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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.

# Autosomal Recessive Cerebellar Ataxias in Europe: Frequency, Onset, and Severity in 677 Patients

Progress in next-generation sequencing has led to an explosion of novel genes and phenotypes of autosomal recessive cerebellar ataxias (ARCAs) in the last decade, with >170 recessive conditions manifesting with ataxia identified.[1] With large-scale natural history and mechanistic treatment trials on the horizon for many ARCAs, up-to-date knowledge is required not only on relative frequencies but also on real-world age and disease severity distributions as key information for trial design planning and recruitment. In this multicenter study, we provide data on the relative frequency of ARCAs in Europe, delineate the spectrum of age at disease onset, and present real-world data on disease severity distributions of patients with ARCA that help to inform future trial planning.

Prospective cross-sectional and longitudinal data from consecutive patients enrolled between 2013 and June 2022 from 23 European sites (Fig. 1A) were included, all collected through the international ARCA Registry.[2] Patients had been eligible for inclusion into the ARCA Registry if they had (1) a genetically confirmed ARCA; and/or (2) onset before age 40 years without evidence of an autosomal dominant family history, repeat expansion in spinocerebellar ataxia genes, or acquired cause, thus representing a stratum of patients with ataxia known to be enriched for recessive ataxia disease.[3,4] Patients with Friedreich's ataxia (FA; n = 112) were not included because (1) FA is already covered in parallel by other European natural history registries (eg, EFACTS),[5] which would lead to a distorted, nonrepresentative frequency estimate in the current study; (2) this study focused on the rare and less well-studied ARCAs; and (3) disease data as investigated in this study are thus already available elsewhere.[5]

A total of 677 patients were included in this study, rendering it the largest European ARCA frequency study to date. Fifty-nine percent had a genetic diagnosis (Fig. 1B), with autosomal recessive spastic ataxia Charlevoix-Saguenay (ARSACS; 13%) and spastic paraplegia type 7 (SPG7; 10%) being the most frequent, followed by RFC1, ataxia with oculomotor apraxia type 2 (AOA2), ataxia telangiectasia (AT), and SYNE1 (all 7%), and then in decreasing frequency, COQ8A (5%), POLG (4%), ANO10 (3%), and AOA1 (3%), and a large number of 62 ultra-rare ARCAs (each ≤2%, often only n = 1–3 patients/ARCA) (Fig. 1C). Age of onset of ARSACS, AT, and COQ8A was typically in the first decade of life (Fig. 1D), whereas SPG7, POLG, and ANO10 started on average in the fourth decade. Patients with RFC1 mutations had a later onset, on average at age 53 (interquartile range: 49–61) years (Fig. 1D). Cross-sectional disease progression estimates (Scale for the Assessment and Rating of Ataxia score [SARA]/disease duration) suggest a relatively faster disease progression for AT (median: 1.4 SARA points/years), but a slower disease progression for ARSACS (0.6 SARA point/years), RFC1 (0.9 SARA point/years), and SPG7 (0.6 SARA point/years) (Fig. 1F,G). Most patients with ARCA currently attending ataxia clinics



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Additional study group contributors of the ARCA Registry/PREPARE consortium are listed in the Appendix.

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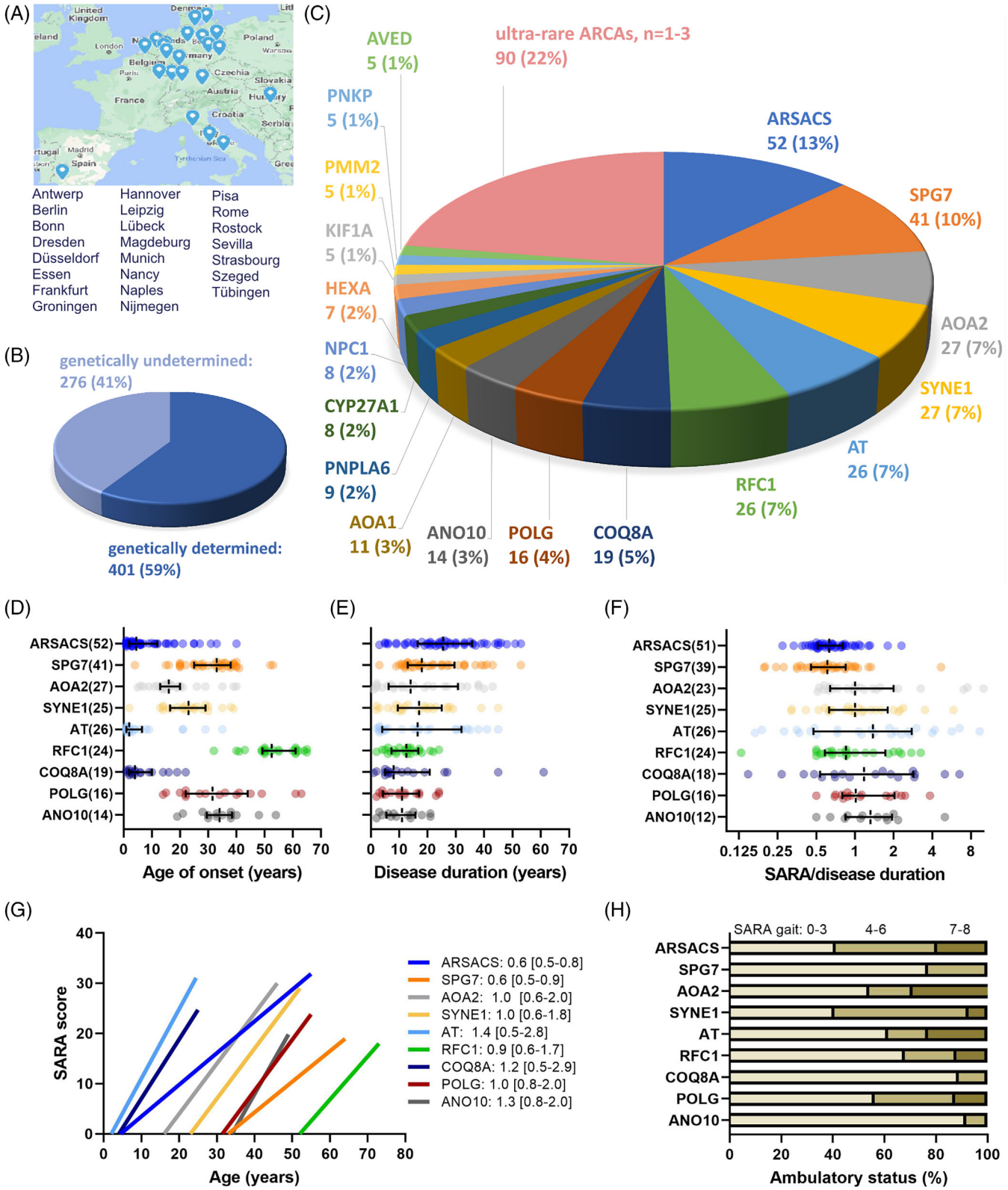


