UK Dementia Research Institute

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The genetics of cerebellar ataxia

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Queen Square MDC MOVEMENT DISORDERS CENTRE

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

The clinico-genetic connection in the postgenomic era

Clinical expertise

Deep phenotyping

Exact genetic diagnosis

Neurogenetics and Lab expertise

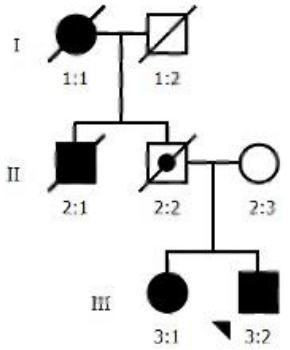
Best pipeline, even beyond standard of care

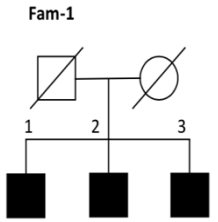
Exclude acquired causes

Table 1. IDENTIFIABLE CAUSES OF NONGENETIC ATAXIA	
Type	**Cause**
Congenital	Developmental
Mass lesion of a specific type	Tumor, cyst, aneurysm, hematoma, abscess, normal pressure or partial obstructive hydrocephalus
Vascular	Stroke, hemorrhage; subcortical vascular disease
Infectious/Post-infectious/ Post-vaccination	Anthrax; Epstein-Barr; enterovirus; HIV; HTLV; prion disease; Lyme disease; syphilis; measles, rubella, varicella; Whipple's disease; progressive multifocal leukoencephalopathy
Post-anoxic, post-hyperthermic, post-traumatic	
Chronic epilepsy	
Metabolic	Acute thiamine (B1) deficiency; chronic vitamin B12 and E deficiencies; autoimmune thyroiditis and low thyroid levels
Toxic *Drug reactions*	Amiodarone, cytosine arabinoside, 5-fluorouracil, lithium, phenytoin, valproic acid, and others
Environmental	Acrylamide, alcohol, organic solvents, organo-lead/mercury/tin, inorganic bismuth/mercury/thallium
Immune-mediated *Vasculitis*	Behcet's, giant cell arteritis, lupus, and others
Paraneoplastic	Anti-Yo, Hu, Ri, MaTa, CV2, Zic 4; anti-calcium channel; anti-CRMP-5, ANNA-1,2,3, mGluR1, TR
Other autoantibodies	Anti-GluR2, GAD, MPP1, GQ1b ganglioside; anti-gliadin (most common – reported also in the inherited syndromes as a possible secondary factor; treated with gluten-free diet)
Anti-immune therapies used in reported cases of immune-mediated cerebellar ataxia	Steroids, plasmapheresis, IVIG, rituximab, mycophenolate mofetil, methotrexate, and others

General ataxia investigations: Susan L. Perlman: Ataxia Disorders. An overview for Physicians (ISBN: 0-943218-14-4)

Inherited Ataxias





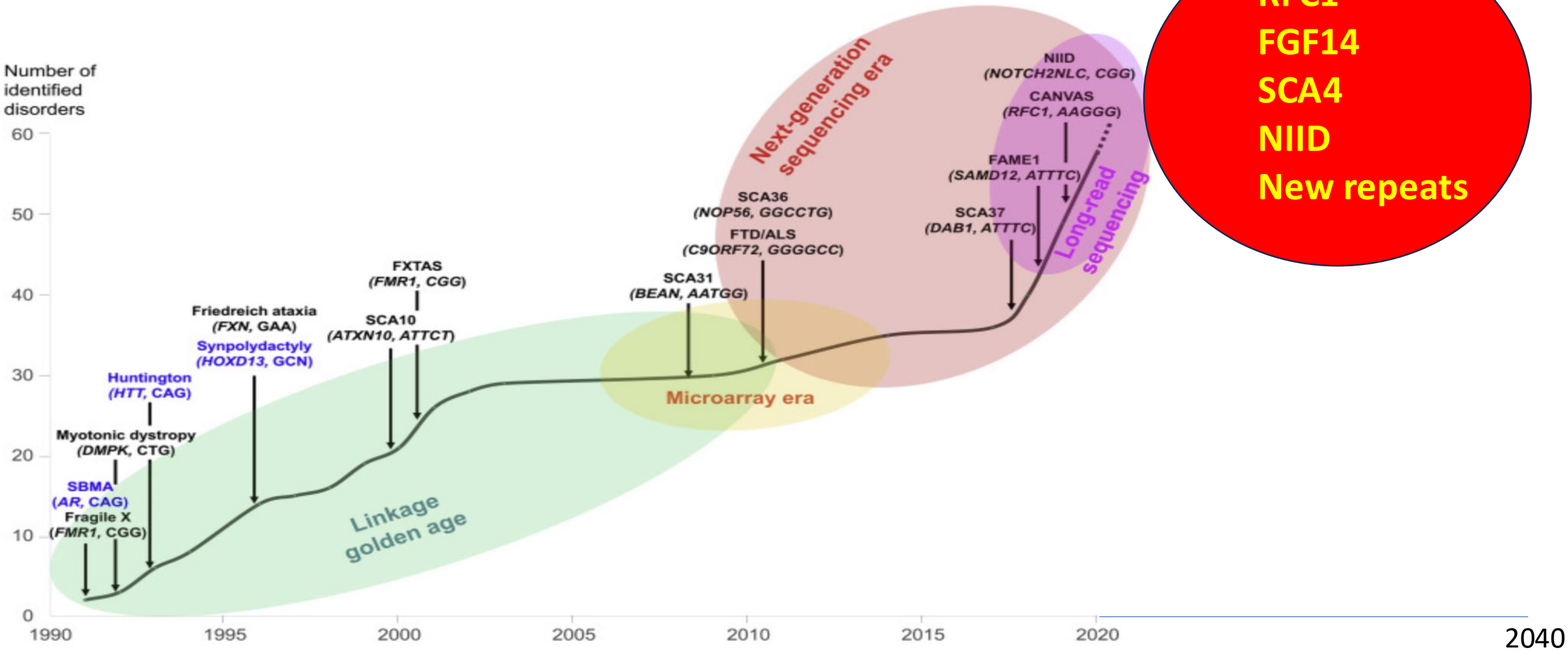
Slowly progressive

- **Early onset (<20yrs)** – Usually Autosomal Recessive
- **Late onset (>20yrs)** – Usually Autosomal Dominant
- **Sporadic or idiopathic** – ILOCA (onset often 40's - 80's), MSA (onset 50-60)

Repeats - timeline

Whole genome long-read sequencing era

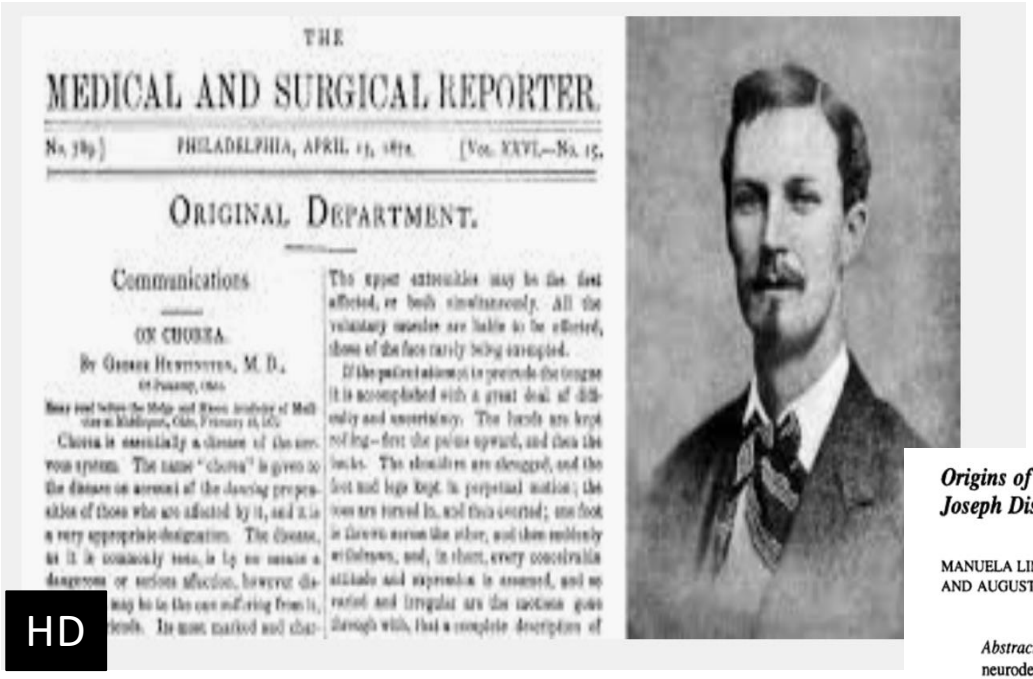
RFC1
FGF14
SCA4
NIID
New repeats



Timeline of repeat expansion discovery in human disorders

Adapted from: Depienne, C AJHG Volume 108, Issue 5, P764-785

Many named neurological disorders are caused by repeat expansions


THE

MEDICAL AND SURGICAL REPORTER.

No. 389.] PHILADELPHIA, APRIL 13, 1872. [Vol. XXVI.—No. 15.

ORIGINAL DEPARTMENT.

Communications

ON CHOREA.

By George Huntington, M. D.,

Chorea is essentially a disease of the nervous system. The name "chorea" is given to the disease on account of the dancing propensities of those who are afflicted by it, and it is a very appropriate designation. The disease, as it is commonly seen, is by no means a dangerous or serious affection, however distressing it may be to the one suffering from it.

The upper extremities may be the first affected, or both simultaneously. All the voluntary muscles are liable to be affected, those of the face rarely being exempted.

If the protrusion is prevented the tongue it is accomplished with a great deal of difficulty and uncertainty. The hands are kept moving—first the palms upward, and then the backs. The shoulders are shrugged, and the feet and legs kept in perpetual motion; the eyes are turned in, and then everted; one foot is thrown across the other, and then suddenly withdrawn, and, in short, every conceivable attitude and expression is assumed, and so varied and irregular are the motions gone through with, that a complete description of

HD

SCA36

Origins of a Mutation: Population Genetics of Machado-Joseph Disease in the Azores (Portugal)

MANUELA LIMA,[1] FRANCINE M. MAYER,[2] PAULA COUTINHO,[3] AND AUGUSTO ABADE[4]

Abstract Machado-Joseph disease (MJD) is an autosomal dominant neurodegenerative disorder of adult onset. In the islands of the Azores (Portugal), MJD reaches the highest prevalence reported worldwide. It has been postulated that it is highly represented in the Azorean population as a result of a founder effect. To test this hypothesis, we reconstructed the ascending genealogies of the 32 Azorean families presently identified as harboring the disease (103 patients), using parish records as the main source of data. These patients were originally from the islands of São Miguel, Terceira, Graciosa, and Flores. The genealogies of the two main Azorean American families (Machado and Joseph) were also reconstructed. To identify the links between the MJD families, we calculated the kinship coefficient between the proponents of these genealogies. The family from Terceira was linked to three different MJD families from Flores through common ancestors. No kinship was observed between the MJD families from São Miguel and families from any other island. Links between the two Azorean American families and Azorean MJD families were found. The founders present in more than one ascendance were identified. Their chronological and geographic distribution indicates that more than one MJD mutation was introduced in the Azores, probably by settlers coming from the Portuguese mainland. The molecular evidence to date corroborates these results, because two distinct haplotypes have been established, one on the island of São Miguel and the other on Flores. Therefore molecular biology studies confirm the accuracy of the conclusions drawn from the genealogical evidence supporting the absence of a founder effect for MJD in the Azorean population.

