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# Autosomal Recessive Cerebellar Ataxias in South America: A Multicenter Study of 1338 Patients

Autosomal recessive cerebellar ataxias (ARCAs) comprise complex genetic ataxia disorders with variable central and peripheral nervous system involvement and systemic changes. They can overlap with other conditions such as hereditary spastic paraplegia, inborn errors of metabolism, and genetic encephalopathies.[1] While usually starting in childhood or young adulthood, late adult-onset may occur. The advanced application of next-generation sequencing has allowed the molecular definition of many previously undetermined ARCAs in the last decade, including many new ARCA genes.[1-4]

There are few reports of epidemiology of ARCA and its frequency in South America. Integration between the ataxia centers in South America is mandatory to better capture the frequency and types of ARCA across this large continent, in particular when now preparing for large-scale natural history and treatment trials in ARCAs.[1] This multicenter study aimed to retrospectively capture the frequency of the most common forms of ARCA across South America, combining data from 11 large ataxia centers in South America: one in Argentina, one in Chile, one in Peru, and eight in Brazil (Fig. 1).

Data from each ataxia center were captured via a standardized questionnaire that included the following questions (see also the list in Fig. 1): (A) number of ARCA patients, defined as an ataxia patient with (i) a molecularly confirmed ARCA diagnosis or (ii) ataxia onset before age 40 years and negative but informative family history; (B) number of ARCA patients with genetic diagnosis versus no genetic diagnosis as of yet; and (C) number of patients of each genetic ARCA subtype. The frequency of patients with specific genotypes was analyzed. A total of 1338 patients were included in this study (Fig. 1) making it the largest ARCA frequency study to date.

In South America, 43% of patients had a positive molecular diagnosis confirming the genetic etiology of ARCA. Friedreich's ataxia was the most common ARCA and corresponded to 57% of the cases with a molecular diagnosis. The second most common form of ARCA was *RFC1* (8%), followed by ataxia telangiectasia (AT) (7%), Niemann–Pick type C (4%), ARSACS (4%), ataxia with oculomotor apraxia

