Genetic Ataxias in Argentina

Care, diagnosis and molecular testing in an 11-year Neurogenetics program

Perez Maturo, Zavala et al. Journal of Human Genetics, 2020

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The diagnostic odyssey was the clinical problem to solve

Genetic heterogeneity met limited access to molecular testing; the program’s answer was to make each test selection more informative.

>50 spinocerebellar ataxia subtypes

>60 recessive ataxia subtypes

10.07 y mean diagnostic delay in solved cases

A clinical care program became a national diagnostic dataset

Prospective evaluation in a tertiary public hospital Neurogenetics Unit, May 2008 to December 2019.

1,250
patients evaluated in the unit

334
included with chronic progressive ataxia

41 y
mean age at evaluation

46%
positive family history

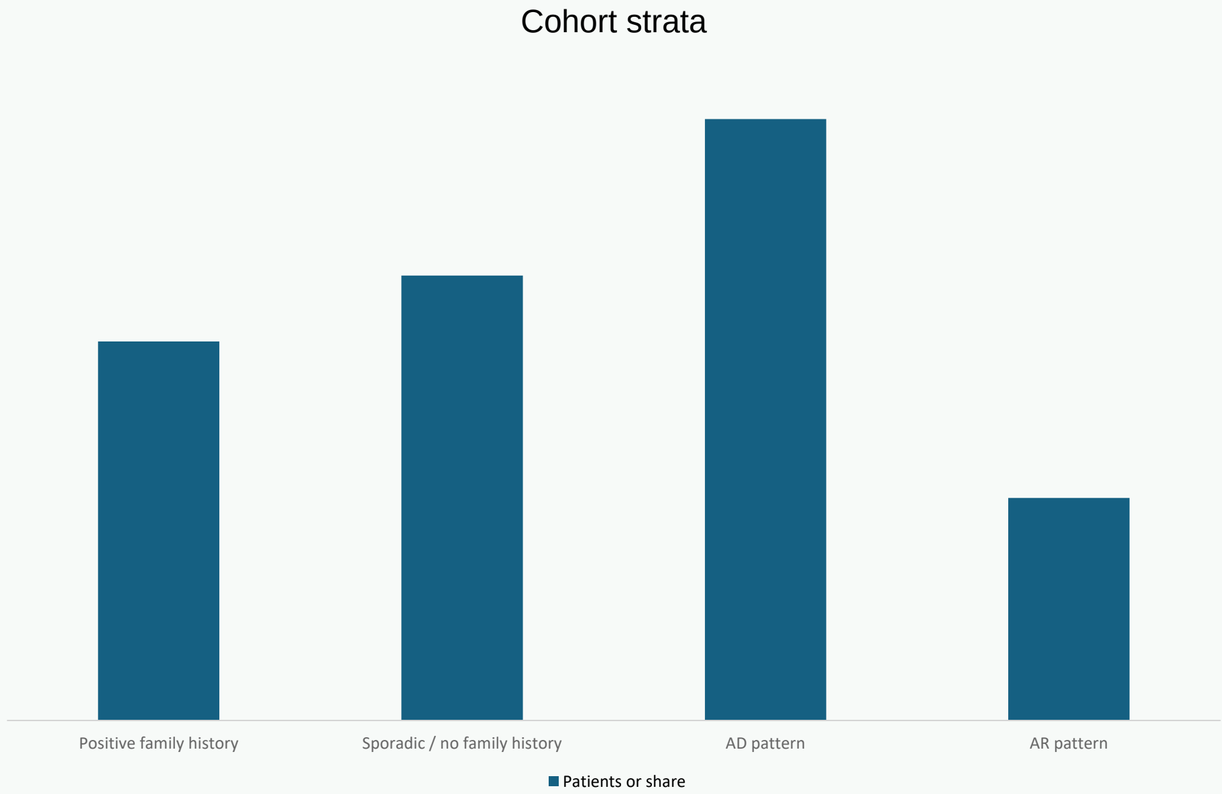
phenotype-first | family-history driven | resource-aware

Cohort: 334 subjects with presumed genetic chronic cerebellar-ataxic dysfunction.

The first diagnostic split was clinical, not technological

Inheritance pattern and orientative phenotype changed the pre-test probability before the lab request.

- **Positive family history**
- **Autosomal dominant**
- **Autosomal recessive**
- **Sporadic / no family history**



Positive family history in 46% of the cohort; among familial cases, AD patterns predominated over AR patterns.