f volcanic origin located in the se mainland. These islands have

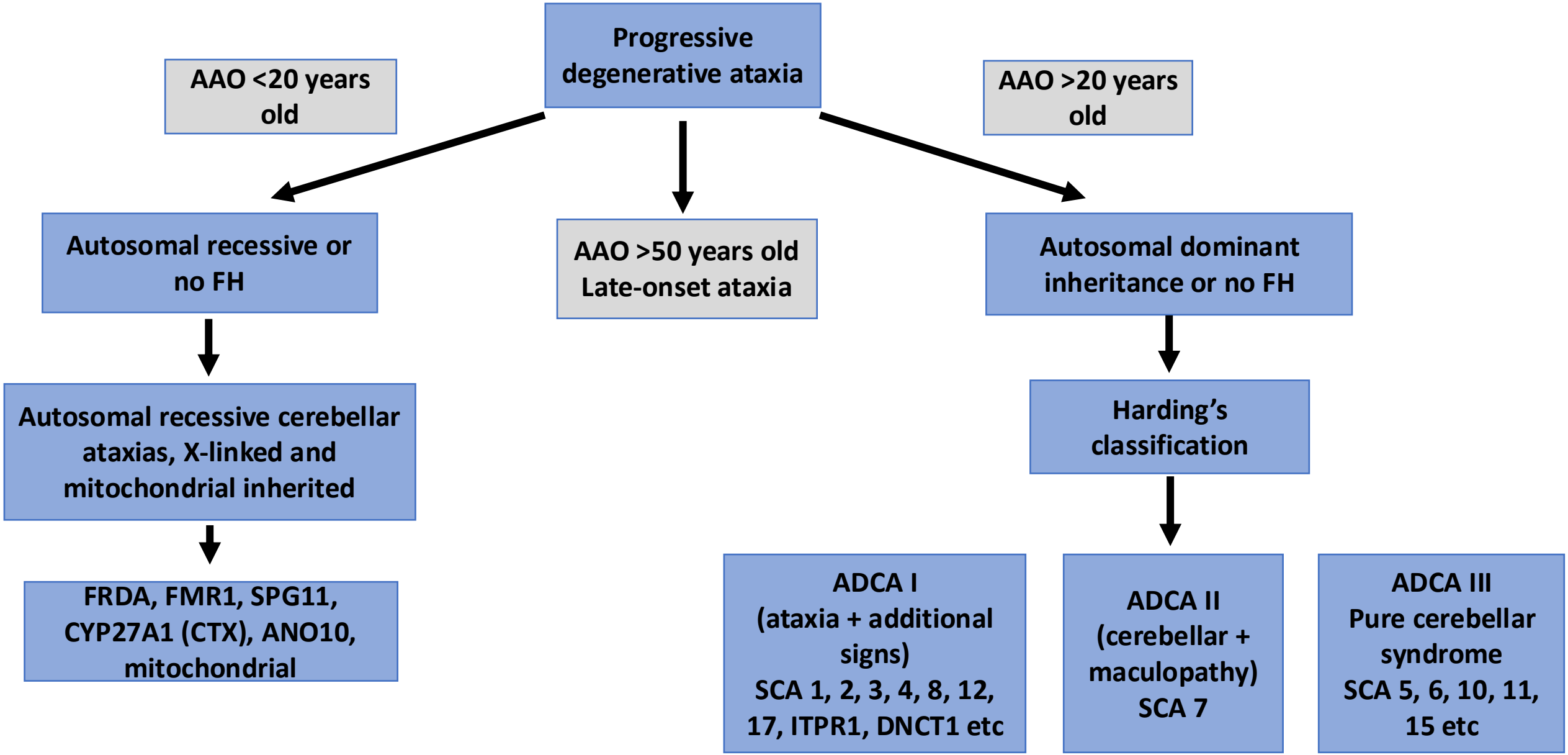
Machado Joseph

Nikolaus Friedreich

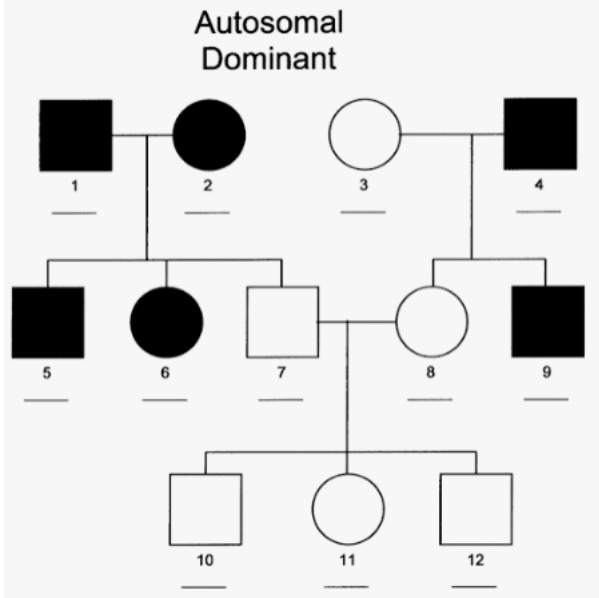
Cuba – SCA2

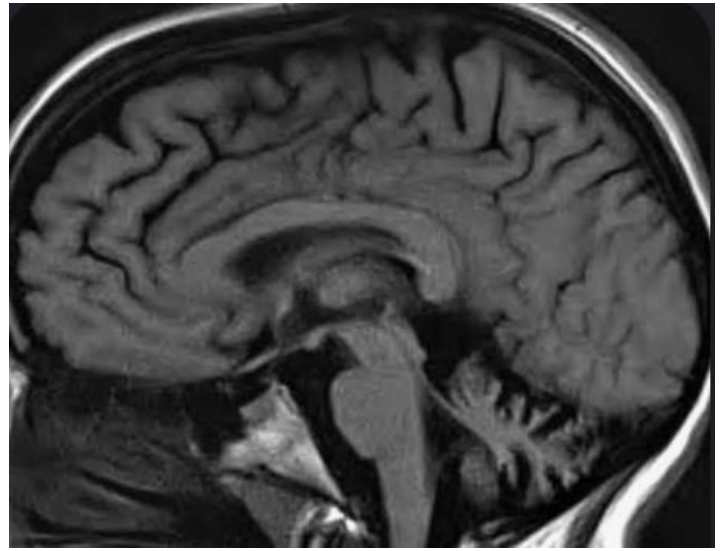
Holguin

Traditional classification



THE DOMINANTLY INHERITED ATAXIAS Associated Features in Differential Diagnosis	
Ataxic Disorder	**Typical Associated Clinical Features Beyond Ataxia and Dysarthria**
SCA1	Hyperreflexia/spasticity, cerebellar tremor, dysphagia, optic atrophy
SCA2	Slow saccades, hyporeflexia, cerebellar tremor, parkinsonism, dementia
SCA3	Nystagmus, spasticity (onset <35y), neuropathy (onset >45y), basal ganglia features, lid retraction, facial fasciculations
SCA4	Sensory axonal neuropathy, pyramidal signs
SCA5	Bulbar signs, otherwise predominantly cerebellar
SCA6	Nystagmus (often downbeat), otherwise predominantly cerebellar, onset >50y
SCA7	Macular pigmentary retinopathy, slow saccades, pyramidal signs
SCA8	Nystagmus, cerebellar tremor
SCA9	(reserved)
SCA10	Nystagmus, seizures
SCA11	Nystagmus, hyperreflexia
SCA12	Nystagmus, arm tremor, hyperreflexia
SCA13	Nystagmus, hyperreflexia, mental and motor retardation, childhood onset (adult onset is without retardation)
SCA14	Head tremor or myoclonus
SCA15	Nystagmus, hyperreflexia
SCA16	Nystagmus, head and hand tremor
SCA17	Dementia, psychosis, extrapyramidal features, hyperreflexia, seizures
SCA18	Nystagmus, Babinski sign, sensorimotor axonal neuropathy
SCA19	Cognitive impairment, nystagmus, tremor, myoclonus
SCA20	Palatal tremor, dysphonia
EA-1	Brief episodes of ataxia or choreoathetosis, interictal neuromyotonia. Phenytoin or carbamazepine responsive
EA-2	Episodes of ataxia lasting hours, interictal nystagmus, fatigue/weakness. Acetazolamide responsive
EA-3	Kinesigenic episodes of ataxia and vertigo, with diplopia and tinnitus. Acetazolamide responsive
EA-4	Episodes of ataxia with diplopia and vertigo, defective smooth pursuit. Not acetazolamide responsive
EA-5	Similar to EA-2, but later onset; generalized, absence, and myoclonic seizures. Acetazolamide responsive
EA-6	Episodic ataxia with alternating hemiplegia, migraine, and seizures
DRPLA	Epilepsy, myoclonus (onset <20y); dementia, psychosis, choreoathetosis (onset >20y)
GSS	Dementia, pyramidal signs

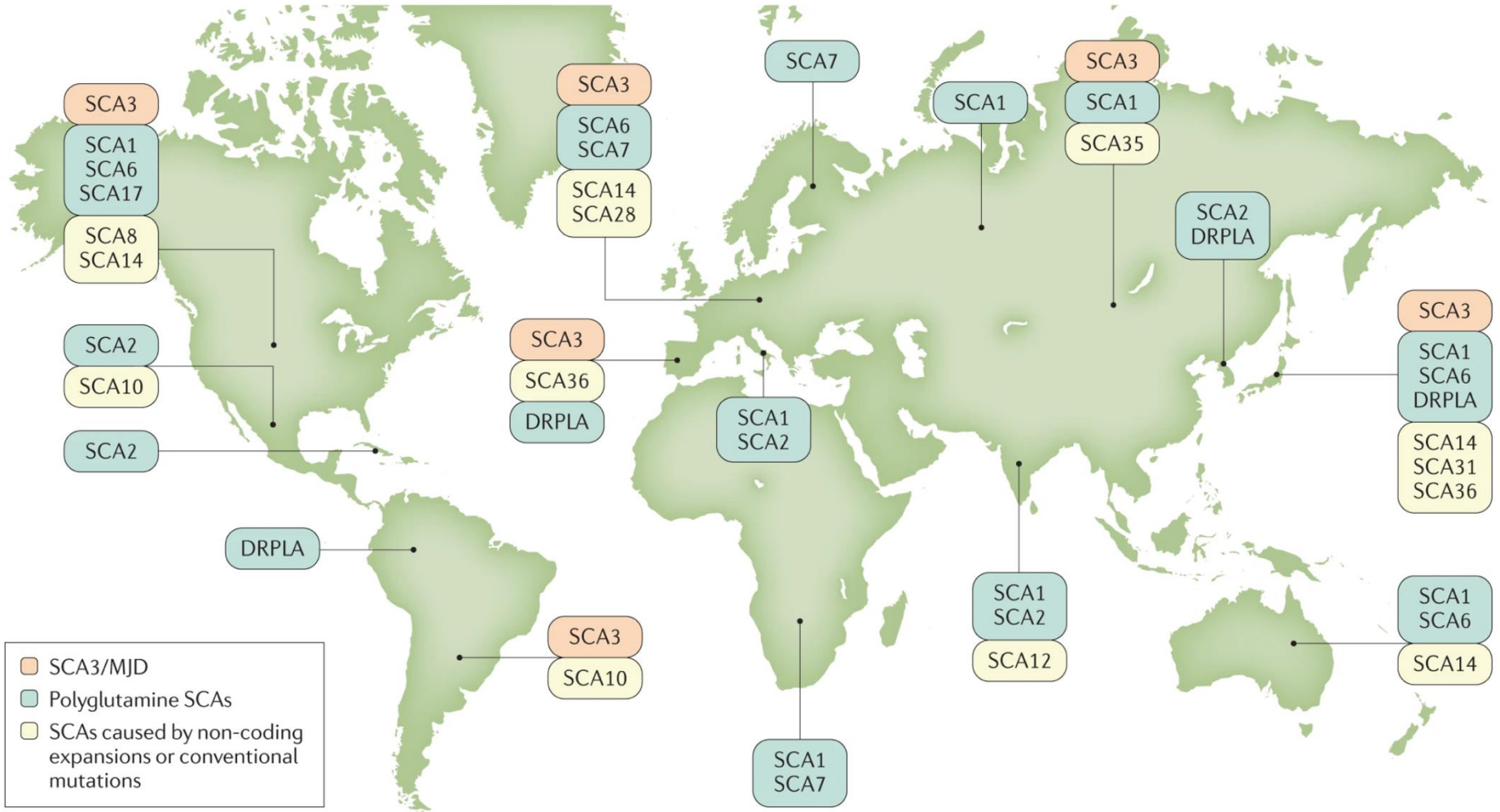




General ataxia investigations: Susan L. Perlman: Ataxia Disorders. An overview for Physicians (ISBN: 0-943218-14-4)

THE DOMINANTLY INHERITED ATAXIAS — Molecular Genetics				
Ataxic Disorder	Gene Locus	Gene/ Product	Mutation	Prevalence
SCA1	6p23	Ataxin-1	CAG expansion/coding exon. Normal <39 repeats. Disease-causing >44. If no CAT interruption, disease-causing 39-44	6-27% of dominant ataxias worldwide
SCA2	12q24	Ataxin-2	CAG expansion/coding exon. Normal <33 repeats, with CAA interruption. Disease-causing >33, with no CAA interruption (two patients with interrupted 34 expansion)	13-18% of dominant ataxias worldwide
SCA3/Machado-Joseph disease	14q24.3-q31	Ataxin-3	CAG expansion/coding exon. Normal <41 repeats. Disease-causing >45. Homozygous mutant genes cause earlier onset, more severe disease	23-36% of dominant ataxias worldwide
SCA4	16q22.1	Expansion in ZFHX3	Single-nucleotide C-T substitution in 5' untranslated region	Families in Utah and Germany; six families in Japan with later onset pure cerebellar syndrome
SCA5	11p11-q11	Spectrin stabilizes the glutamate transporter EAAT4	In-frame deletions; missense mutations	Lincoln family in US; families in Germany and France
SCA6	19p13	CACN 1A/P/Q type calcium channel subunit (disease mechanisms may result from both CAG repeat and channelopathy processes)	CAG expansion/coding exon. Normal <19 repeats. Disease-causing >19. Homozygous mutant genes cause earlier onset, more severe disease. Allelic with EA-2 (gene truncations) and hemiplegic migraine (missense mutations)	10-30% of dominant ataxias worldwide
SCA7	3p21.1-p12	Ataxin-7. Component of TFTC-like transcriptional complexes (disease mechanisms may result from both CAG repeat and transcriptional dysregulatory processes)	CAG expansion/coding exon. Normal <28 repeats. Disease-causing >37. Intermediate 28-36, may expand into disease range, especially with paternal transmission	2-5% of dominant ataxias worldwide; may be more common in Sweden and Finland
SCA8	13q21	Normal product is an untranslated RNA that functions as a gene regulator. Evidence for a translated polyglutamine protein (Ataxin-8) from an anti-parallel transcript has also been found	CTG expansion at 3' end. Normal <80 repeats. Disease-causing 80-300, although expansions in this range occur in non-ataxic persons and in other neurologic diseases. Expansions >300 may not cause disease in SCA8 pedigrees	2-4% of dominant ataxias worldwide; genetic testing results may be open to interpretation

SCA worldwide distribution



Spinocerebellar ataxia, Klockgether et al, Nature Reviews Disease Primers volume 5, Article number: 24 (2019)

SCA2

Presence of Spinocerebellar Ataxia Type 2 Gene Mutation in a Patient with Apparently Sporadic Parkinson's Disease: Clinical Implications

D-E Shan, R-S Liu, C-M Sun, S-J Lee, K-K Liao, B-W Soong

Movement Disorders
Volume 19

SCA3

mdc370449

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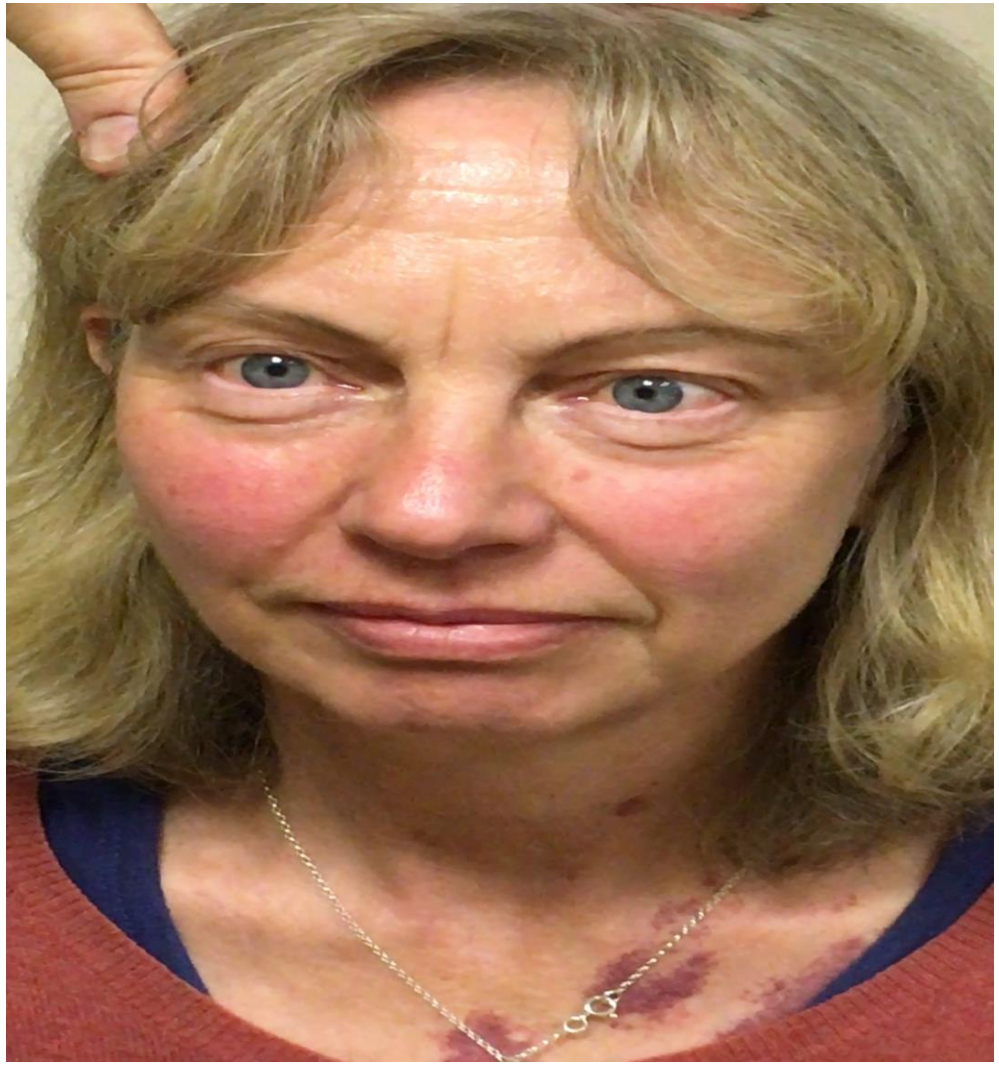
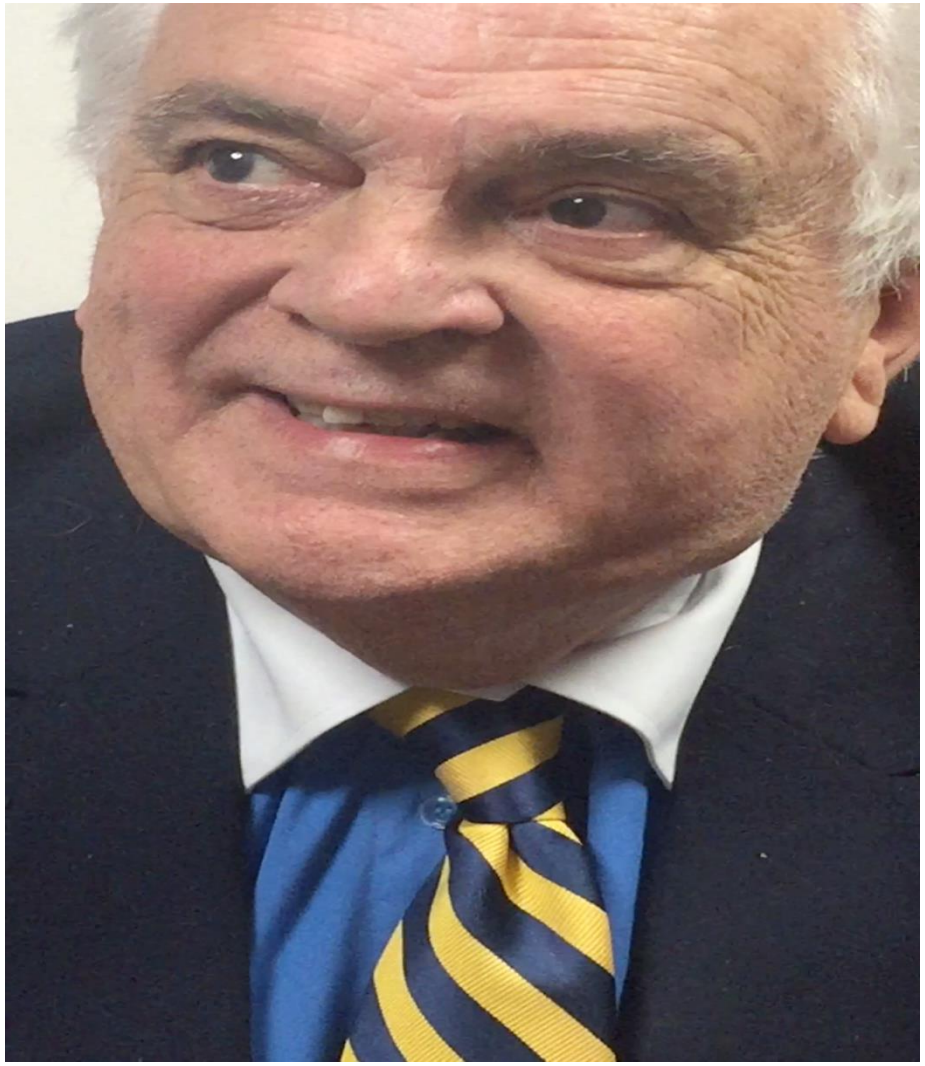
SCA6

