As Frequent as Polyglutamine Spinocerebellar Ataxias: SCA27B in a Large German Autosomal Dominant Ataxia Cohort

Intronic GAA repeat expansions in the fibroblast growth factor 14 gene (*FGF14*) have recently been shown to be a common cause of adult-onset degenerative ataxia (spinocerebellar ataxia 27B [SCA27B], MIM: 620174),[1,2] but frequencies in strictly consecutive SCA cohorts are unknown. Here we studied the relative frequencies of SCA27B in a cohort of genetically undetermined autosomal dominant cerebellar ataxia (ADCAs) and relative to other forms of genetically confirmed SCAs.

ADCA Screening

We screened a consecutive cohort of 79 German patients from 51 families with genetically undetermined ADCA for the intronic *FGF14* GAA repeat expansion. All index patients were negative for SCA types 1, 2, 3, 6, 7, and 17 and negative on either exome or short-read genome sequencing. Detailed inclusion criteria and methods are outlined in the Supporting Information.

Twenty-Six of 51 families (26/79 patients) were found to carry a *FGF14* $(GAA)_{\geq 250}$ expansion, thus accounting for 31% of patients with ADCA (Fig. 1A). Although only expansions of at least 250 GAA repeat units were considered pathogenic[1,2] and used for the current frequency analysis, we identified one family with late-onset largely pure cerebellar ataxia, and thus compatible with SCA27B,[3] in which the index patient had a repeat count of 256 GAA units, whereas her affected mother had a repeat count of 234 repeat units (Supporting Information Fig. S2). This indicates that the pathogenic threshold might be even be lower than the previously established cutoff of 250 repeat units. This hypothesis warrants further confirmation in future larger segregation and population studies.

Moreover, a $(GAAGGA)_n$ repeat expansion was found in three index patients. This hexanucleotide expansion did not segregate with disease in all three families (Supporting Information Fig. S1). This provides further evidence for previous observations suggesting that non-GAA repeat expansions are unlikely pathogenic[1] and warrants caution on recent discussions of its pathogenicity.[4]

Frequency Relative to Other SCAs

We next compared the frequency of SCA27B with other forms of SCAs in a consecutive cohort of genetically determined patients with SCA (n = 320 index patients; for inclusion criteria, see Supporting Information Data S1). SCA27B comprised 16% (52/320) of all SCA index patients (including 36 patients without an autosomal dominant family history), representing the second most common cause of SCA in this German cohort. SCA27B had a similar frequency as the common polyglutamine SCAs SCA1 (38/320, 12%), SCA2 (28/320, 9%), SCA3 (61/320, 19%), and SCA6 (38/320, 12%) (Fig. 1B).

The median age at onset in patients with SCA27B was 55 years (interquartile range [IQR], 46–64 years), which was later than in the SCA3 (median, 40 years; IQR, 31–47 years), SCA2 (median, 34 years; IQR, 26–44 years), and SCA1 patients at our center (median, 33 years; IQR, 27–37 years) and more similar to the SCA6 patients (median 56; IQR, 48–64). Our findings confirm the previously reported[1-3,5] late age at onset for SCA27B, even though our ADCA screening cohort was, unlike previous screening cohorts,[1,3,5] not age stratified. Interestingly, one patient with SCA27B stood out with age at onset of chronic progressive gait ataxia at 27 years (size of expansion: 308 GAA repeat units). He showed a slow disease progression, as exemplified by a Scale for the assessment and rating of Ataxia (SARA) score of 15 points after 25 years of disease, consistent with previous reports of overall slow disease progression in SCA27B.[3]

Although the strength of this study is the investigation of a strictly consecutive cohort of autosomal dominant ataxias, it is limited by the fact that the frequency of SCA27B was studied only in a central European cohort from a single center. Future larger international multicenter studies are needed to investigate its frequency in cohorts of unexplained autosomal dominant ataxia from other regions and continents, while also analyzing and accounting for potential referral/ascertainment patterns and founder effects.