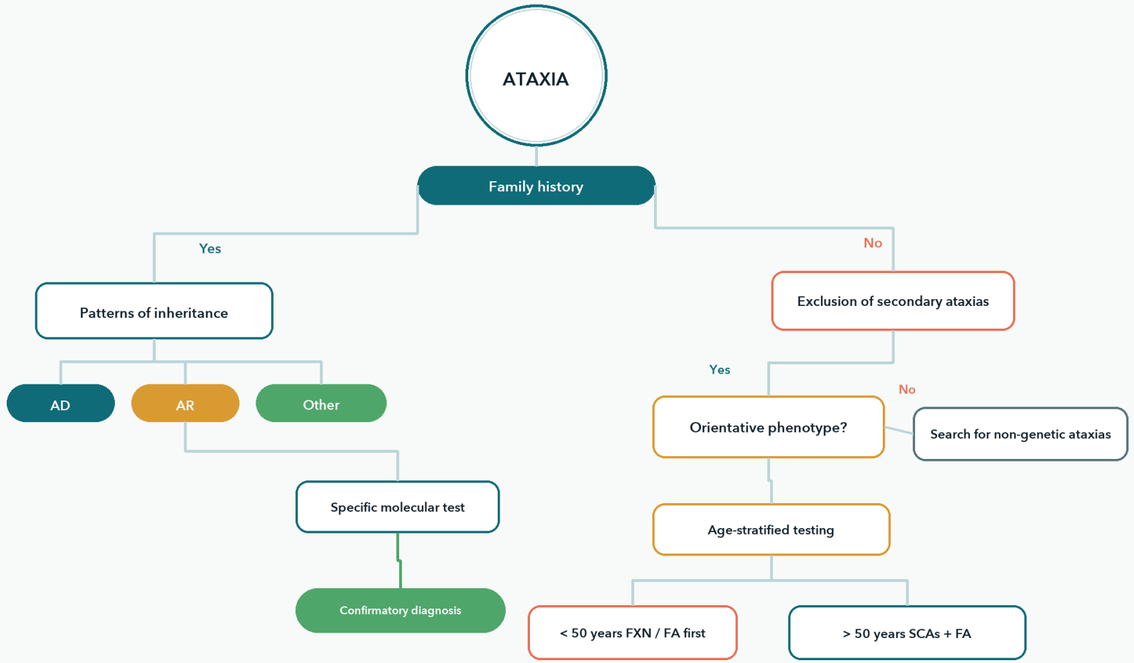
A rational diagnostic algorithm kept testing aligned with probability

The published workflow begins with clinical stratification and escalates only when first-tier tests do not explain the case.

1. Define AD, AR or sporadic presentation
2. Prioritize repeat expansions and single genes
3. Use NGS for residual complex or atypical cases
4. Return the result to counseling and family care

a. **Clinical triage before sequencing**

Family history, phenotype and age at onset determine the first molecular test.

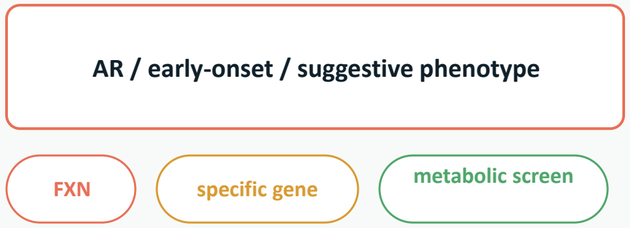


Adapted from the diagnostic algorithm published in Perez Maturo et al., 2020.

First-tier testing was deliberately targeted

The objective was not to test less; it was to test in the order most likely to answer the clinical question.

Repeat-expansion testing first when dominant inheritance and phenotype matched common SCA entities.



Friedreich ataxia and selected recessive genes remained high-yield entry points before broader NGS.

Testing priorities are summarized from the published algorithm and Results section.

One in three patients reached a molecular diagnosis

Yield rose sharply when pedigree information indicated inherited disease.

