Elucidating the Diagnostic Yield and Allelic Characteristics of *FGF14* Repeat Expansions in Adult Ataxia Through Whole Genome Sequencing

Hongzheng Dai[1,2], Haowei Du[1], Katharina Schulze[1,2], Chung Wah Wu[1,2], Weihong Jin[2], Kelly Schoch[3], Vandana Shashi[3], Nicolas Abreu[4], Connolly Steigerwald[4], Janet Rucker[4], Jennifer Cedeno[5], Emile Moukheiber[6], Liana Rosenthal[6], Ankur Butala[6], Weiyi Mu[5,6], Chelsea Chambers[7], Giorgio Sirugo[8], Daniel J. Rader[8], Marjorie Risman[8], Yi-An Ko[8], Anna Raper[8], Ellen Macnamara[9], Camilo Toro[9], Liesbeth Vossaert[1,2], Linyan Meng[1,2], Patricia Ward[1,2], Christine Eng[1,2], Undiagnosed Diseases Network, Fan Xia[1,2], Bo Yuan[1,2]

1. Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX 77030, USA
2. Baylor Genetics, Houston, TX 77021, USA
3. Division of Medical Genetics, Department of Pediatrics, Duke University School of Medicine, Durham, NC 27710, USA
4. Department of Neurology, NYU Grossman School of Medicine, New York City, NY 10017, USA
5. Department of Genetic Medicine, Johns Hopkins University, Baltimore, MD 21287, USA
6. Department of Neurology, Johns Hopkins University, Baltimore, MD 21287, USA
7. Department of Neurology, University of Virginia, Charlottesville, VA 22903, USA
8. Division of Translational Medicine and Human Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA
9. Undiagnosed Diseases Program, National Genome Research Institute, National Institutes of Health, Bethesda, MD 20892, USA

BACKGROUND

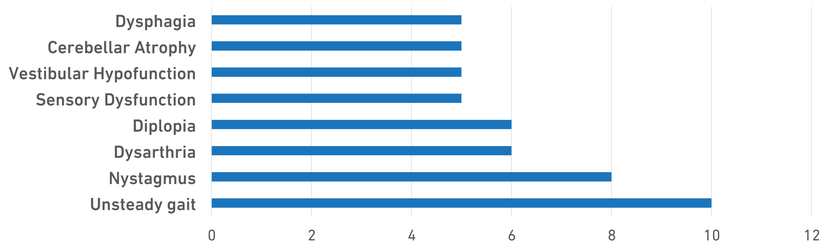
- Adult ataxia is a progressive neurodegenerative disorder characterized by impaired coordination of muscle movements with features including unsteadiness, incoordination, slurred speech, and oculomotor abnormalities.
- The diagnostic yield for adult ataxia by next-generation sequencing is over 30%. However, other testing methodologies are thought to be able to increase this yield further[1].
- Recent progress with long-read sequencing has identified a deep intronic GAA expansion in *FGF14* as a cause of late-onset spinocerebellar ataxia 27B (SCA27B)[2]. This large *FGF14* repeat expansion poses detection challenges for short-read sequencing.
- This *FGF14* expansion may be present in 10-30% of European and Indian cohorts of patients with unsolved adult-onset ataxia, and could be as high as 60% in French-Canadian patients from Quebec[3].
- We present molecular findings from a clinical WGS cohort and a general population cohort to further characterize the allelic architecture and phenotypic correlation of this genetic cause of adult ataxia.

RESULTS

We identified 17 new adult ataxia cases with SCA27B (aged 53 to 90 years old)

In our cohort, cases had 252 to 550 GAA repeats

Several cases had additional neurological symptoms:



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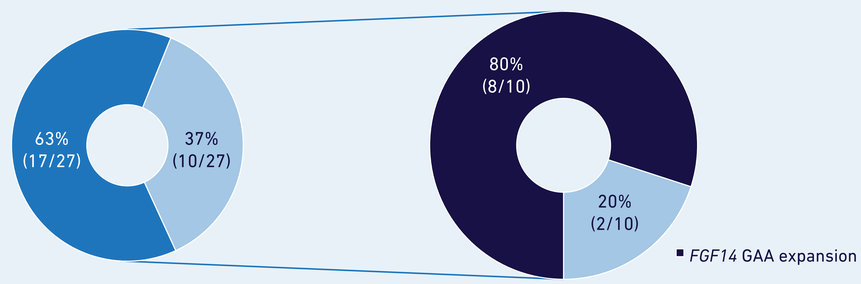
METHODS

- Short tandem repeat (STR) calling for the *FGF14* intronic expansion locus was performed by WGS using 150 base pair paired-end reads at 40X read coverage on average per genome.
- STR results were reviewed for phenotypic correlation and reflexed to repeat-primed PCR and gel sizing for confirmation.
- Previous unsolved adult ataxia cases suspicious for SCA27B were also examined retrospectively for possible *FGF14* expansion.
- Population characterization of *FGF14* repeats was performed prospectively for a cohort of 265 unrelated individuals.

GENETIC INSIGHTS IN ONE ATAXIA CLINIC



27 total adult ataxia cases underwent WGS, of which 10 cases received a diagnosis

***FGF14* GAA expansion contributed to a significant number of total and diagnosed cases in this clinic.**

CONCLUSIONS

We applied a strategy to detect *FGF14* expansion through WGS combined with repeat-primed PCR and gel sizing for patients with adult ataxia. These results show that *FGF14* expansions causing SCA27B are a significant contributor to adult-onset ataxia. Incorporating repeat expansion analysis for this gene can improve diagnostic assessment and clinical management for adult ataxia cases.

References:
1 Spinocerebellar ataxia 27B: A novel, frequent and potentially treatable ataxia. PMID: 38279833
2 An intronic GAA repeat expansion in FGF14 causes the autosomal-dominant adult-onset ataxia SCA27B/ATX-FGF14. PMID: 37267898
3 Deep intronic FGF14 GAA repeat expansion in late-onset cerebellar ataxia. PMID: 36516086