AAO50

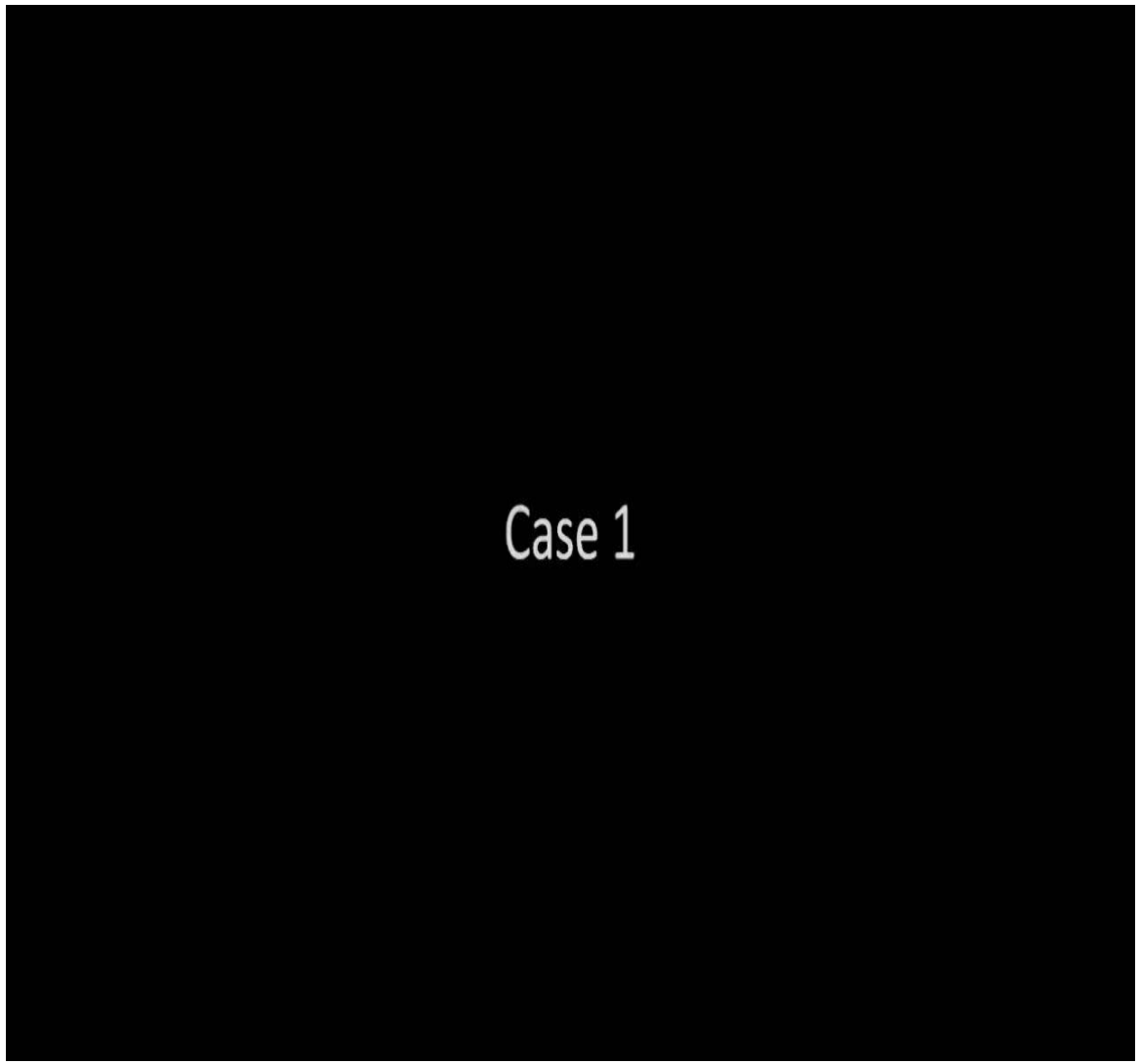


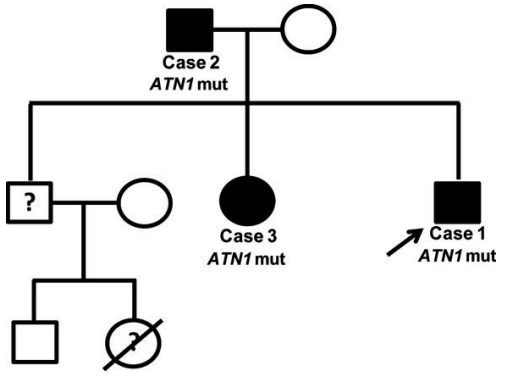
AAO35

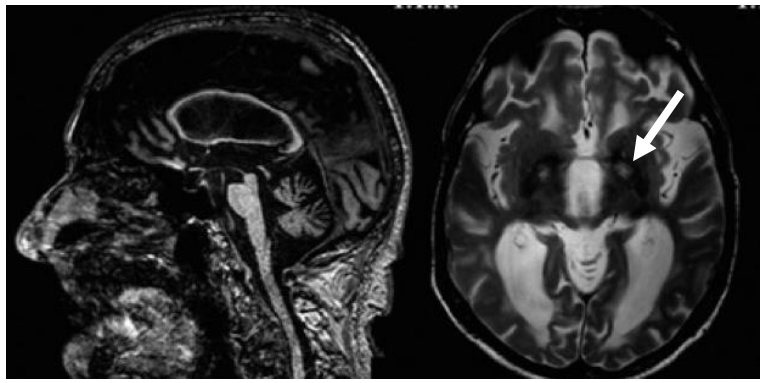


Same number of repeats – likely genetic modifying factors

Gowers Case







Case 1: A 57-year-old, with unremarkable medical and pharmacological history, complained of a progressive gait imbalance for 7 years.

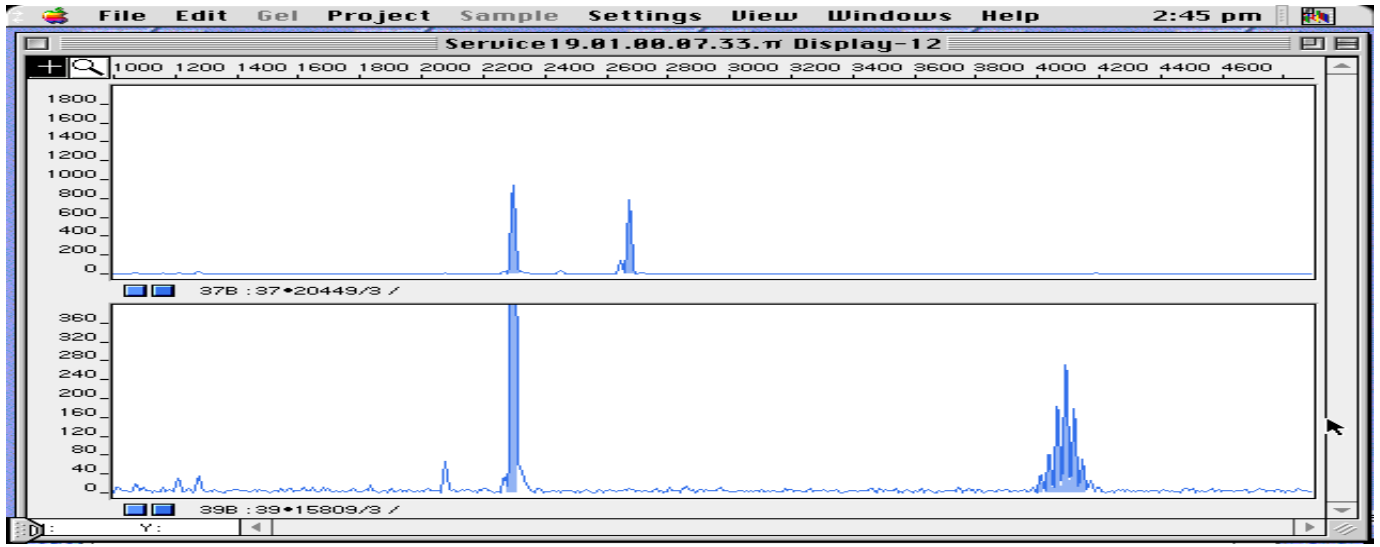
His father (case 2), a 91-year-old, presented progressive cognitive decline and gait difficulties for 10 years.

The sister of case 1 (case 3), a 60-year-old woman, presented a mild postural tremor of upper limbs for 1 year.

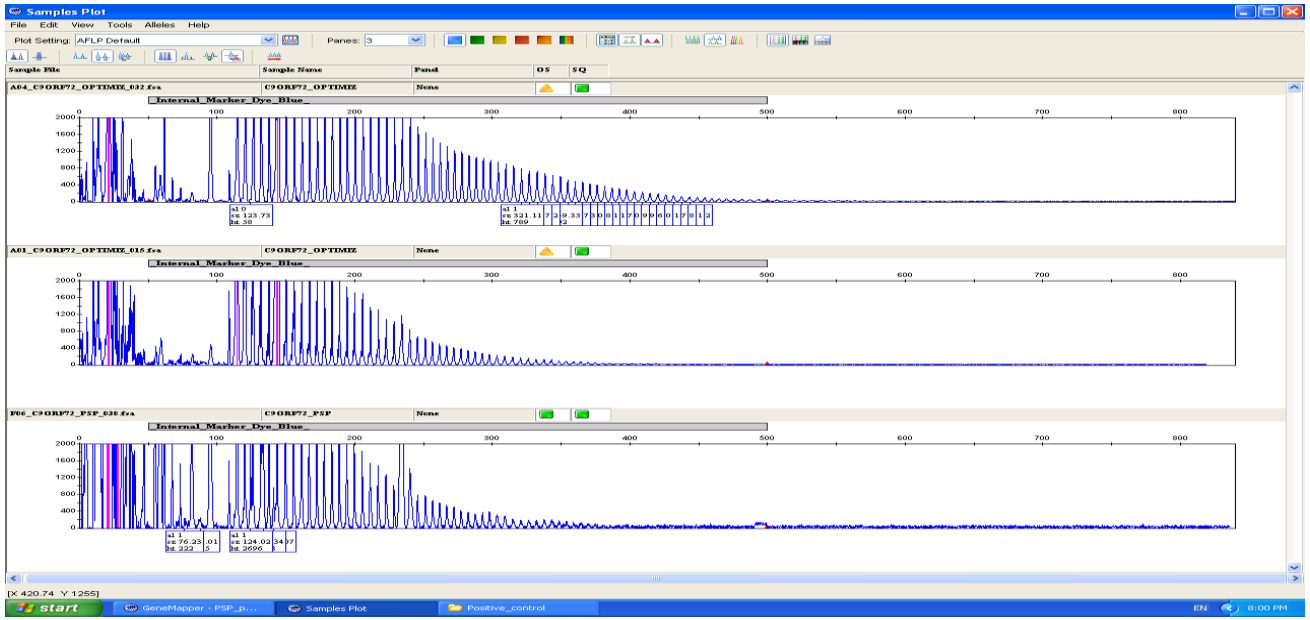
Movement Disorders Clinical Practice, Volume: 2, Issue: 3, Pages: 313-315, First published: 22 May 2015, DOI: (10.1002/mdc3.12179)

Repeat diseases

SCA1, 2, 3, 6
7, 12, 17, HD,
MD, Kennedy's



Very large repeat
diseases
Such as C9ORF72
and RFC1



Often over 150 repeats (GGGGCC). Not amenable to MiSeq or HiSeq

Question 1

What is the initial genetic test that should be done in a dominantly inherited ataxia?

A. Exome or genome sequencing to identify point mutations in known ataxia genes

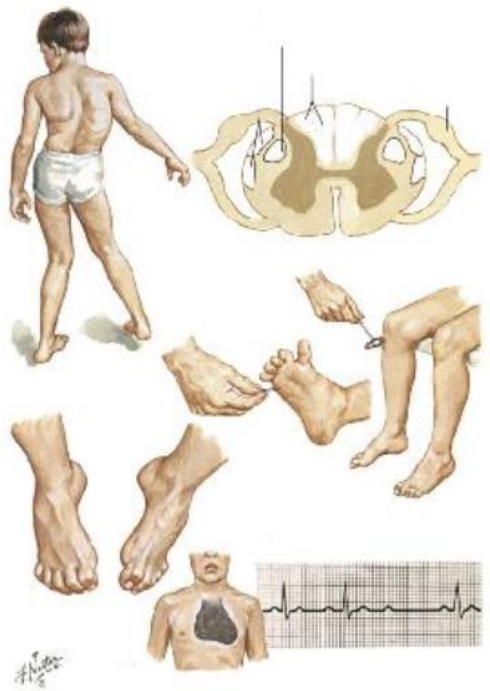
B. SCA repeat expansions, mainly focusing on SCAs1-3, 6, 7

C. Microarray for deletions

Recessive ataxias

THE RECESSIVELY INHERITED ATAXIAS Molecular Genetics				
Phenotype	**Ataxic Disorder**	**Disease**	**Gene/Protein**	**Gene**
Friedreich's ataxia-like	Friedreich's ataxia	FRDA	Frataxin	FXN
	Ataxia with vitamin E deficiency	AVED	-Tocopherol transfer protein	TTPA
	Abeta-lipoproteinemia	ABL	Microsomal triglyceride transfer protein	MTP
	Refsum's disease	–	Phytanoyl-CoA hydroxylase	PHYH
			Peroxisome biogenesis factor 7	PEX7
Friedreich's ataxia-like with cerebellar atrophy	Late-onset Tay-Sachs disease	LOTS	ß-Hexosaminidase A	HEXA
	Cerebro-tendinous xanthomatosis	CTX	Sterol-27 hydroxylase	CYP27
	DNA polymerase related disorders	MIRAS	DNA polymerse	POLG1
	Infantile onset spinocerebellar ataxia	IOSCA	Twinkle,Twinky	C10orf2
Early onset cerebellar ataxia with retained reflexes (EOCARR)	Ataxia-telangiectasia	AT	Ataxia- telangiectasia, mutated	ATM
	Ataxia-telangiectasia- like disorder	ATLD	Meiotic recombination 11	MRE11
	Ataxia with oculomotor apraxia type 1	AOA1	Aprataxin	APTX
	Ataxia with oculomotor apraxia type 2	AOA2	Senataxin	SETX
	Autosomal recessive ataxia of Charlevoix-Saguenay	ARSACS	Sacsin	SACS

FRDA
Usually homozygous or compound heterozygous repeat expansion in FXN.
Can be a combination of expansion + point mutation



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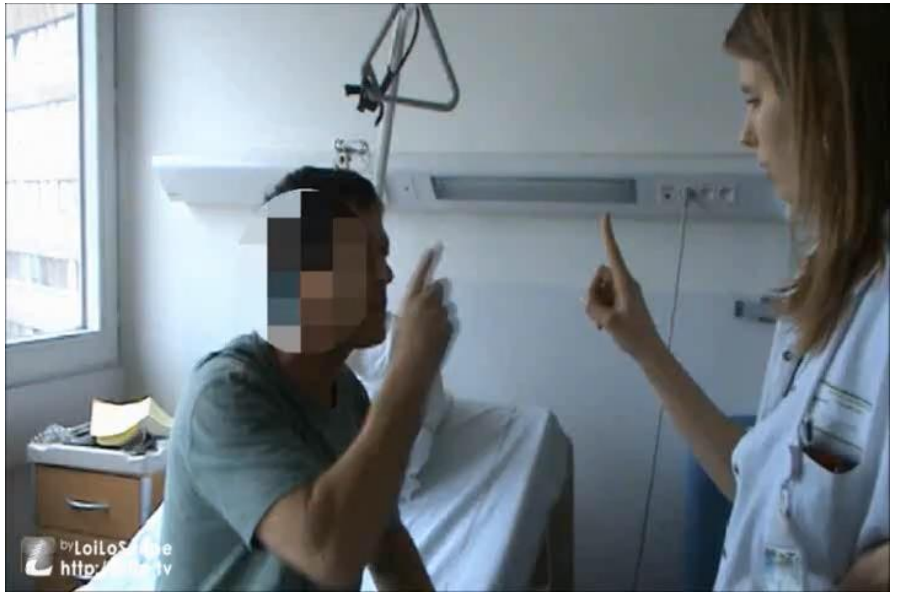
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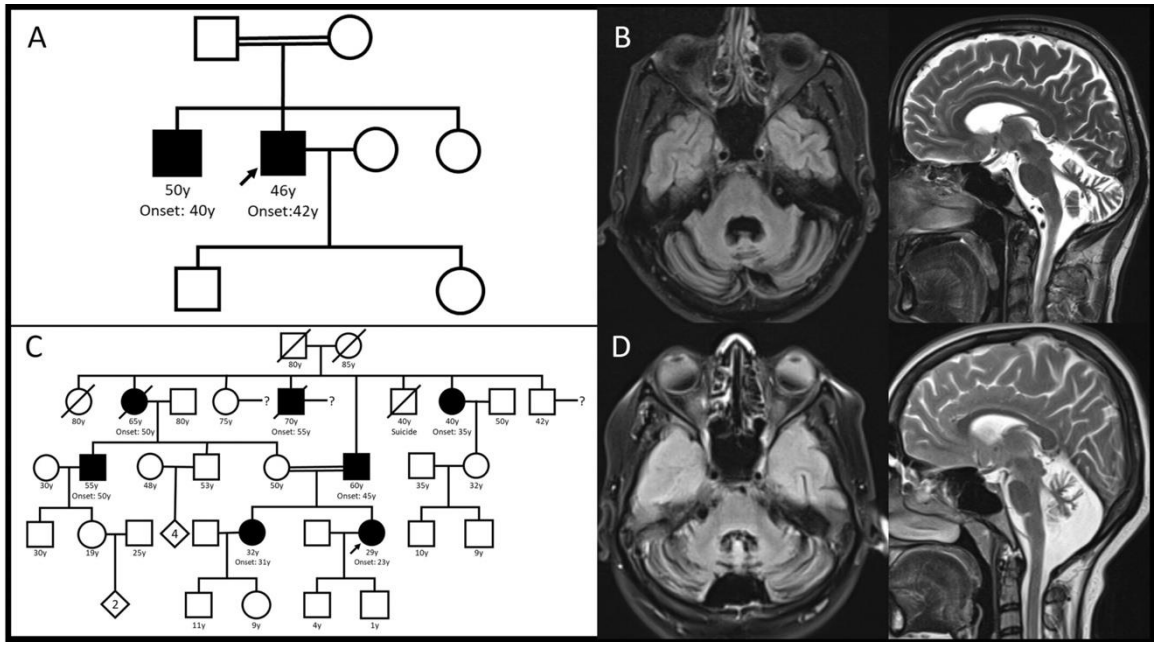
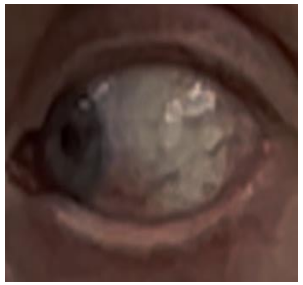
ANO10-Related Spinocerebellar Ataxia