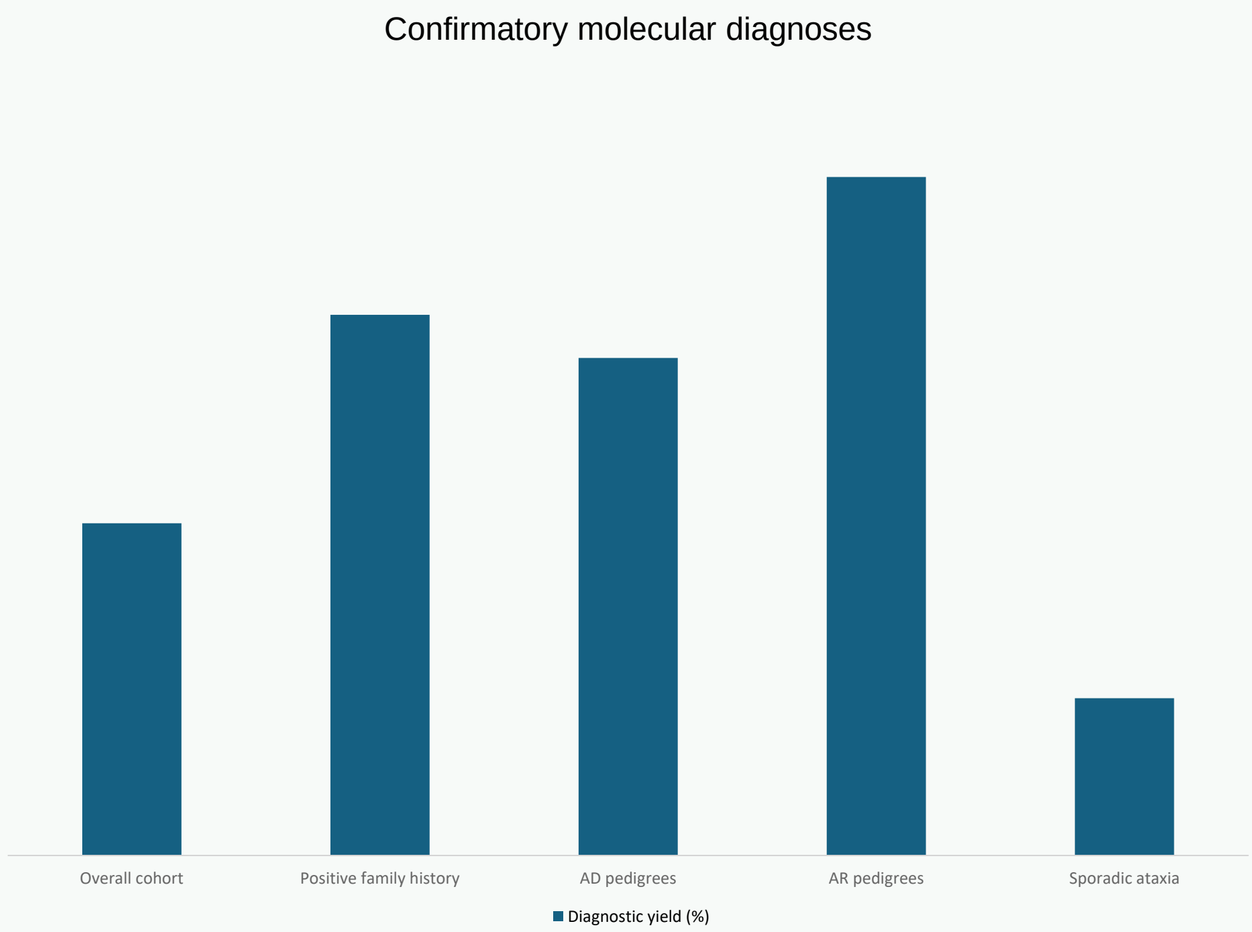
113

patients with final molecular diagnosis

33.8%

overall diagnostic yield

The operational result: clinical stratification made molecular testing productive even before broad NGS availability.



AD: autosomal dominant; AR: autosomal recessive. Values from Tables 1-2 and Results.

Pedigree information changed the diagnostic odds

Family history was a practical triage variable, not only descriptive epidemiology.