Our findings highlight the immediate need to integrate SCA27B in the diagnostic workup of ADCA in clinical practice,

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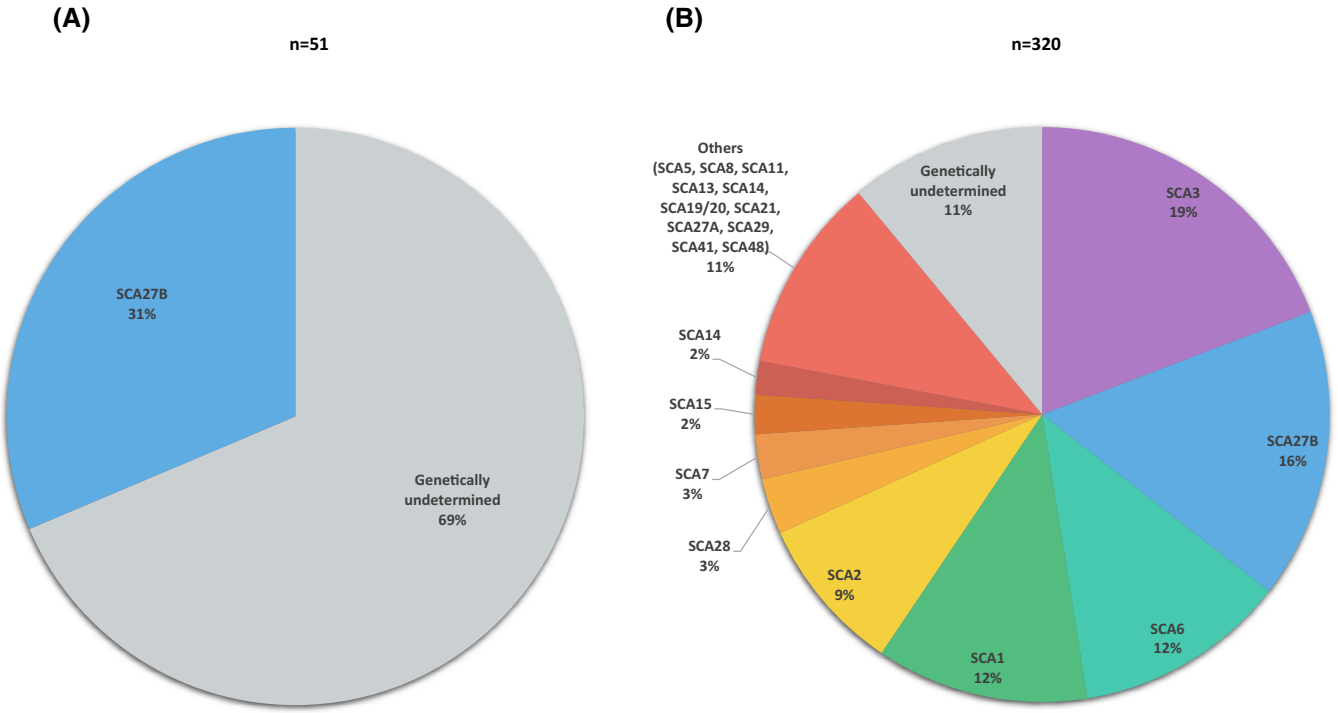

FIG. 1. (**A**) Frequency of spinocerebellar ataxia 27B (SCA27B) in a consecutive cohort of 51 genetically undetermined ADCA families. (**B**) Frequency of SCA27B relative to other SCAs in a consecutive German cohort of 320 index patients. The frequency of SCA27B (16%) was in a similar range as the frequency of the common polyglutamine SCAs SCA1, SCA2, SCA3, and SCA6. [Color figure can be viewed at wileyonlinelibrary.com]

especially because patients with SCA27B may benefit from treatment with 4-aminopyridine.[3]

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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.