Video-e1
Case-1

Video-e2
Case-2

Movement Disorders, Volume: 40, Issue: 2, Pages: 385-386, First published: 08 January 2025, DOI: (10.1002/mds.30107)

Question 2

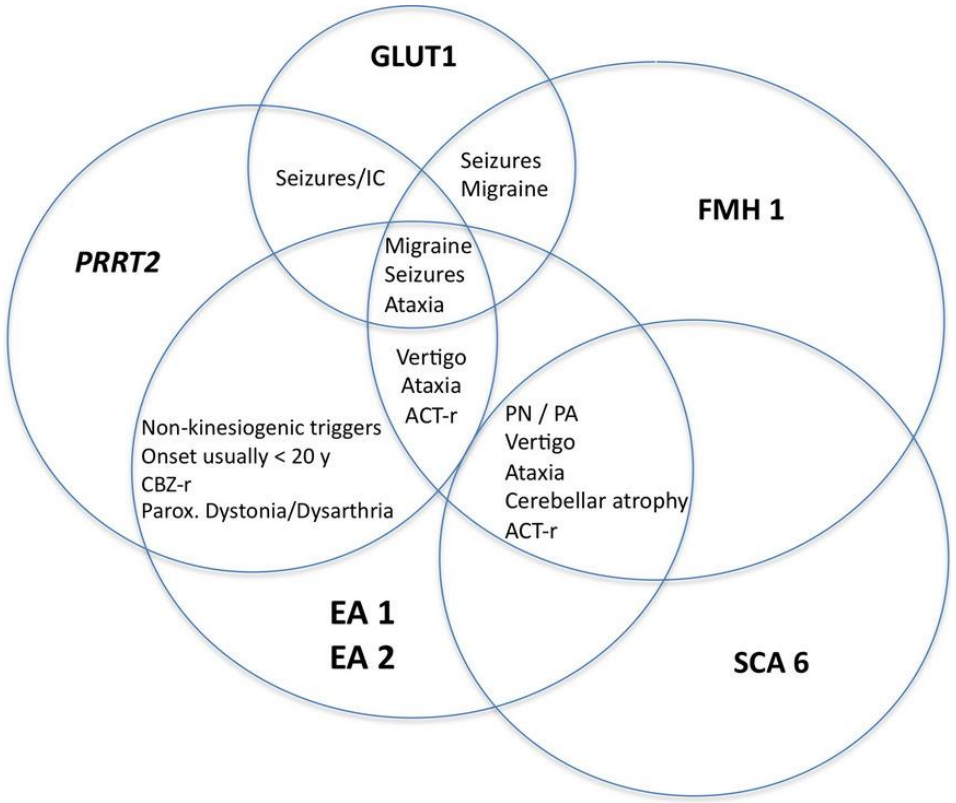
In Friedreich's ataxia what are the genetic causes?

1. Biallelic repeat expansions and rare point mutations in the Frataxin gene

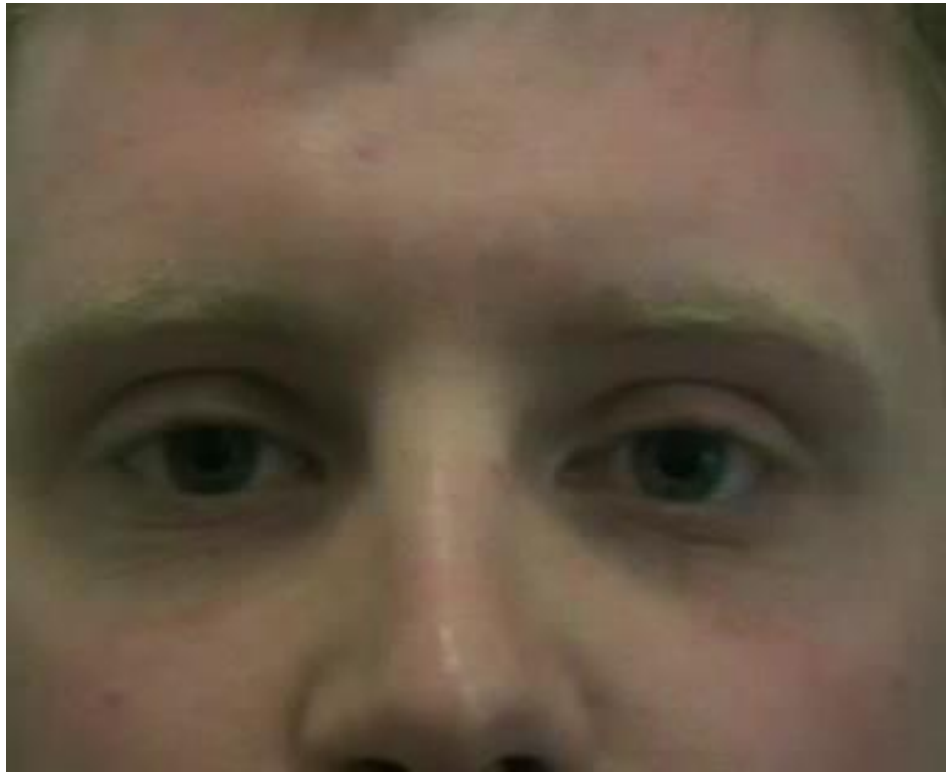
2. Homozygous repeat expansions

3. Chromosome 9 deletions and point mutations in the Frataxin gene

The Clinical Spectrum of Autosomal-Dominant Episodic Ataxias



FGF14



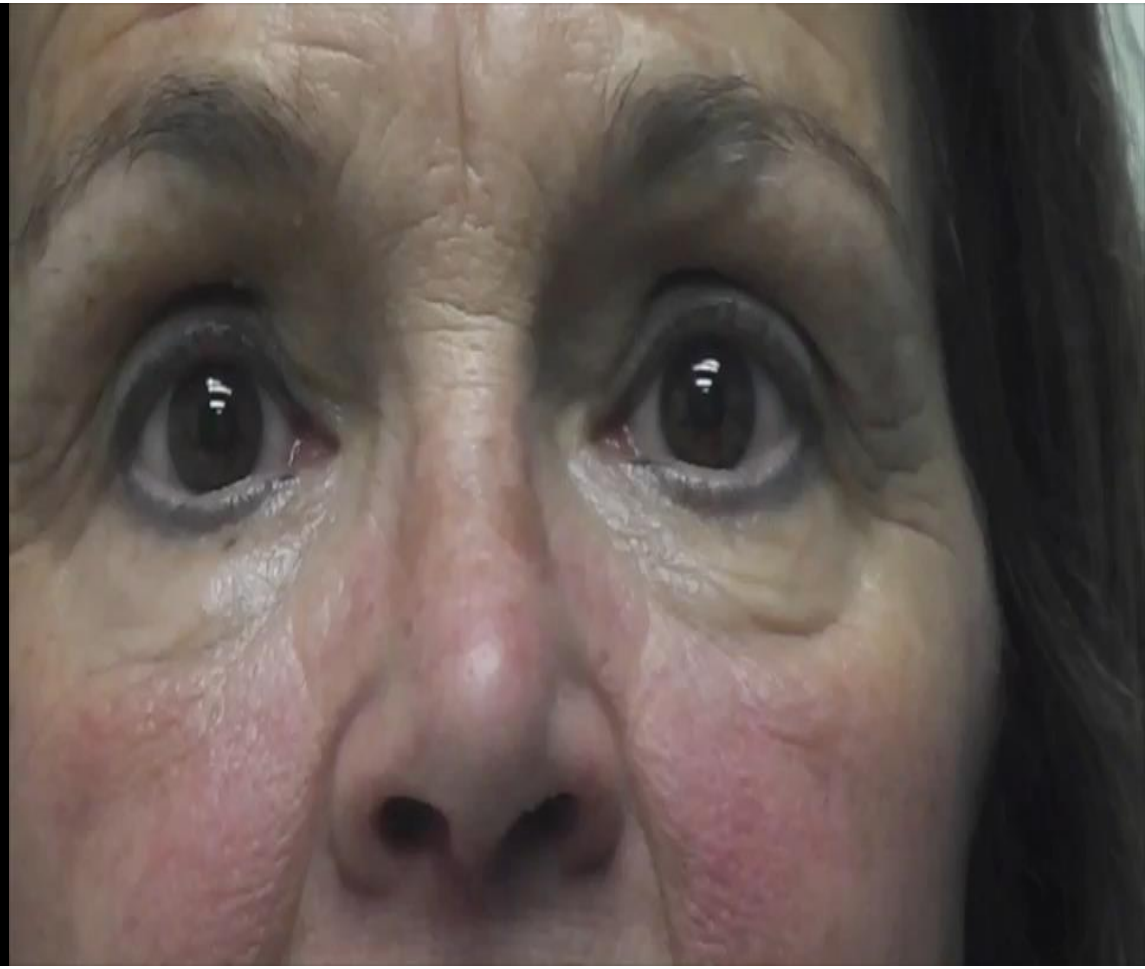
mds25489

Movement Disorders Clinical Practice, Volume: 1, Issue: 4, Pages: 285-290, First published: 28 July 2014, DOI: (10.1002/mdc3.12075)

NPC

68y diagnosed PD, reported slurred speech and balance falls at 55y. Developed word-finding difficulty, slow thinking, forgetfulness, clumsiness, hand tremors, abnormal gait

mdc313085-sup-0002-videos2.mp4



61y referred as PSP. first symptoms were a slowly progressive wide-based gait balance disturbances then slurred speech at 48 years. later dysphagia with liquids and vertical gaze difficulties

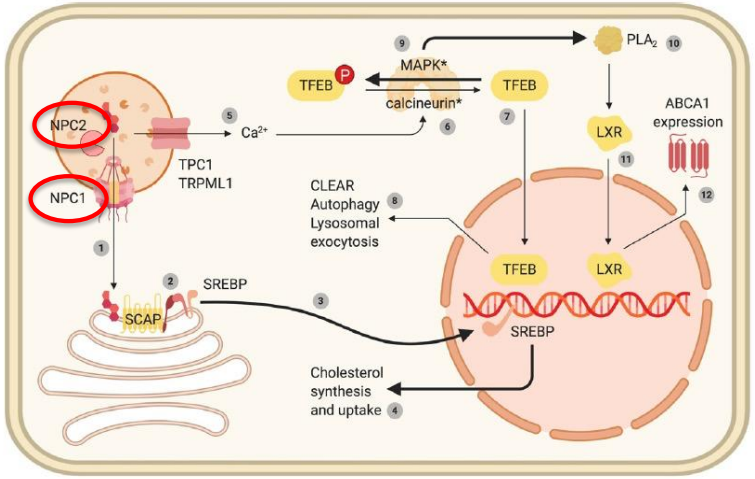
mdc313085-sup-0001-videos1.mp4

Niemann Pick Disease type C

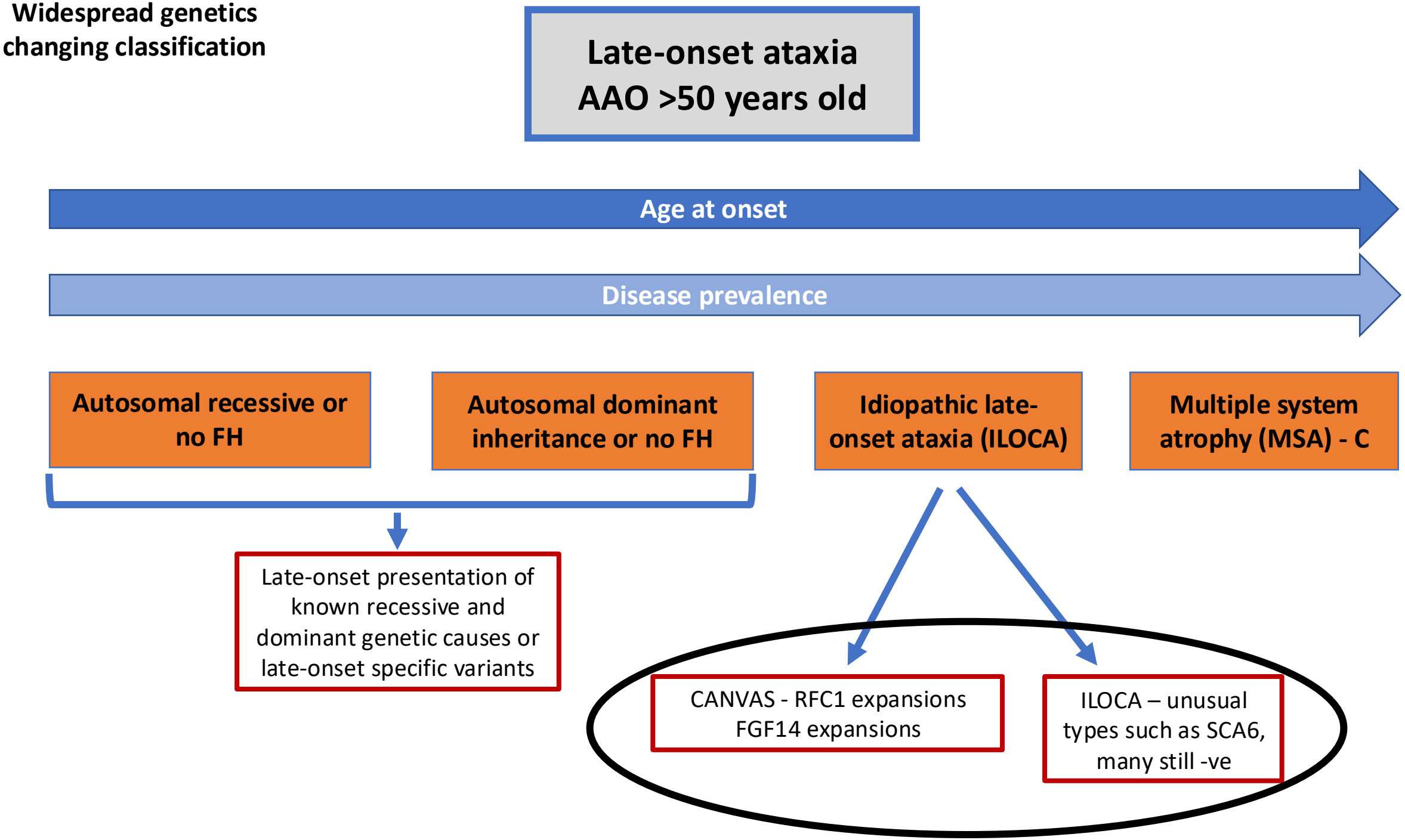
***NPC1* gene (95%)**
***NPC2* gene (5%)**

- Rare neurovisceral **lysosomal storage disorder** caused by biallelic variants in either *NPC1* (~95%) or *NPC2* (~5%)
- *NPC1* and *NPC2* encode two proteins involved in intracellular trafficking of cholesterol and other lipids
- Deficiency of either protein leads to accumulation of unesterified cholesterol, gangliosides, and other lipids within the lysosome/late endosome compartment.

Presentation	Age onset	Clinical manifestations
Early infantile	<2 years	Fetal ascites; neonatal liver disease; prolonged jaundice; pulmonary infiltrates.
Late infantile	2 to <6 years	Hypotonia and developmental delay; with time, vertical supranuclear saccadic palsy becomes; clumsiness; ataxia.
Juvenile	6 to <15 years	Clumsiness; ataxia; academic difficulties; global cognitive impairment; regression; vertical supranuclear gaze palsy; seizures; gelastic cataplexy; dystonia and/or spasticity.
Adolescent/adult	> 15 years	All of the neurologic and/or psychiatric manifestations (early-onset dementia; treatment-resistant depression; schizophreniform illness; apparent bipolar disease).
Other	Various	Some individuals present with isolated splenomegaly in childhood, and may not develop neurologic manifestations for many years. Occasionally, adults have splenomegaly without neurologic manifestations.