55%

yield with positive family history

16%

yield in sporadic ataxia

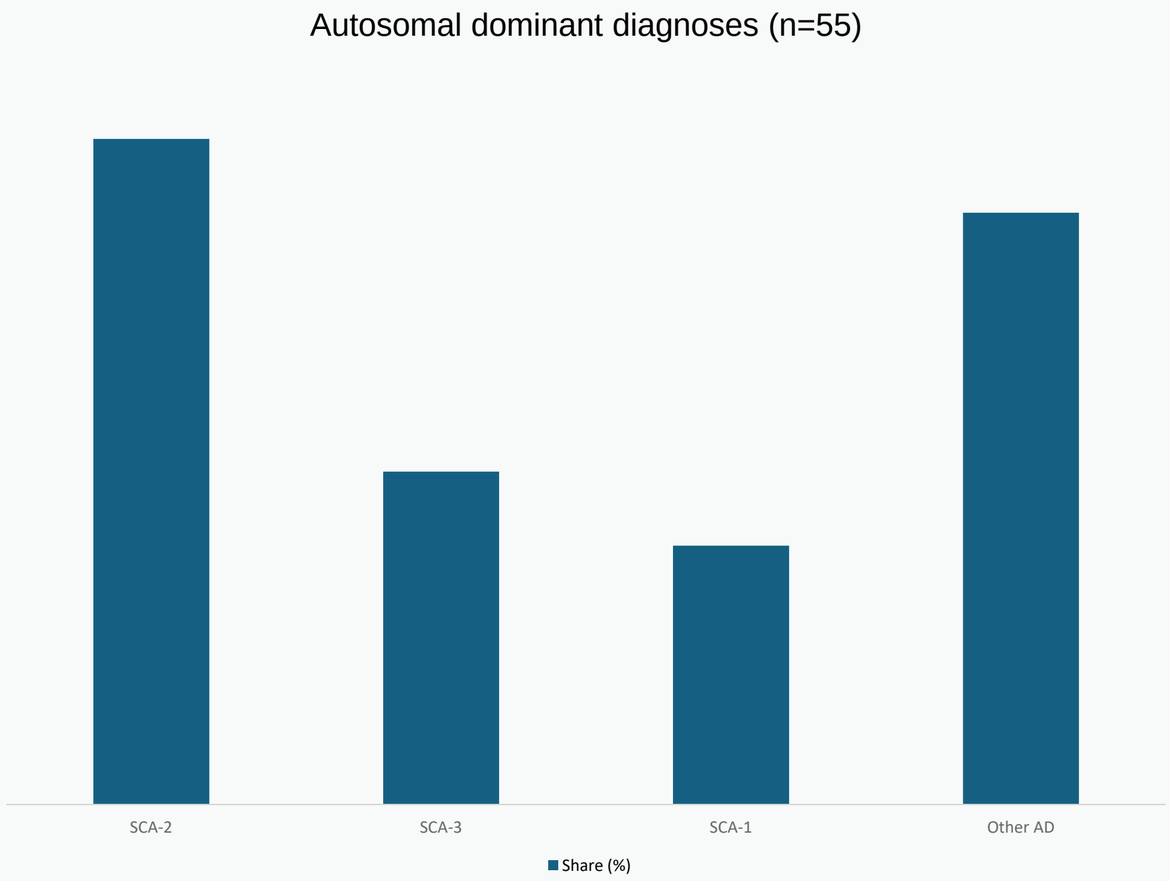
The sporadic group still carried monogenic diagnoses, but the algorithm had to work harder and avoid low-yield sequential testing.

Stratum	Solved / total	Yield
AD pedigrees	41 / 81	50.6%
AR pedigrees	20 / 29	69.0%
Sporadic ataxia	29 / 179	16.0%

Counts and percentages summarized from the paper Results section.

Dominant ataxias were led by SCA-2

The Argentinean molecular landscape contrasted with the global emphasis on SCA-3.



36%

SCA-2 among AD diagnoses

clinical clue — markedly slow horizontal saccades in 15/20 SCA-2 cases

MRI clue — brainstem atrophy and hot-cross-bun-like changes supported suspicion

AD distribution from Results; SCA-2 phenotype flags summarized from Results and Discussion.

Recessive disease was dominated by Friedreich ataxia, then fragmented

After FXN, the recessive landscape dispersed across many genes.