**FIG. 1.** Frequency distribution, age at onset ranges, disease durations, cross-sectional progression trajectories, and severity status of ARCAs in Europe. (**A**) This multicenter study recruited patients with ARCA from 23 centers in Europe. (**B**) Frequency of genetically determined versus still genetically undetermined patients with ARCA. (**C**) Frequencies of the different ARCA genotypes among the genetically defined ARCA patients. Median and interquartile range of (**D**) onset age, (**E**) disease duration, and (**F**) cross-sectional disease progression (SARA score/disease duration in years) of the main ARCA types. (**G**) Average trajectories of cross-sectional disease progression of the main ARCA types based on median onset and SARA score at last visit. (**H**) Ambulation status (stratified by the SARA gait item) of the main ARCA types. AOA2, ataxia with oculomotor apraxia type 2; ARCA, autosomal recessive cerebellar ataxia; ARSACS, autosomal recessive spastic ataxia of Charlevoix-Saguenay; AT, ataxia telangiectasia; RFC1/ANO10/COQ8A/POLG/SYNE1, ataxia related to respective gene; SARA, Scale for the Assessment and Rating of Ataxia; SPG7, spastic paraplegia type 7. [Color figure can be viewed at wileyonlinelibrary.com]

already have on average >10 years' disease duration, with patients with ARSACS even being on average 26 years into their disease (Fig. 1E). Most SPG7, COQ8, and ANO10 patients currently attending ataxia clinics are still ambulatory, whereas >40% of patients with ARSACS, SYNE1, AOA2, or POLG cannot walk independently anymore (Fig. 1H).

This large multicenter study provides a comprehensive overview on the frequency of non-FA ARCAs in Europe. It confirms the relatively high frequency of ARSACS, RFC1, and AT in ARCAs, as recently observed in a large South American ARCA cohort.[3] The high frequency of SPG7 might have been missed in the South American ARCA cohort because SPG7 has for long not been sequenced as part of the ataxia genetic workup. The larger number and more comprehensive spread of rare ARCAs in this European cohort probably reflect broader availability of large-scale next-generation sequencing as a diagnostic tool in Europe.

This study takes the next step toward trial readiness for ARCAs in Europe. The large number of ultra-rare ARCAs highlights the need for novel treatment programs focusing on nano-rare ARCAs, developing, eg, even mutation-specific treatments for these n-of-few ARCAs.[6] Molecular treatment trials will need to consider that most ARCA patients available for recruitment in real-world settings will already be >10 years into their disease, with a substantial share of patients no longer walking independently (in particular from ARSACS, SYNE1, AOA2, or POLG). Also, some ARCAs show a fairly slow disease progression (ARSACS, RFC1, SPG7; for detailed analyses, see Traschütz et al[7]), indicating the need for either large sample sizes, longer trial duration, and/or more sensitive nonclinical outcome measures in upcoming trials.

This study is limited by its incomplete coverage of *all* ataxia centers in Europe and its focus on non-FA ARCAs. However, it might provide a representative perspective on the real-world trial availability of these rare, so far grossly understudied ARCAs in Europe.

## Ethics Statement

This study was approved by the Ethics Committee of the Medical Faculty Tübingen (598/2011BO1).

## Financial Disclosures

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## Data Availability Statement

Data available on request from the authors.

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## APPENDIX

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