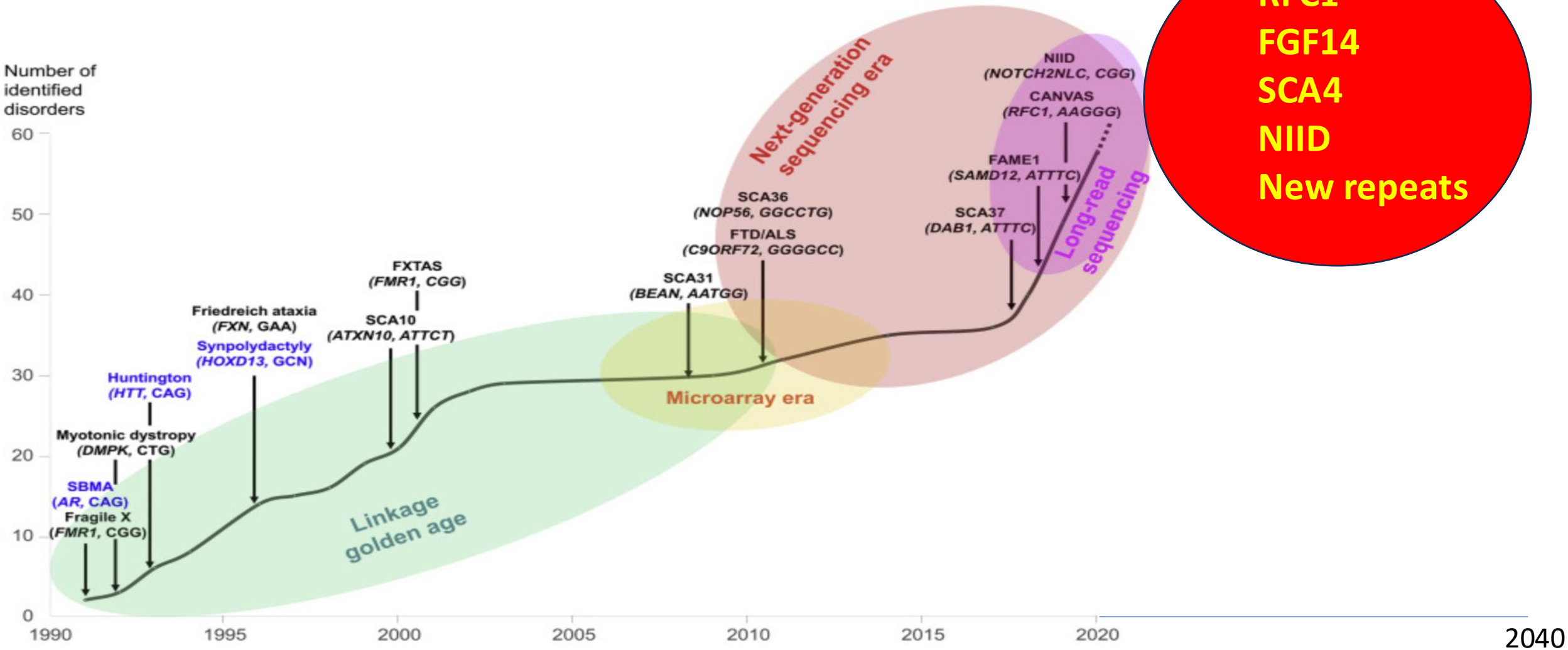
Widespread genetics changing classification



Repeats - timeline

Whole genome long-read sequencing era

RFC1
FGF14
SCA4
NIID
New repeats



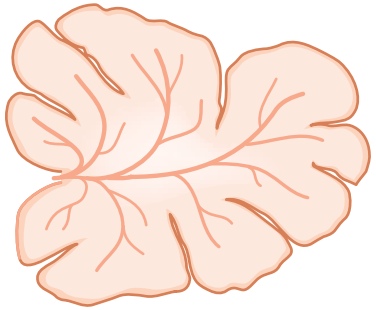
Timeline of repeat expansion discovery in human disorders

Adapted from: Depienne, C AJHG Volume 108, Issue 5, P764-785

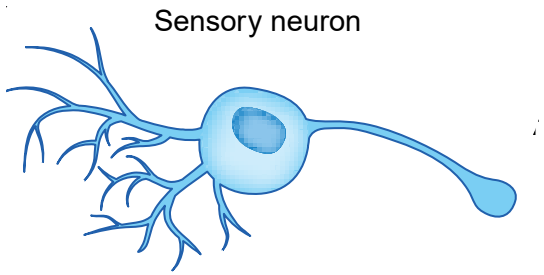
Phenotypic spectrum; Sensory neuropathy <---> CANVAS <---> ILOCA

Chronic cough

Cerebellum

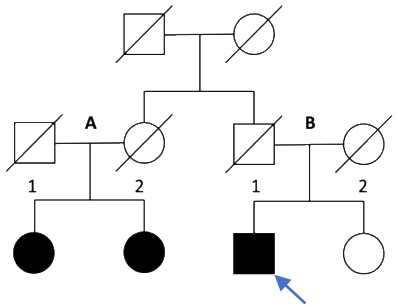


Sensory neuron

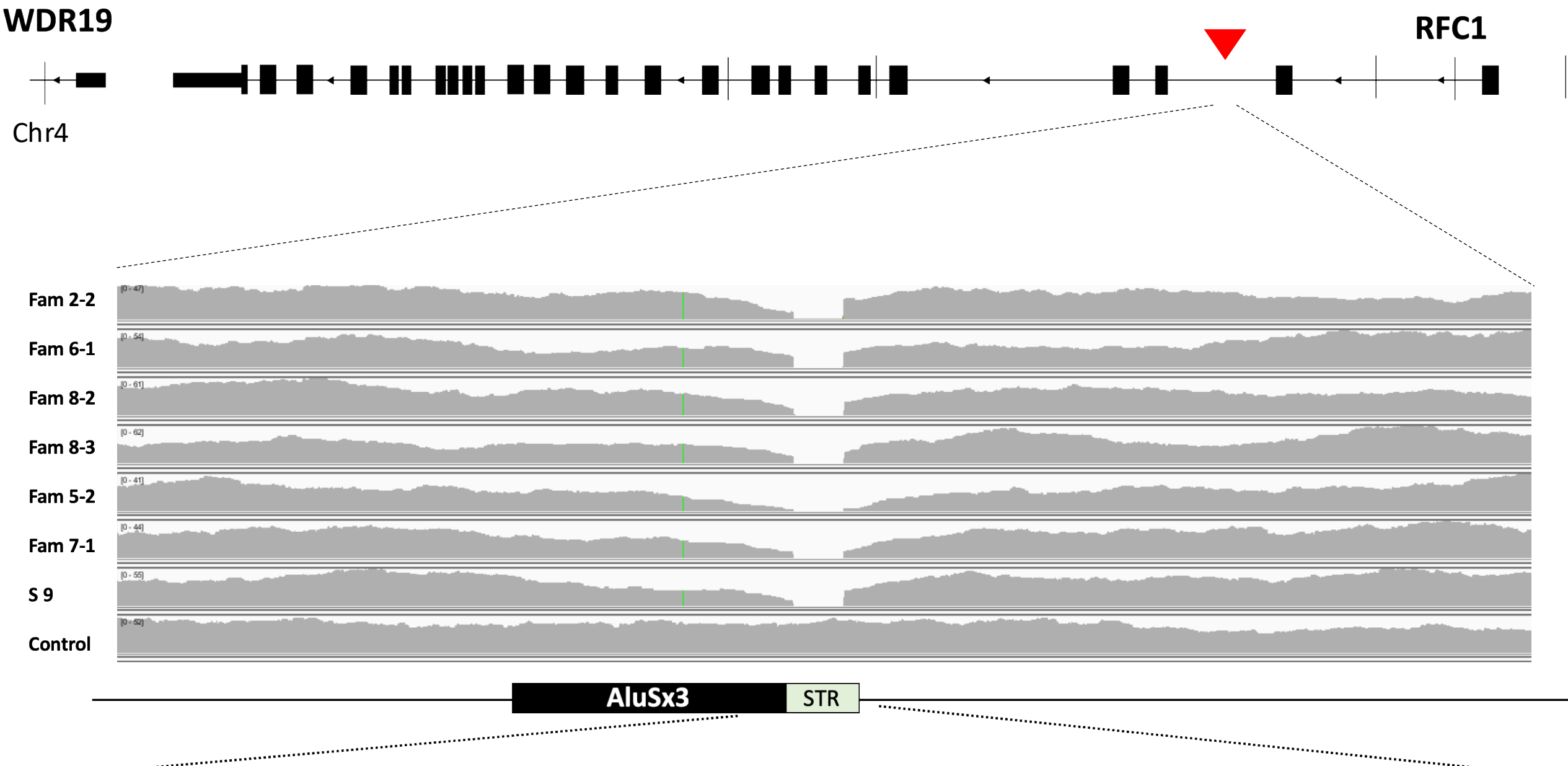


Vestibular labyrinth

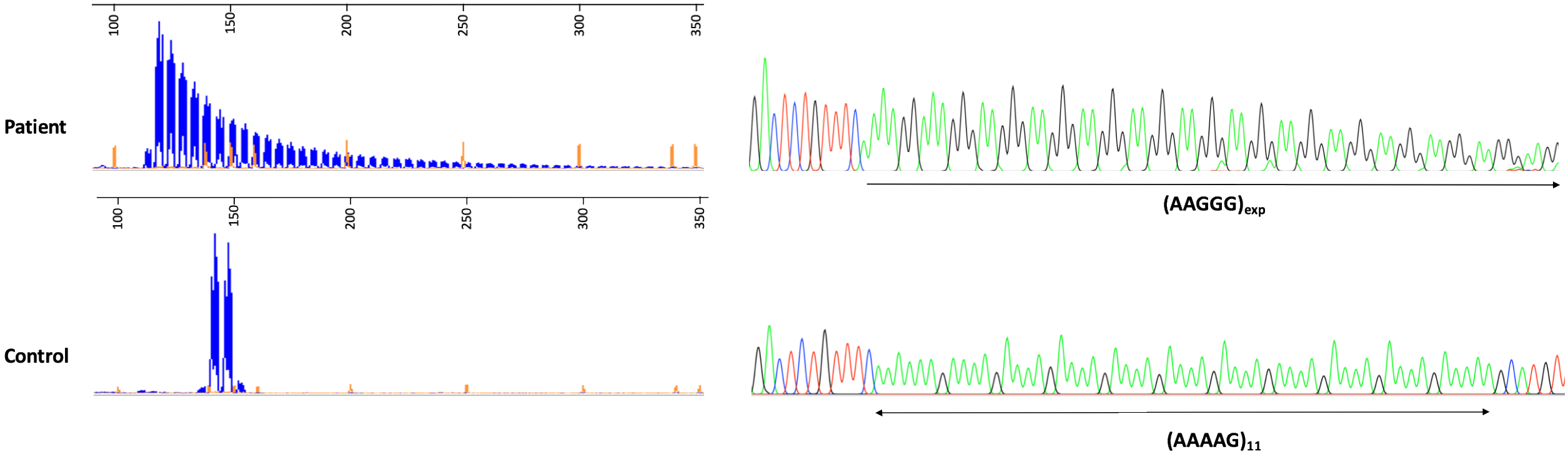
CANVAS – ~30%



WGS analysis reveals reduced coverage of an intronic STR in *RFC1*



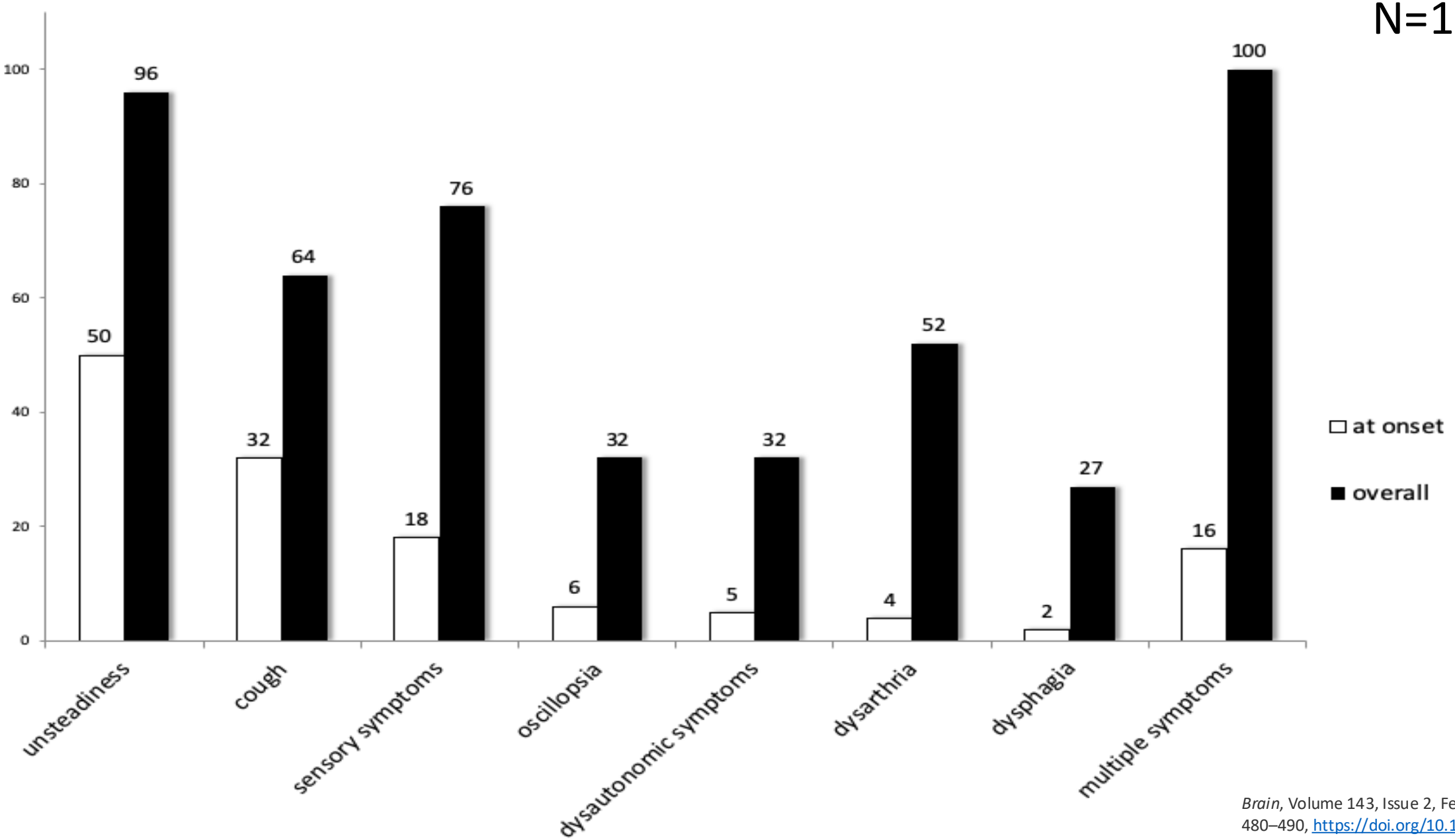
Repeat-primed PCR and long-range PCR confirm AAGGG expansion in familial and sporadic CANVAS cases



Out of **150 patients with sporadic late-onset ataxia and 33 (22%) carried the recessive AAGGG repeat expansion**, The percentage increased to 63% (32 out of 51) in cases with late-onset cerebellar ataxia and sensory neuronopathy and 92% (11 out of 12) in cases will full CANVAS – Cortese, Nat Genet 2019

(A) Symptoms at disease onset and during disease.

N=100



Brain, Volume 143, Issue 2, February 2020, Pages 480–490, https://doi.org/10.1093/brain/awz418

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Deep Intronic *FGF14* GAA Repeat Expansion in Late-Onset Cerebellar Ataxia

FGF14 expansion, ~30% late-onset ataxia

Episodic features — no./total no. (%)	56/121 (46)
Mean age at onset of episodes — yr	55±13
Mean age at onset of permanent ataxia — yr	59±11
Signs and symptoms — no./total no. (%)	
Nystagmus	
Downbeat nystagmus	50/119 (42)
Gaze-evoked horizontal nystagmus	65/119 (55)
Diplopia or visual blurring	57/120 (48)
Cerebellar dysarthria	63/118 (53)
Gait ataxia	113/118 (96)
Appendicular ataxia	94/118 (80)
Vertigo or dizziness	33/114 (29)
Postural tremor	18/114 (16)
Cerebellar atrophy on MRI — no./total no. (%)	67/91 (74)

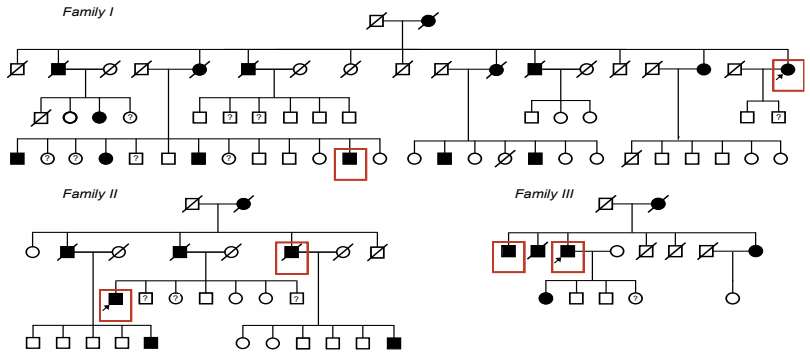
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

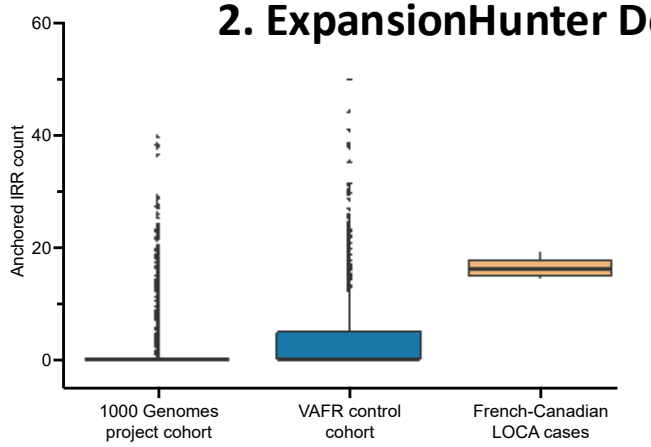
Deep Intronic *FGF14* GAA Repeat Expansion in Late-Onset Cerebellar Ataxia

FGF14 expansion

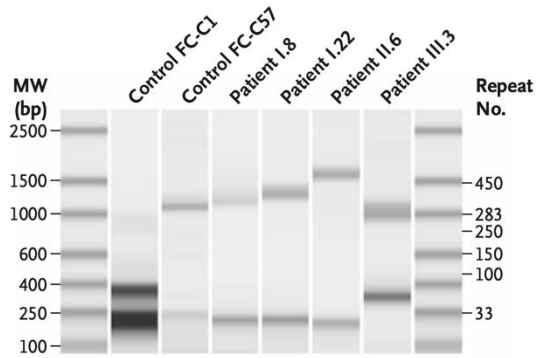
1. Whole-Genome Sequencing

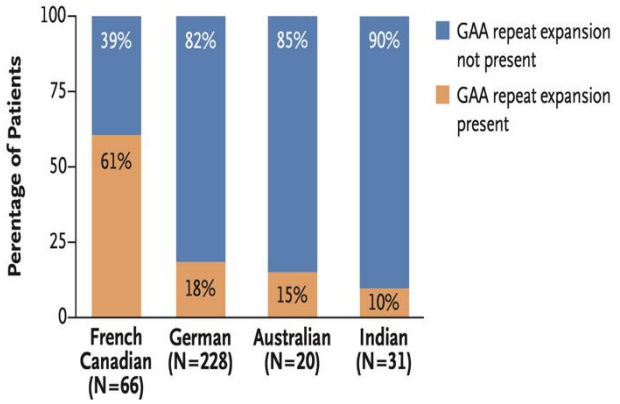


2. ExpansionHunter DeNovo



3. Molecular Validation





Rafehi et al., AJHG 2023, Pellerin, D., et al., N. Engl. J. Med. 2023.