58

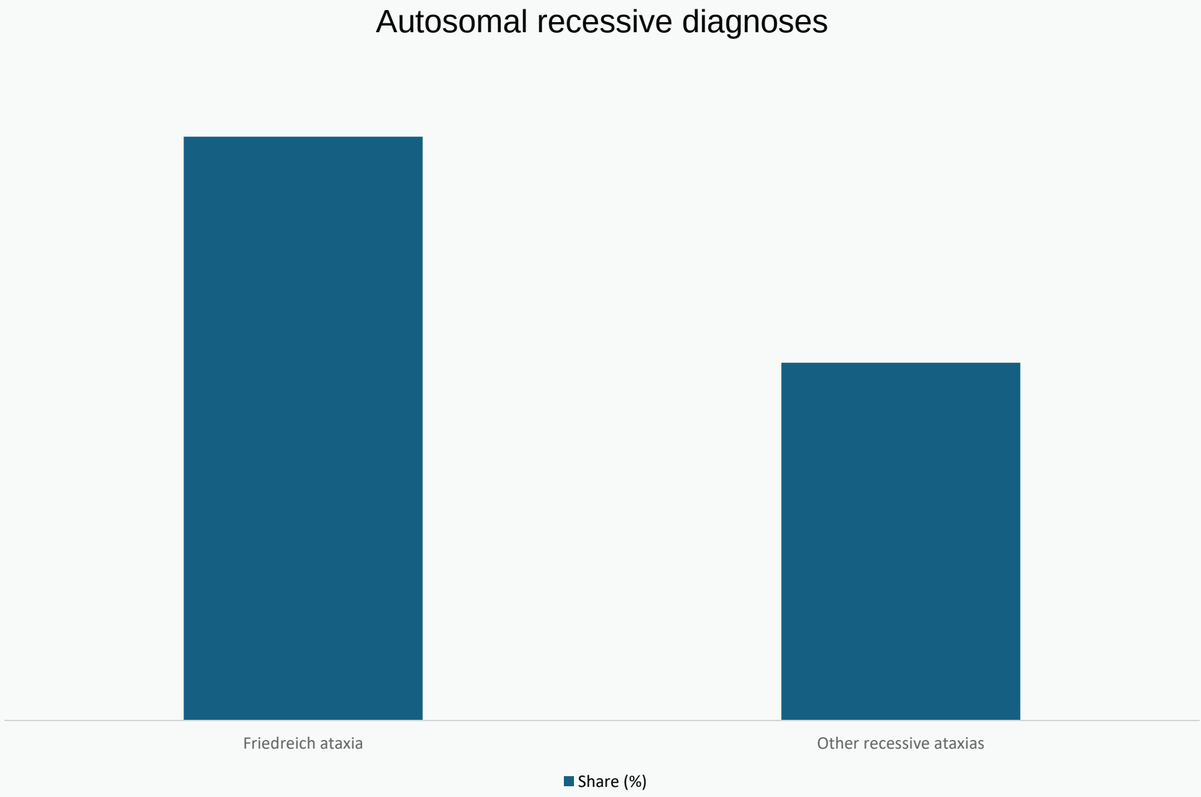
AR diagnoses

62%

Friedreich ataxia

12

non-FA recessive genes



AR group: 58 subjects. Other recessive ataxias included multiple rare genes.

Phenotypic red flags guided molecular choice

The source deck’s red-flag table was rebuilt here as an editable clinical comparison.

Feature	SCA-2 (dominant)	Friedreich ataxia (recessive)
Oculomotor flags	Markedly slow horizontal saccades in 75% of cases	Macro-square waves and hypometric saccades
Extra-cerebellar signs	Parkinsonism and polyneuropathy in the clinical spectrum	Myocardiopathy, pes cavus and diabetes as systemic clues
MRI findings	Brainstem atrophy and signal intensity changes; hot-cross-bun-like pattern	Cerebellar atrophy primarily in advanced disease; otherwise often normal early

75% corresponds to 15/20 SCA-2 cases with markedly slow horizontal saccades. FA feature counts are summarized from Results.

NGS solved the hard residual cases

Panels, exomes and genome sequencing were used after nondiagnostic first-tier testing.

