written informed consent was obtained from all study participants before enrollment.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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