FGF14 expansion clinical features of spinocerebellar ataxia 27B (SCA27B)

CORE CLINICAL FEATURES

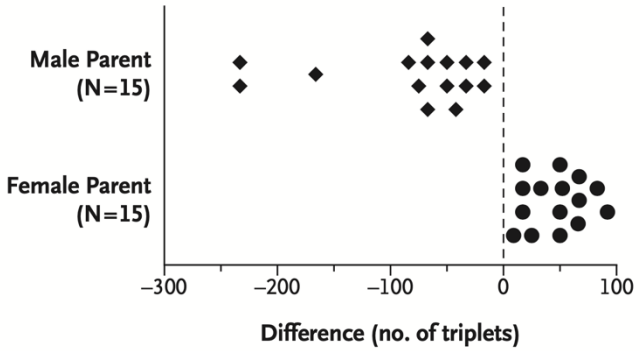
- Slowly progressive pan-cerebellar syndrome
  - Average AOO: 60y (range: 30-90)
- Episodic onset (50%)
- Downbeat nystagmus (50%)
- Visual disturbances (diplopia, oscillopsia)
- Intolerance to alcohol and physical activity
- Vertigo and/or dizziness (30%)

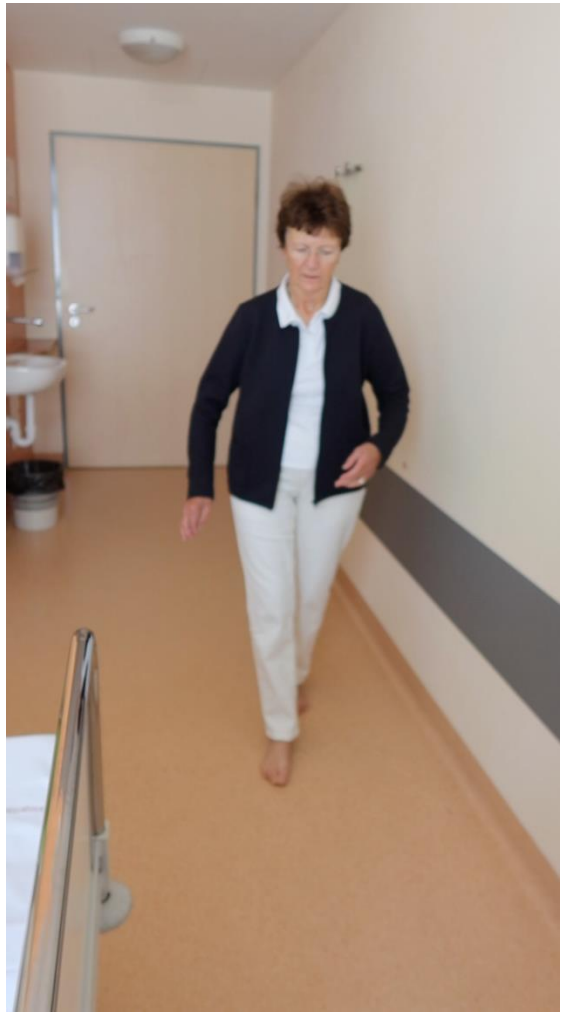
VARIABLE FEATURES

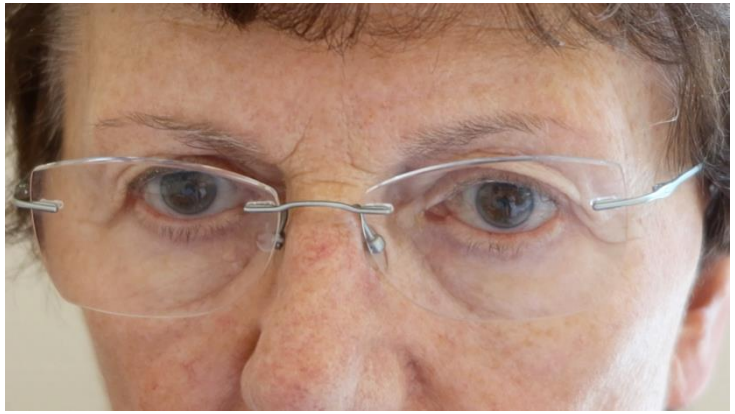
- Postural tremor
- Autonomic dysfunction
- Pyramidal tract signs (mild)

RADIOLOGICAL FEATURES

- Isolated cerebellar atrophy (75%)



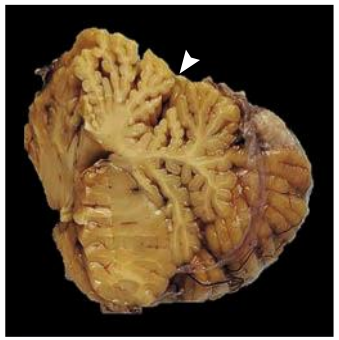


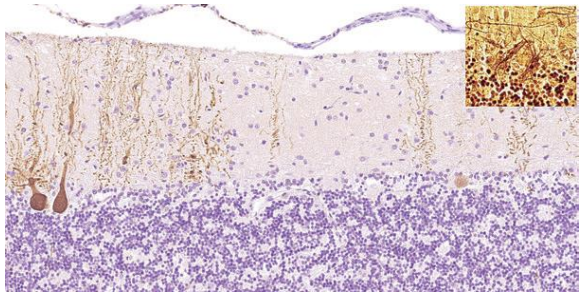


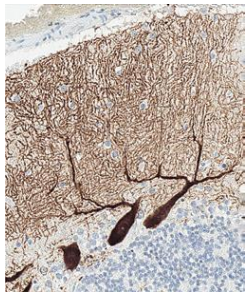
Rafehi et al., AJHG 2023, Pellerin, D., et al., N. Engl. J. Med. 2023.
Thank you to Dr Mathilde Renaud for kind sharing of videos

FGF14 GAA repeat expansions cause haploinsufficiency

Neuropathological findings





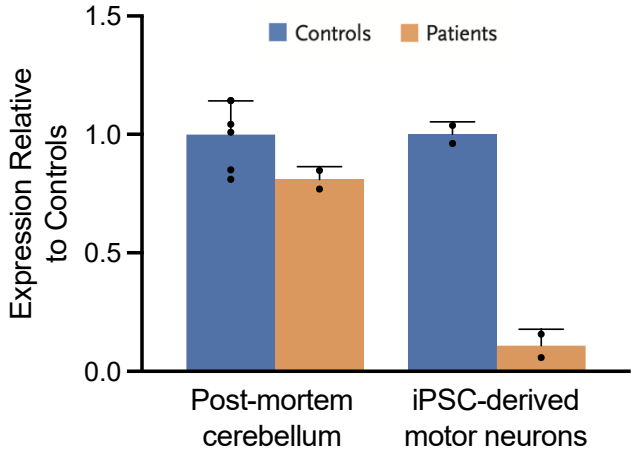


Patient **Control**

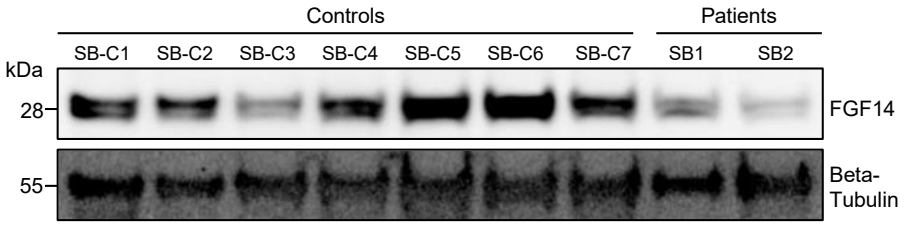
- Widespread depletion of Purkinje cells
- Gliosis of molecular layer
- Mild cell loss in granule cell layer

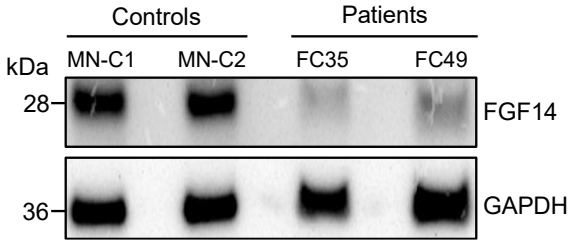
Expression

qPCR - *FGF14* Transcript 2 Expression

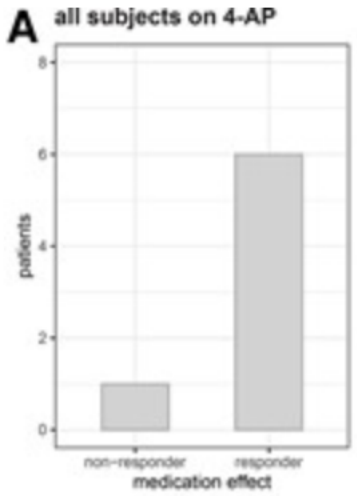


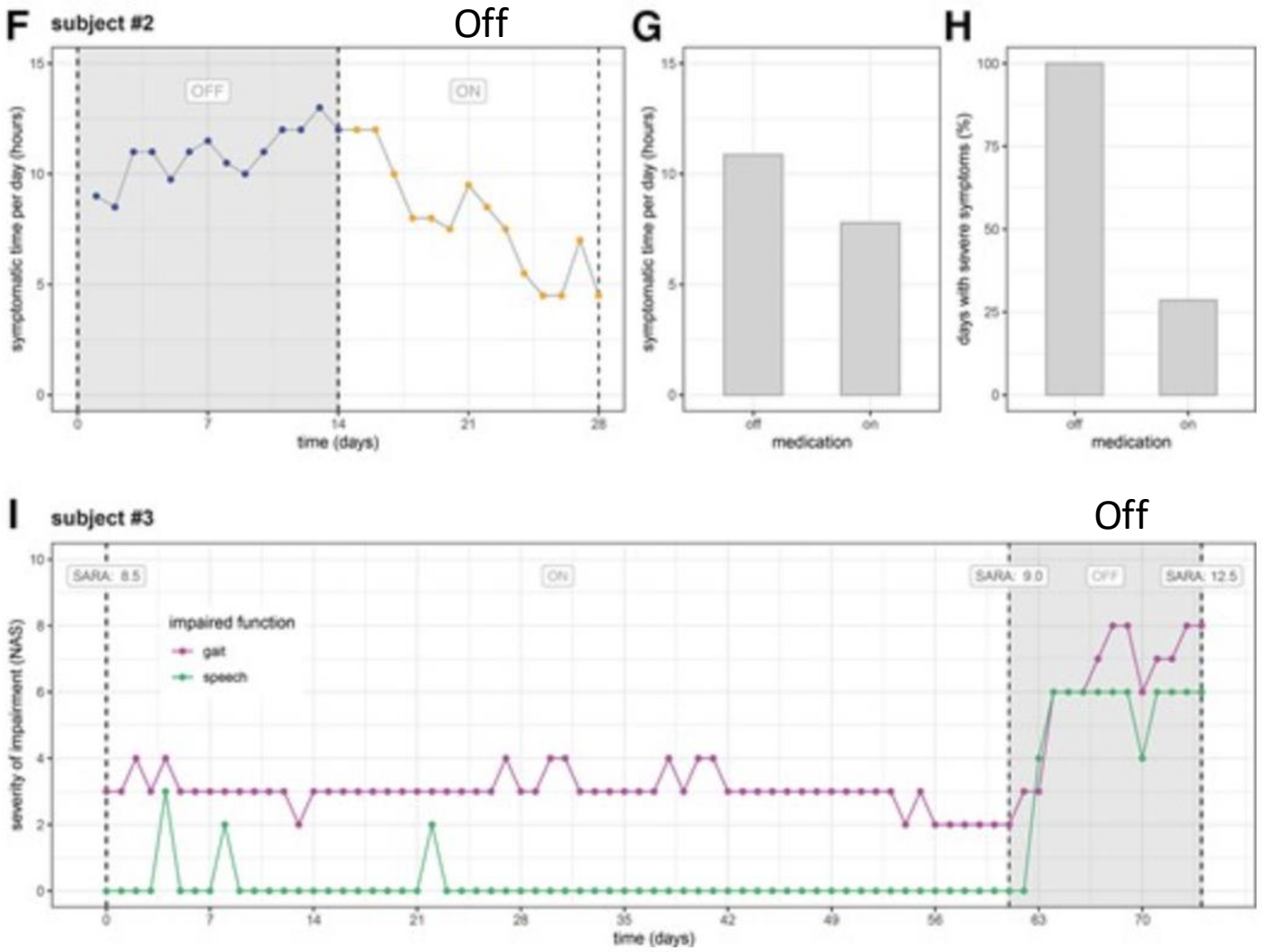
Immunoblot





Treatment response of GAA-*FGF14* patients to 4-AP





Wilke et al, *Brain*, Volume 146, Issue 10, October 2023, Pages 4144–4157

Question 3

In late onset ataxia (over age 50 years) which two genes are the main genetic causes?

1. SCA2 and SCA3 expansions
2. RFC1 and FGF14 expansions
3. Frataxin and CACNA1A point mutations

Ataxia, developed walking problems and myoclonus

Progressive myoclonic ataxia, speech problems.
Progressive cognitive decline

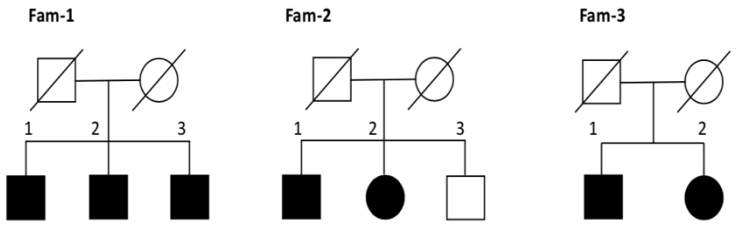
Progressive myoclonic ataxia, e. g.;
Lafora body disease
Myoclonic epilepsy with ragged red fibers
North Sea progressive myoclonus epilepsy
Action myoclonus-renal failure syndrome

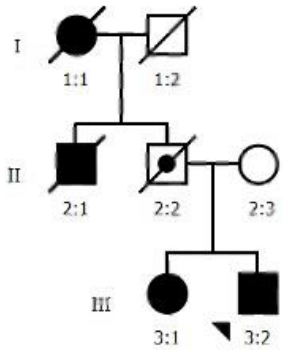
Best 2022 diagnostic approach:

1. Exome or genome sequencing Current
2. Sequence EPM2A/SCARB2 only 10 years ago
3. Do an axillary skin biopsy 20 years ago

https://doi.org/10.1002/mds.25114

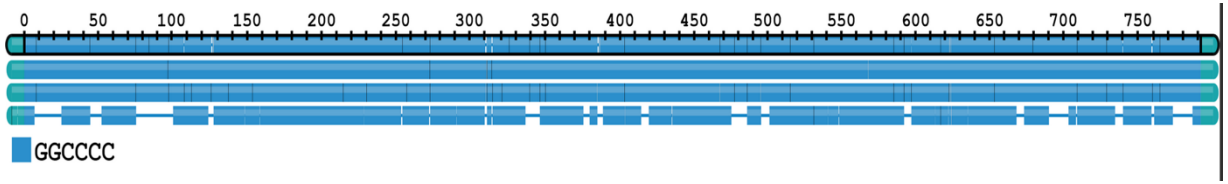
What about the WGS –ve patients and families