26

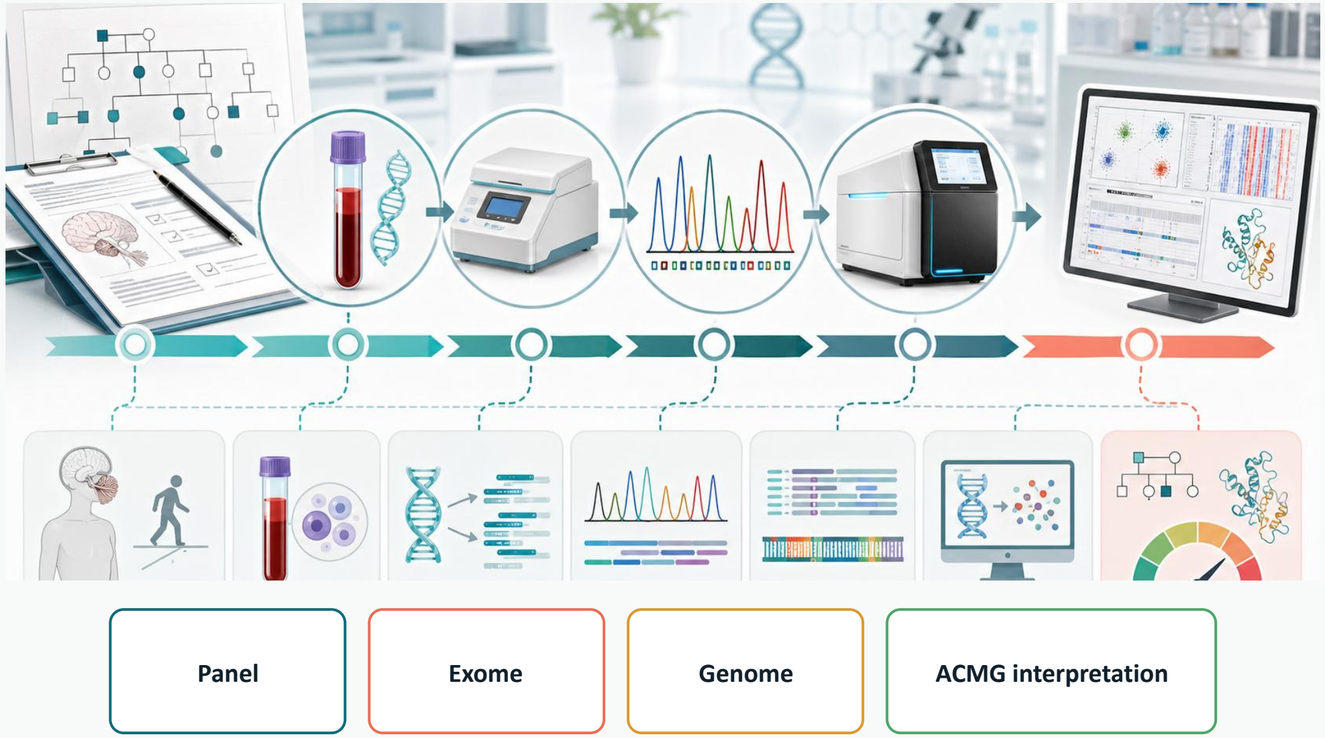
patients requiring NGS-based assays

17/26

diagnostic NGS results

65%

NGS diagnostic yield

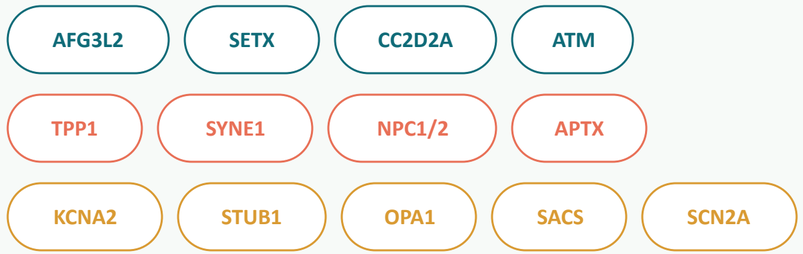


The value was not only yield: NGS reduced nonspecific testing when complex or atypical phenotypes escaped repeat-expansion and single-gene tests.

NGS subset: multigene panels, exome sequencing and whole genome sequencing.

The residual cases were genetically diverse

NGS did not reveal one hidden common diagnosis; it exposed the long tail of ataxia genetics.



rare

variants across multiple inheritance models

The program’s diagnostic logic had to accommodate repeat expansions, single-gene testing, panels, exomes and genome sequencing without losing the clinical phenotype.

Genes listed are representative examples from NGS diagnoses reported in the paper.

Molecular diagnosis changed care, not only nomenclature

A confirmed subtype supports counseling, family testing, surveillance and a rational testing pathway for future patients.

- **Subtype-specific counseling**
- **Cascade testing and reproductive advice**
- **Risk surveillance and anticipatory care**
- **Smarter testing for the next family**

Care implications synthesized from the study conclusion.

Algorithm, gene, panel: a scalable diagnostic model

The study lays groundwork for rational genetic diagnostic programs for ataxias in Argentina.

1

Know the local subtype distribution

2

Use phenotype to prioritize tests

3

Deploy NGS as targeted rescue

4

Convert diagnosis into family care

The remaining gap is access: broader public availability of state-of-the-art molecular diagnosis is needed to shorten the odyssey.

Paper DOI: 10.1038/s10038-020-0785-z

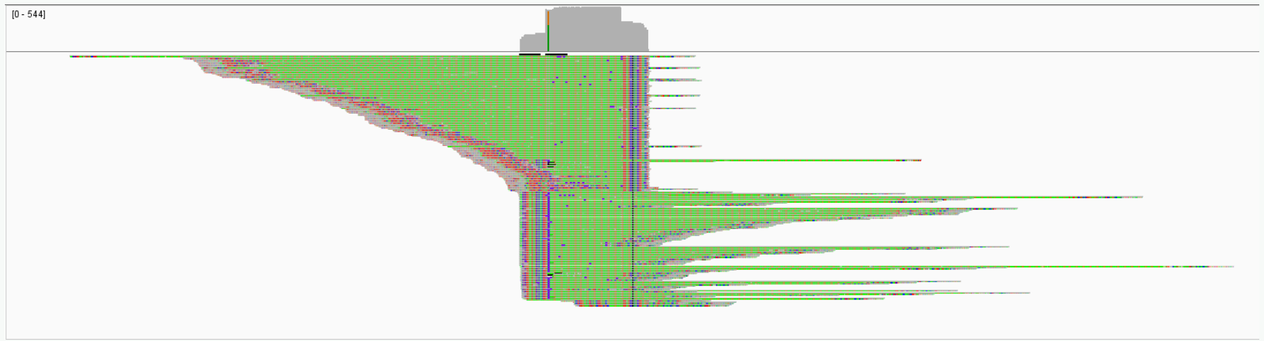
The next diagnostic frontier is late-onset ataxia

After panels and WES, CANVAS and SCA27B make the blind spot visible: pathogenic repeat expansions outside the coding exome.