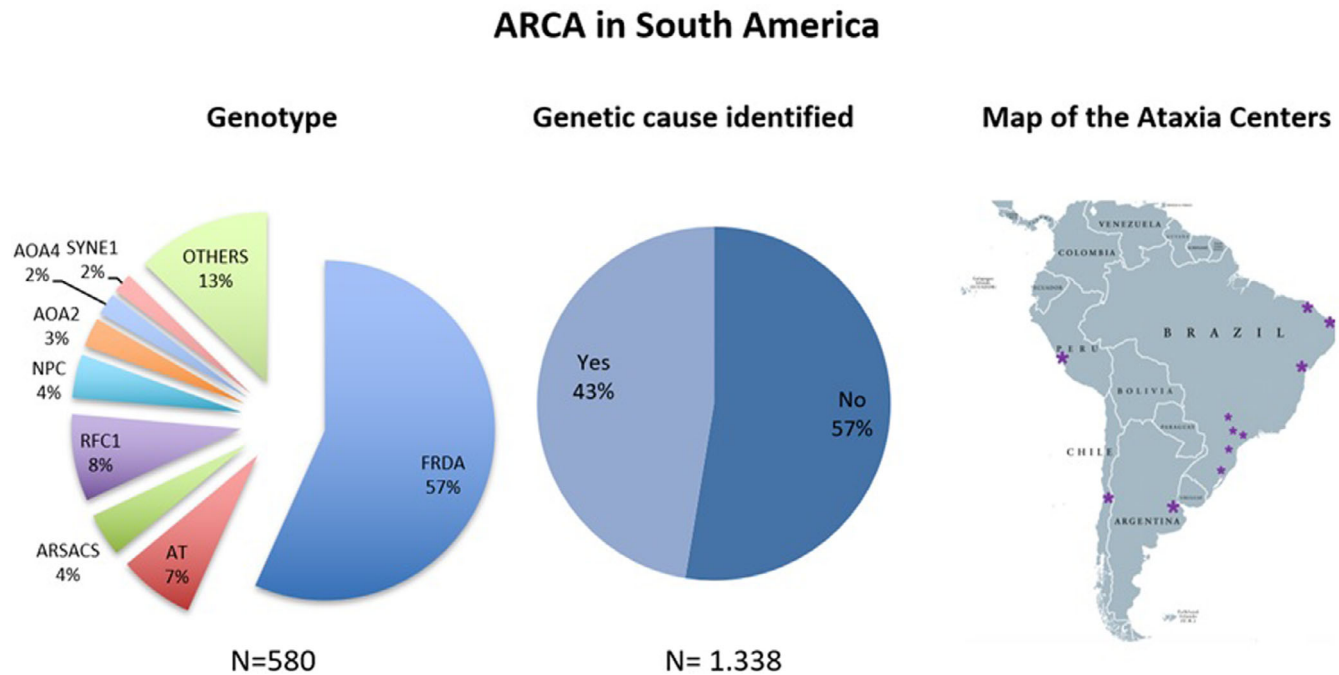


**FIG. 1.** Frequency of the main genotypes of patients with autosomal recessive cerebellar ataxia (ARCA) in South America, including both molecularly defined ARCA and genetically still undetermined ARCA. The figure also depicts the main Ataxia Centers in South America that participated in this epidemiological investigation. FRDA, Friedreich's ataxia; AT, ataxia telangiectasia; ARSACS, autosomal recessive spastic ataxia of Charlevoix-Saguenay; NPC, Niemann–Pick type C; AOA, ataxia with oculomotor apraxia. [Color figure can be viewed at wileyonlinelibrary.com]

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(AOA) type 2 (3%), AOA type 4 (2%), and *SYNE1* ataxia (2%). Other less common forms of ARCA represented 13% of the cases, including AOA type 1, *ANO10*, and *STUB1* (Supplemental Material).

This is the first multicentric study that provides information about epidemiology and frequency of ARCA in South America, and the largest ARCA frequency study worldwide. Our data are compatible with the literature regarding the most common forms of ARCA, but highlight the fact that ARSACS and NPC1 might be more common than previously thought, and provide the first real-world frequency estimates for the fairly recently identified RFC1 ARCA.[5]

This study is limited by its retrospective nature. Also, it is possible that patients with undetermined ataxia are still poorly investigated through exome sequencing in South America. This, however, renders our population an interesting opportunity to identify new genes and knowledge on epidemiological features in ARCA. Moreover, our observations are relevant to the current planning of upcoming gene therapy and clinical trials in ARCAs.

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## Data Availability Statement

Data sharing not applicable - no new data generated, or the article describes entirely theoretical research

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## References

1. Synofzik M, Puccio H, Mochel F, Schols L. Autosomal recessive cerebellar ataxias: paving the way toward targeted molecular therapies. Neuron 2019;101:560–583.
2. Beaudin M, Matilla-Dueñas A, Soong BW, et al. The classification of autosomal recessive cerebellar ataxias: a consensus statement from the Society for Research on the Cerebellum and Ataxias Task Force. Cerebellum 2019;18:1098–1125.
3. da Graça FF, Peluzzo TM, Bonadia LC, et al. Diagnostic yield of whole exome sequencing for adults with ataxia: a Brazilian perspective. Cerebellum 2021;21:49–54;
4. Rangel DM, Nobrega PR, Saraiva-Pereira ML, Jardim LB, Braga-Neto P. A case series of hereditary cerebelar ataxias in a highly consanguineous population from Northeast Brazil. Parkinsonism Relat Disord 2019;61:193–197.
5. Synofzik M, Nemeth AH. Recessive ataxias. Handb Clin Neurol 2018;155:73–89.

## 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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