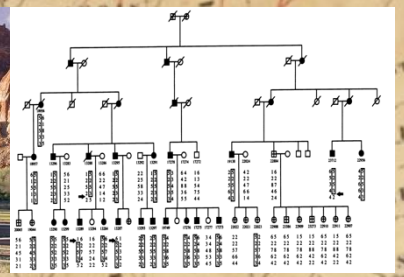
Familial disease
Genome –ve
Trio/Quad

Long-read sequencing



Louis Ptáček

Utah



RESKARTA

från

SVERIGE till NORRA AMERIKA

ÖFVER

HULL, LIVERPOOL & NEW-YORK

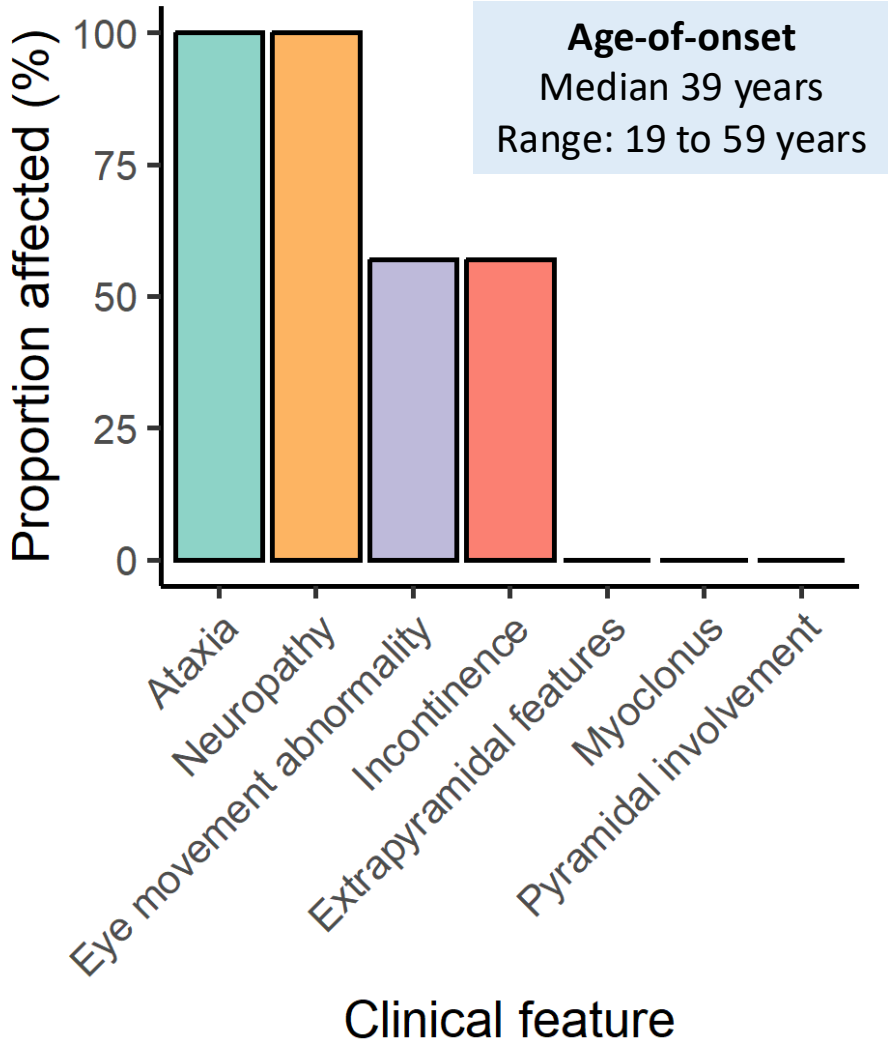
Frederick Nelson

GÖTEBORG

Nya Haga N:o 10.

Map from raremaps.com

Clinical manifestation of spinocerebellar ataxia type 4 (SCA4)

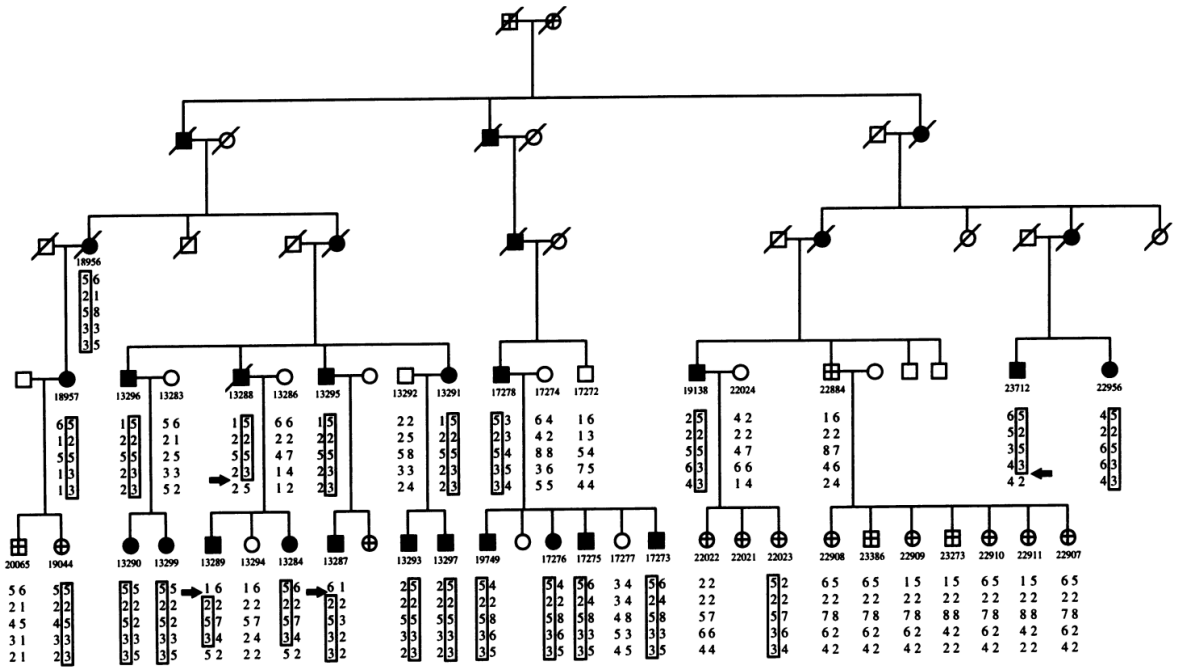


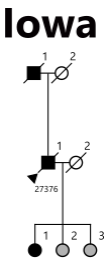
Am. J. Hum. Genet. 59:392–399, 1996

Autosomal Dominant Spinocerebellar Ataxia with Sensory Axonal Neuropathy (*SCA4*): Clinical Description and Genetic Localization to Chromosome 16q22.1

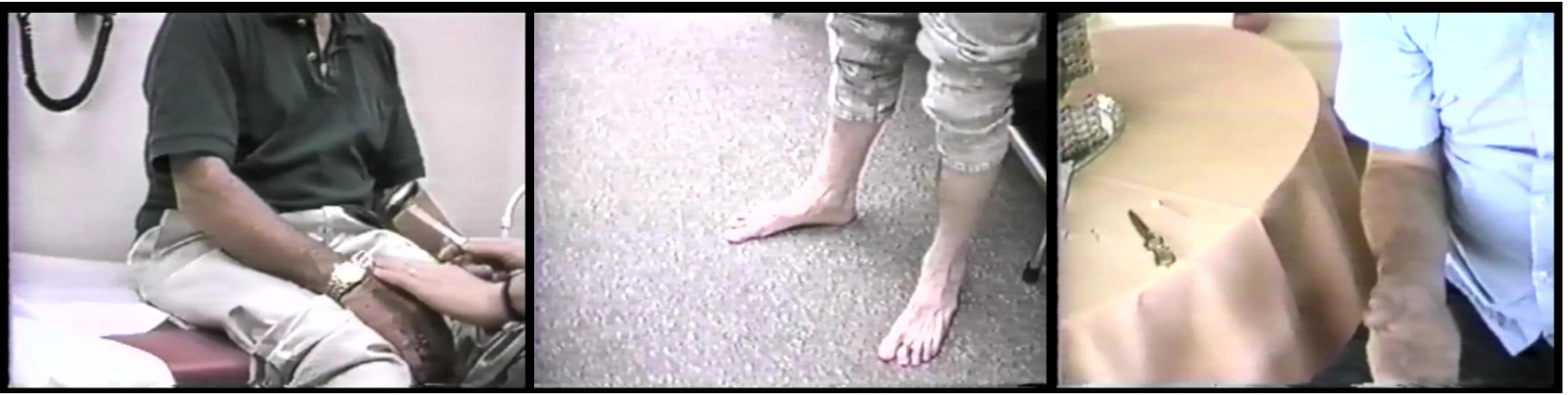
K. Flanigan,[1] K. Gardner,[1] K. Alderson,[5] B. Galster,[1] B. Otterud,[2,3] M. F. Leppert,[2,3] C. Kaplan,[3] and L. J. Ptáček[1,2,3,4]

Departments of [1]Neurology and [2]Human Genetics and Programs in [3]Human Molecular Biology and Genetics and [4]Neuroscience, University of Utah Medical Center, and [5]Salt Lake City Veterans Affairs Medical Center, Salt Lake City





3 different individuals from the same family with varying ages of onset



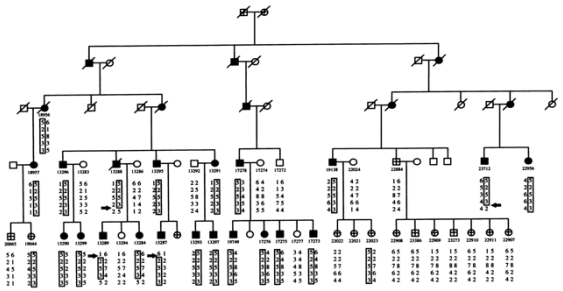
62-year-old M
Symptom onset: 59 years

35-year-old M
Symptom onset: 25 years

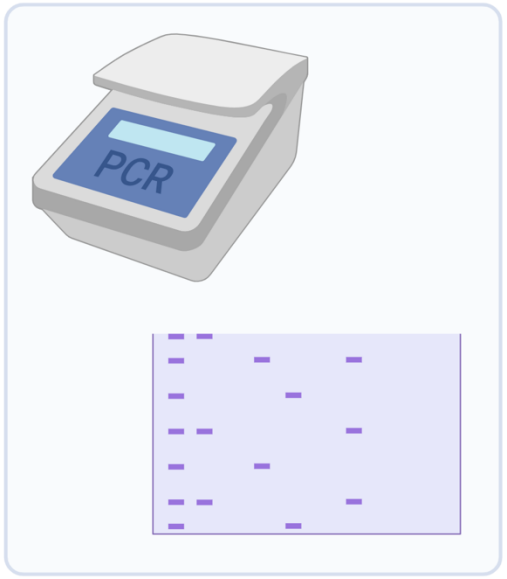
56-year-old M
Symptom onset: 35 years

Years after symptom onset

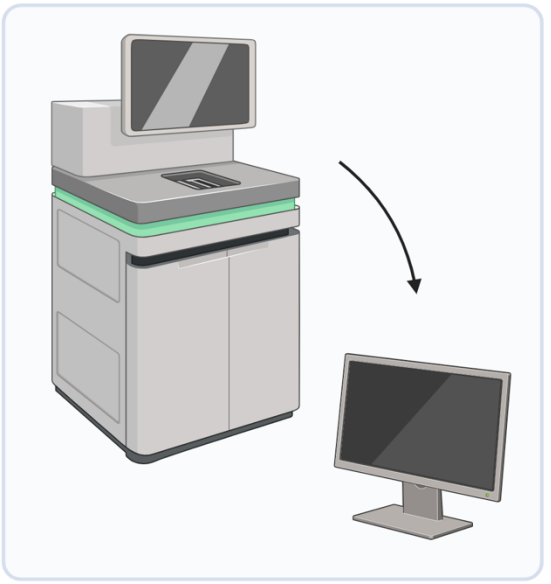
Methods for repeat expansion detection



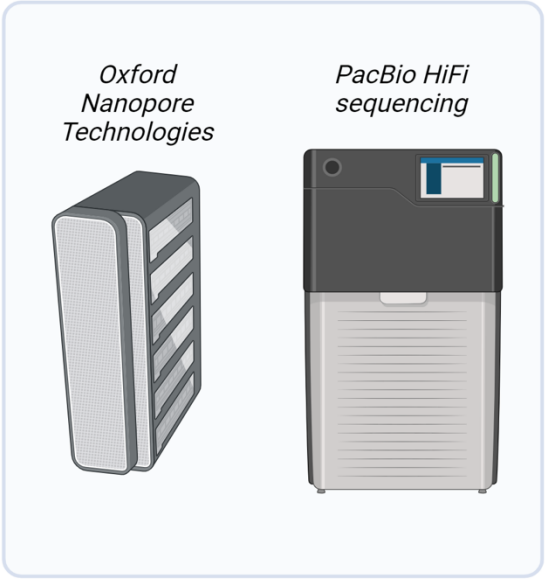
Methods for repeat expansion detection



Repeat prime polymerase chain reaction (RP-PCR) and/or Southern blotting

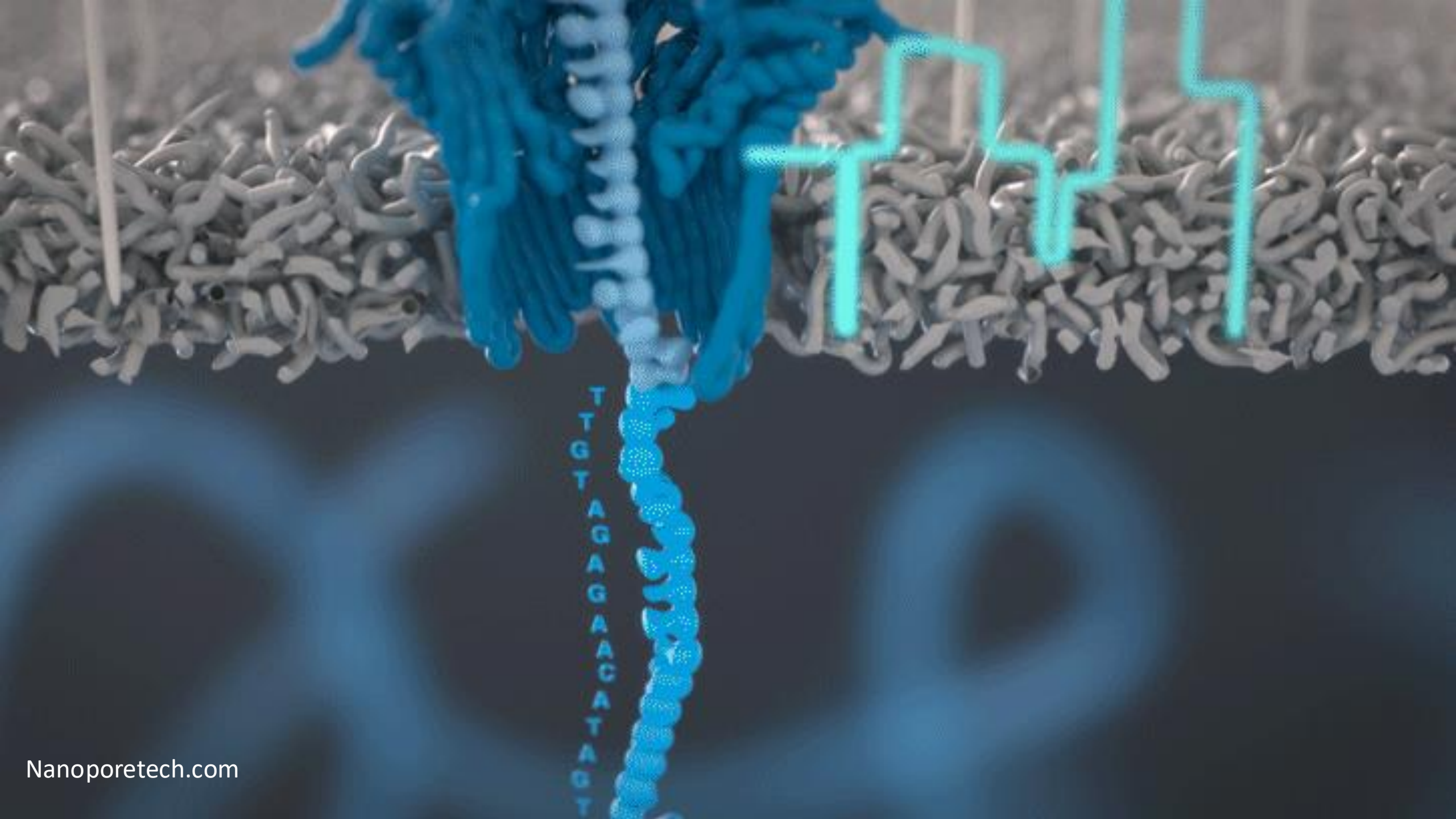


Short-read genome sequencing with *post-hoc* bioinformatic analysis



Long-read genome sequencing

Chen …….Ptacek, Mov Disord 2024 Mar;39(3):486-497

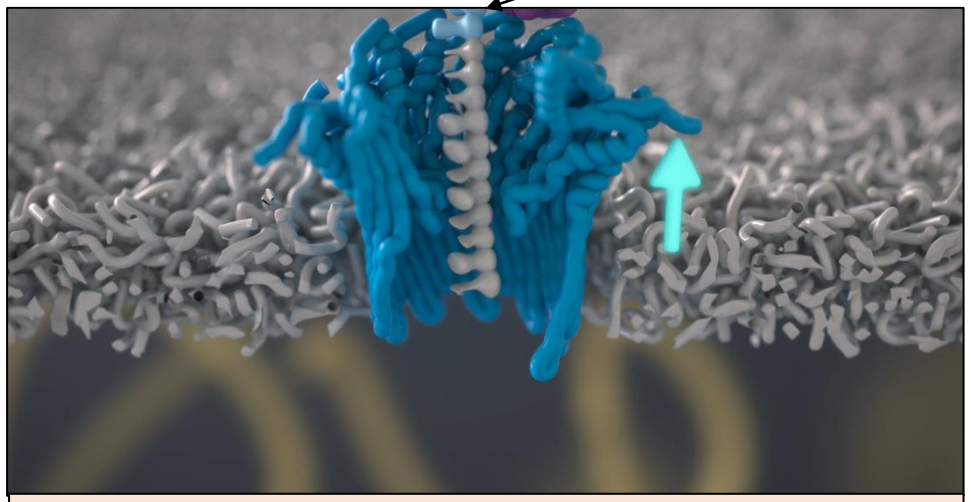


Nanoporetech.com

Real-time target enrichment through adaptive sampling – see protocol

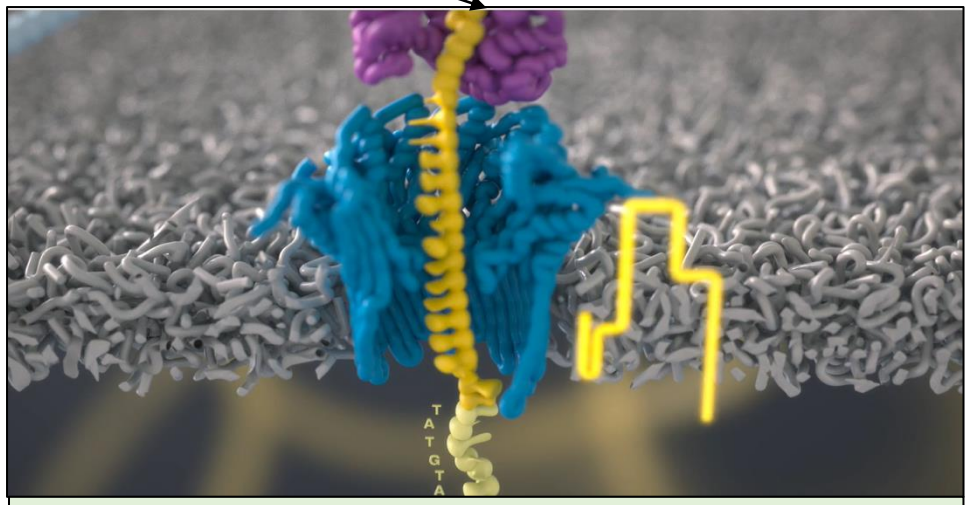
Input **region of interest:** 16q22 in this case