CANVAS
RFC1 biallelic repeat expansion

SCA27B
FGF14 intronic GAA expansion

Shared diagnostic issue
Late-onset phenotype + negative WES



Oxford Nanopore long reads can span the repeat and show the allele architecture directly, instead of inferring it from missing or clipped short-read signal.

Late-onset cerebellar ataxia: LOCA. CANVAS: cerebellar ataxia, neuropathy, vestibular areflexia syndrome.

A negative WES does not rule out genetic ataxia

For LOCA, the critical question becomes: what kind of variant was the assay unable to see?

Short-read / WES blind spots

Intronic repeats, long insertions, structural variants and low-mappability regions

What long reads add

End-to-end molecules that cross the repeat and preserve phase, motif and size

Clinical trigger

Onset after 50, ocular motor signs, episodic vertigo/spells or CANVAS pattern

The source deck framed SCA27B as a classic LOCA blind spot for WES due to a deep intronic GAA expansion in FGF14.

Two late-onset patterns should prompt repeat-expansion testing

The point is not to order long reads for everyone; it is to recognize the phenotypes where they answer a specific question.

Clinical pattern	CANVAS / RFC1	SCA27B / FGF14
Core phenotype	Late-onset cerebellar ataxia with sensory neuronopathy and bilateral vestibular areflexia	Late-onset cerebellar ataxia, often with downbeat or gaze-evoked nystagmus
History clues	Chronic cough, sensory symptoms, oscillopsia, imbalance in darkness	Episodic vertigo or spells early, progressive gait instability and dysarthria
Molecular target	Biallelic pathogenic RFC1 repeat expansion	Heterozygous intronic FGF14 GAA repeat expansion
Assay logic	Target the repeat motif and zygosity	Size the expanded GAA allele and assess repeat structure

Clinical pattern summary built from the late-onset ataxia source deck and established repeat-expansion testing logic.

Long-read sequencing: SCA27B patient NR

Oxford Nanopore reads directly show the expanded FGF14 GAA allele.

NR

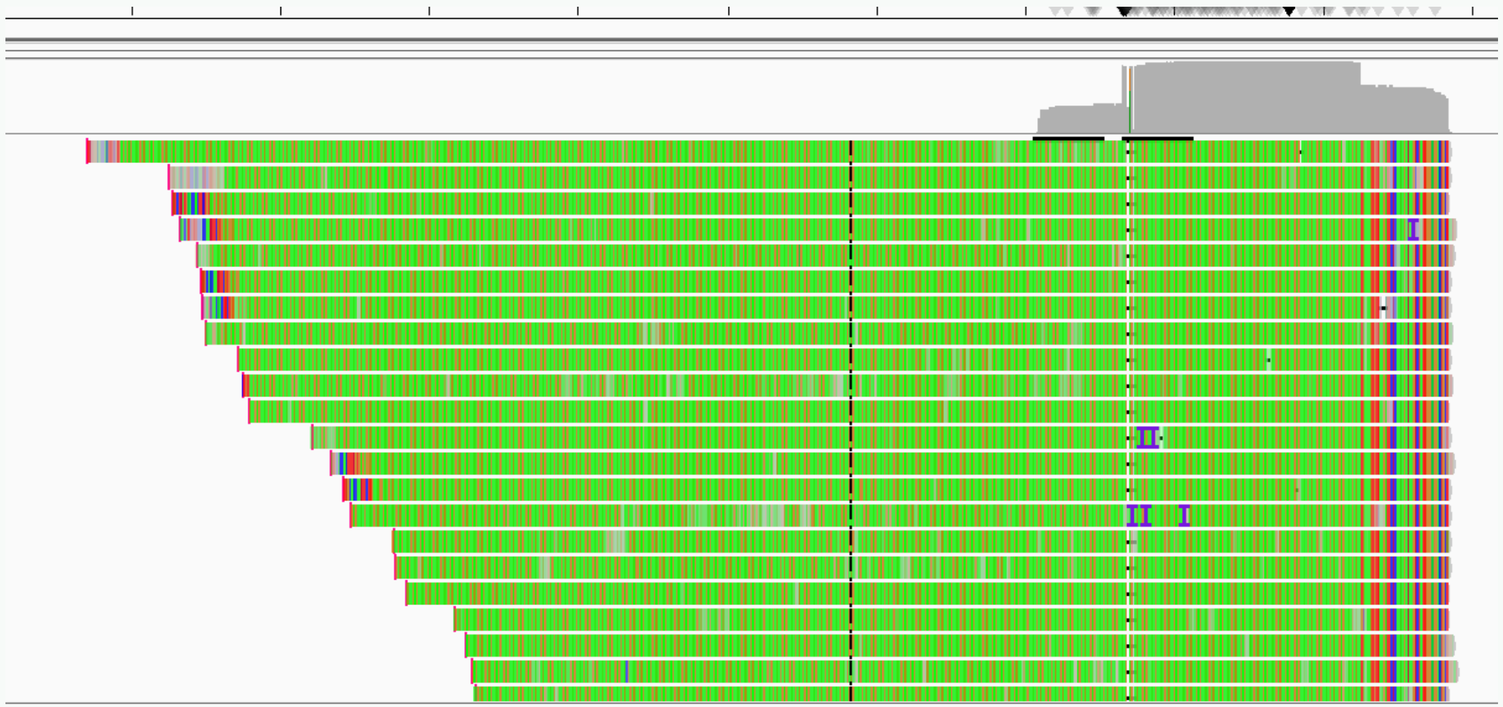
patient identifier in source deck

855 bp

trimmed amplicon read

GAA x285

expanded repeat estimate



In a live diagnostic workflow, this converts a clinical suspicion into a molecular diagnosis that standard WES would miss.

Alignment image and values from the attached late-onset ataxia presentation.

Long reads turn the program from algorithm to assay design

The same principle that structured ataxia testing now extends to non-coding repeat expansions.

JP

second SCA27B patient

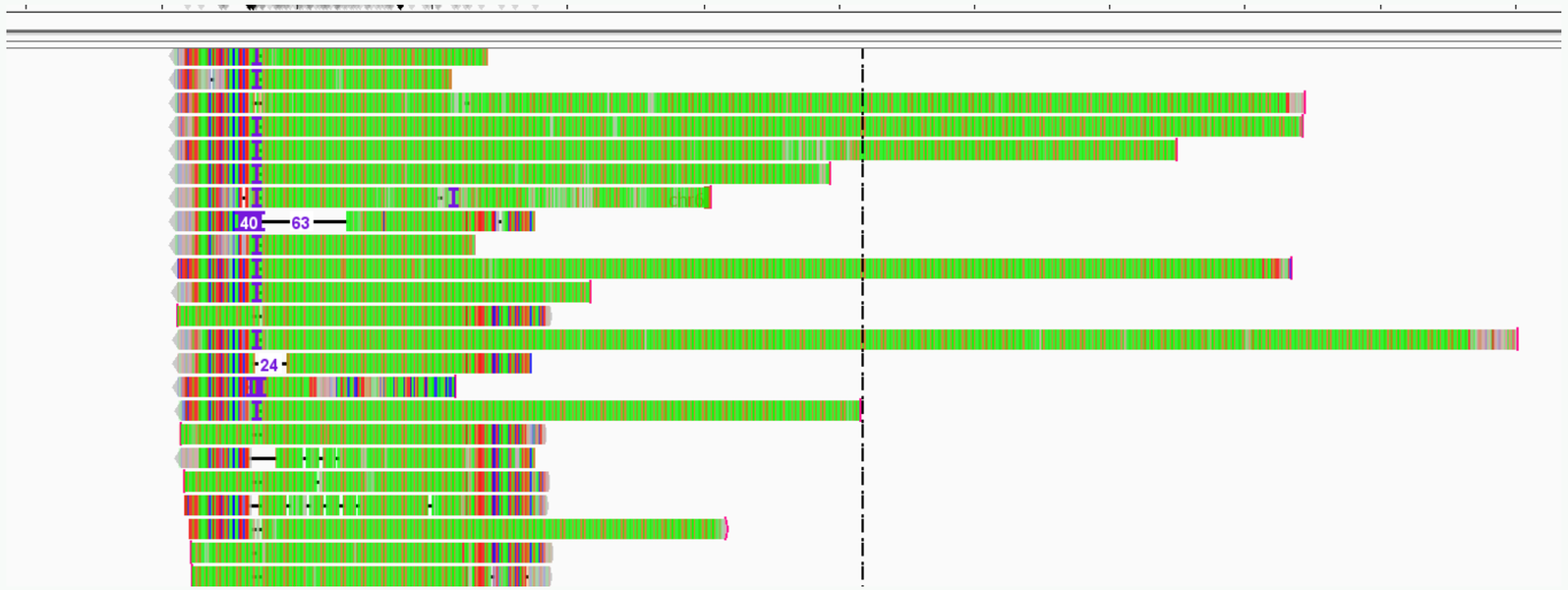
890 bp

amplicon read

GAA x296

expanded repeat estimate

Closing message: phenotype selects the locus; long reads resolve the allele.



Recognize LOCA pattern

Test RFC1 / FGF14 repeats

Use ONT when sizing matters

Return result to family care

Oxford Nanopore alignment image and repeat estimate from the attached source presentation.

Thank you very much to my team!

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