NO



DNA ejected from pore for further sequencing

YES



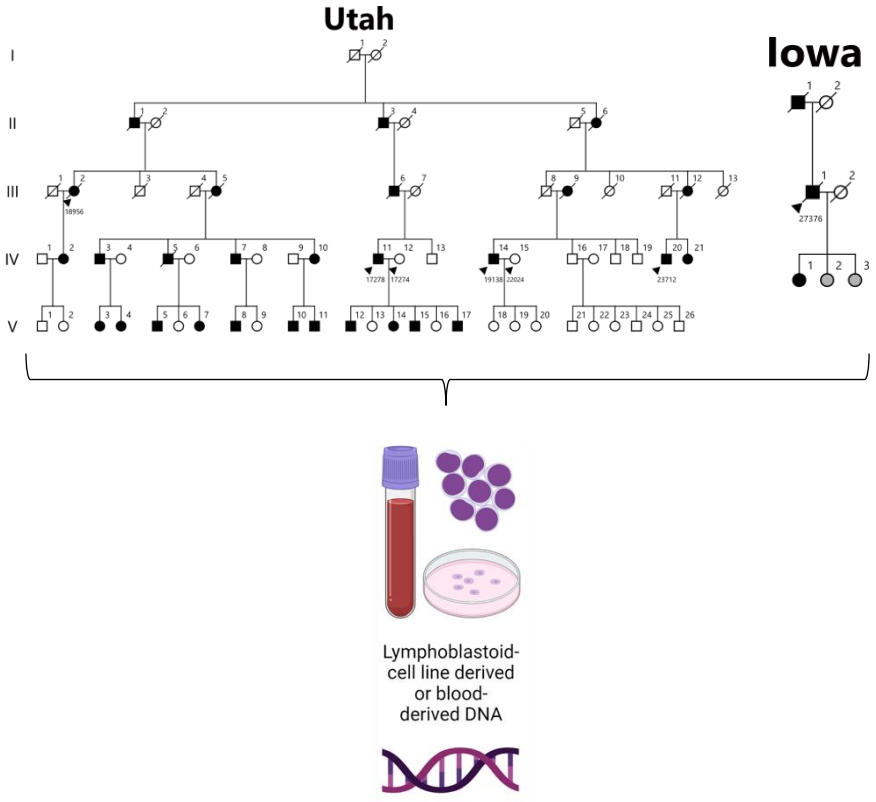
Sequencing continues of the target strand

Protocol Citation: claire.anderson, Hannah Macpherson, Emil Gustavsson, Jasmaine Lee, zhongbo.chen 2023. Native Barcoding (SQK-NBD114) gDNA for Adaptive Sampling using Oxford Nanopore Technologies. **protocols.io** https://dx.doi.org/10.17504/protocols.io.kxygx3qx4g8j/v1

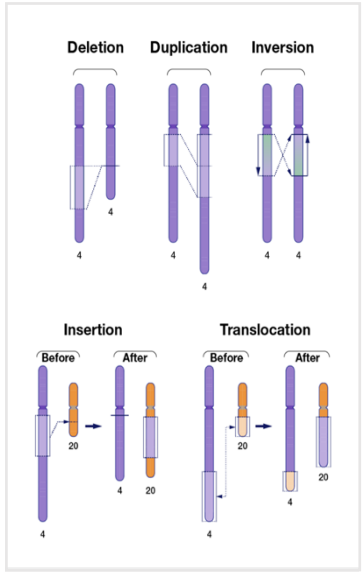
Images adapted from nanoporetech.com

Segregating structural variation without *a priori* specification of variant type, size or motif

Long-read sequencing over 16q22 region of linkage

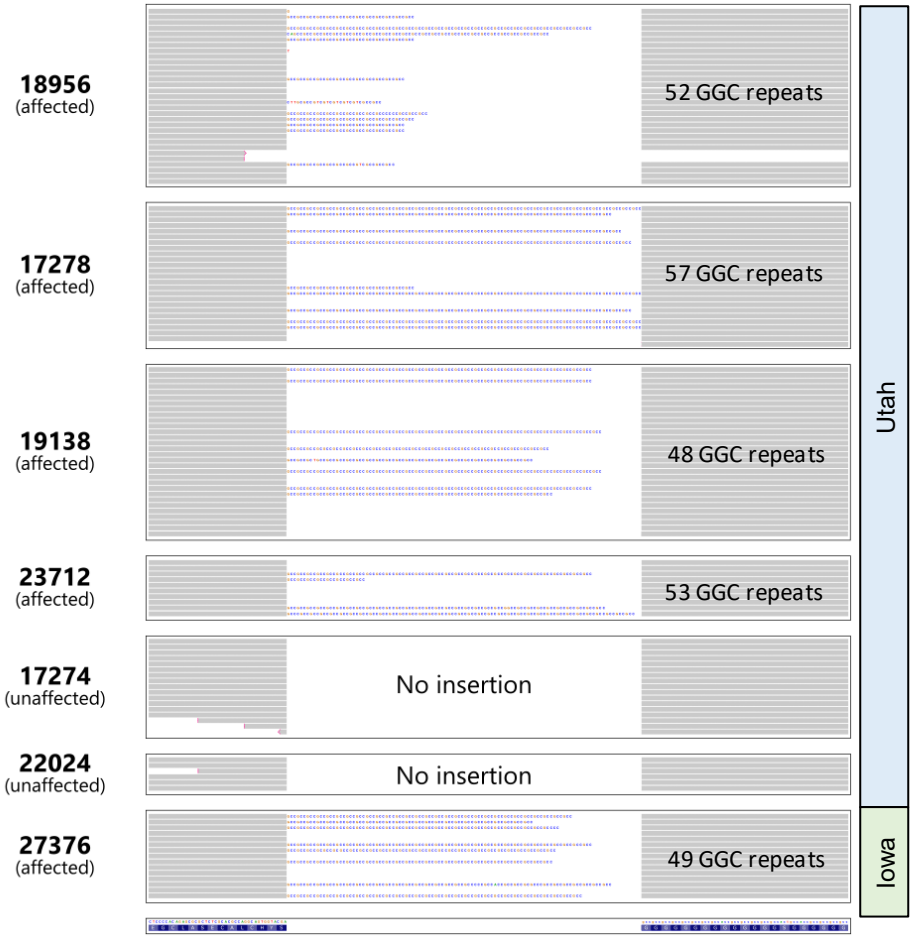


Structural variant calling



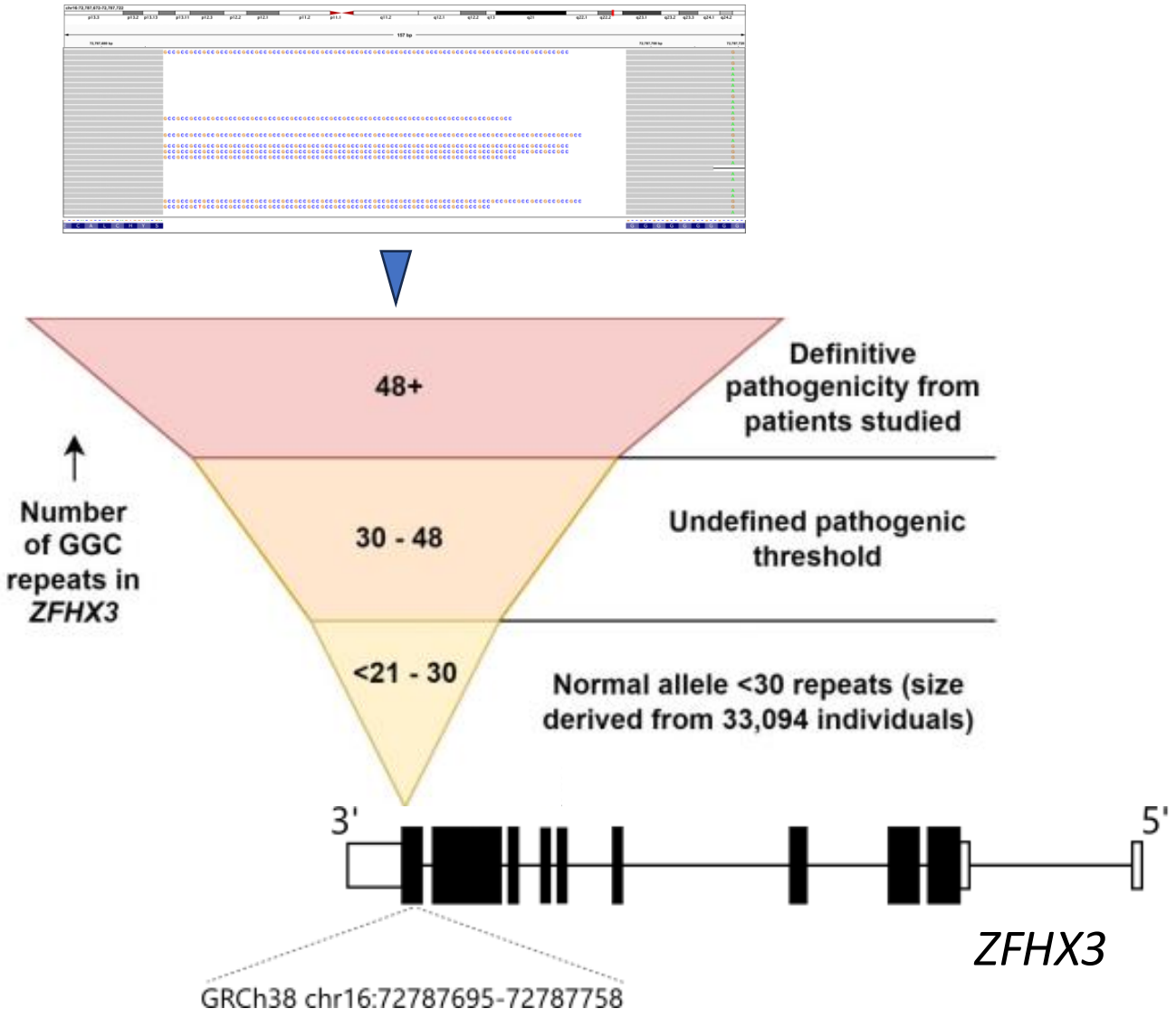
Structural variants: >50bps

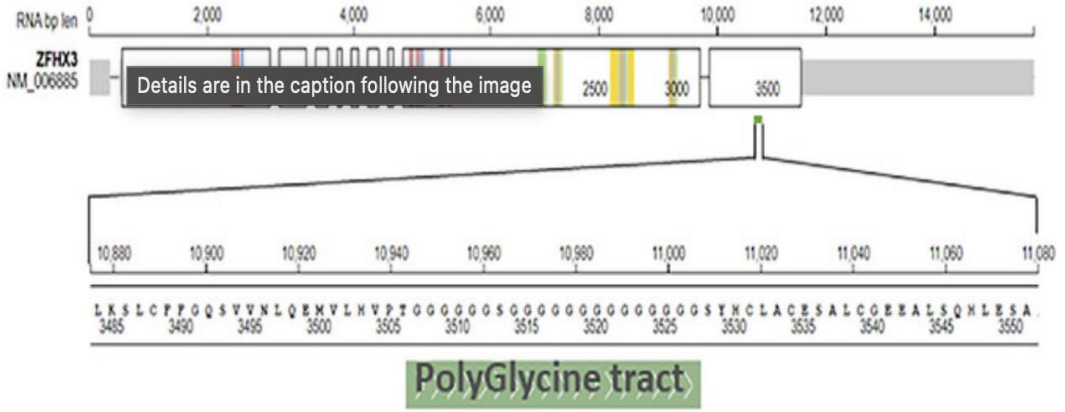
GGC expansion: Segregating insertion in *ZFHX3*



ZFHX3

Exonic GGC repeat expansion in *ZFHX3*





Four SCA4 paper: Andreas Puschmann and colleages (AJHG), Per Svenningsson and colleagues (J Intern Med) and Stephan Pulst and colleagues (Nat Genet).

Any undefined SCA family; we use either PacBio Revio WGS or ONT genome

Thanks for your attention

Grateful for kind invitation and hosting.

Grateful to all patients and families
Grateful to our funders
UCL Queen Square – clinicians and the neurogenetics lab
We are grateful to many international collaborators worldwide
and we are keen to collaborate with others.

NEUROGENETICS
QUEEN SQUARE

Prof. Houlden's Lab

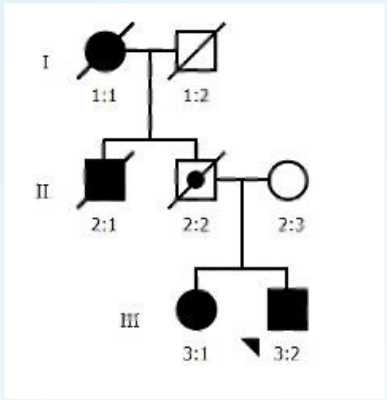
NHNN/UCL Teams

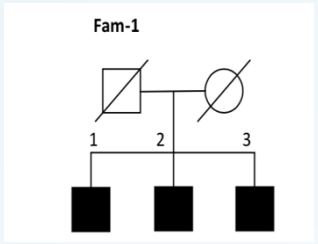
Queen Square MDC
MOVEMENT DISORDERS CENTRE

Thanks to Profs Kailash Bhatia, Andrew Lees, Nick Wood,
Niall Quinn and others for many slides and videos

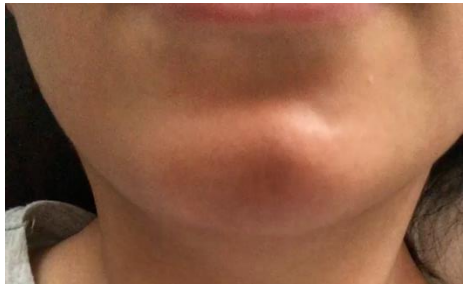
Call for collaborations

Long-read sequencing

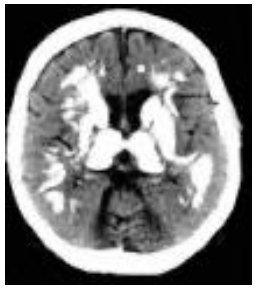




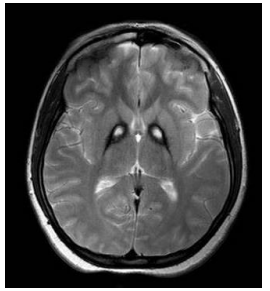
Hereditary geniospasm



Fahr's disease

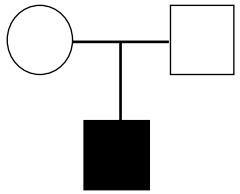


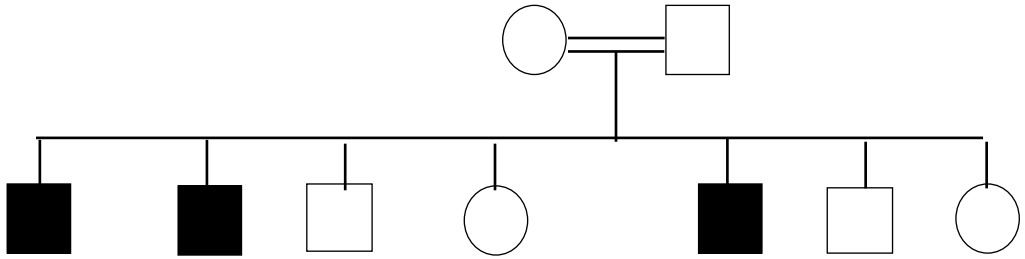
NBIA syndromes



Non-HD adult-onset chorea

Dystonia/Parkinsonism of unknown etiology





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