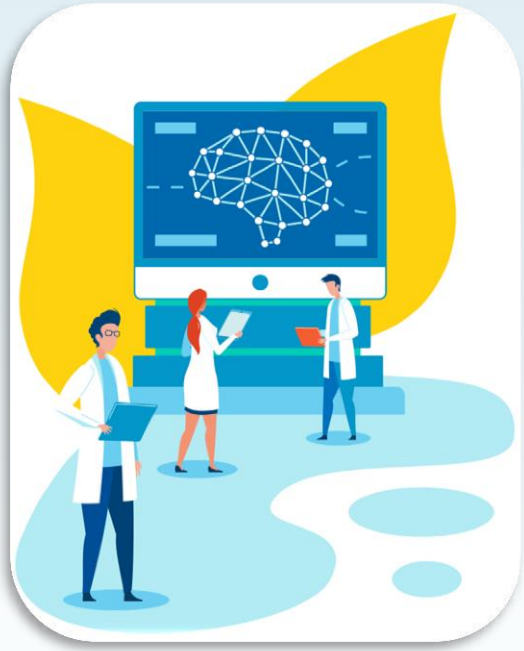
European Reference Network for rare or low prevalence complex diseases
Network Neurological Diseases (ERN-RND)

ean european academy of neurology

European Reference Network for rare or low prevalence complex diseases
Network Neuromuscular Diseases (ERN EURO-NMD)

UCL

Joint webinar series



The inherited ataxias

Paola Giunti

UCL Queen Square Institute of Neurology
London, UK

DG ‚Ataxia and HSP'
14 January 2020

General information about the webinars

- RARE neurological, neuromuscular and movement disorders
- 30-35min presentation
- 15min Q&A session at the end (please write your questions in the Q&A)
- Target audience: neurologists, residents, paediatric neurologists, geneticists from RND members, RND affiliated partners, and non-RND HCPs across Europe and worldwide
- Recorded Webinar and presentation to be found at the latest 2 weeks after on: http://www.ern-rnd.eu/education-training/past-webinars/
- Further useful information: www.ern-rnd.eu/disease-knowledge-hub/ataxia/
- Post-webinar survey (2-3min): satisfaction, topic ideas for next webinars

The Inherited ataxias: Clinical and genetic aspects

ERN-RND Webinar
14-01-2020

Paola Giunti

Ataxia Centre
Queen Square, Institute of Neurology UCL

London

Webinar Questions

- What is your professional background? (Single choice)
- a. Neurologist
- b. Neuropediatrician
- c. Nurse
- d.Physiotherapist
- e. Geneticist

Cerebellar Ataxia

- Greek: *a*-(without), *-taxis* (order): lack of order, coordination.

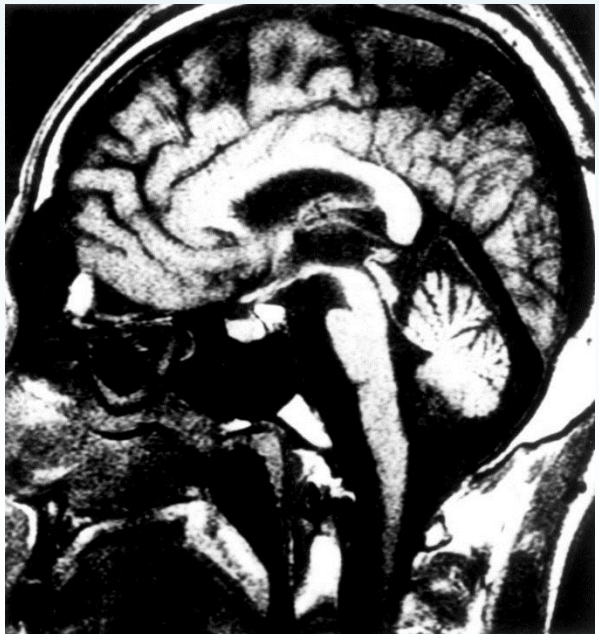
- Cerebellar syndrome:
  1. **Gait ataxia**: loss of balance with unsteady, irregular, wide-based gait with swaying and risk of falls.
  2. **Limb ataxia**: movements are irregular, fragmented, tremolous.
  3. **Eye movements**: interrupted, not calibrated, fixation may be unstable with or without double vision.
  4. **Speech**: slurred, impairment of speed and volume.

Inherited ataxias

- Hereditary ataxias may be congenital, episodic, or progressive.
- Inheritance may be autosomal dominant, autosomal recessive, X-linked or mitochondrial.
- Prevalence 8.9/100,000 (*Mancuso M, 2014*).

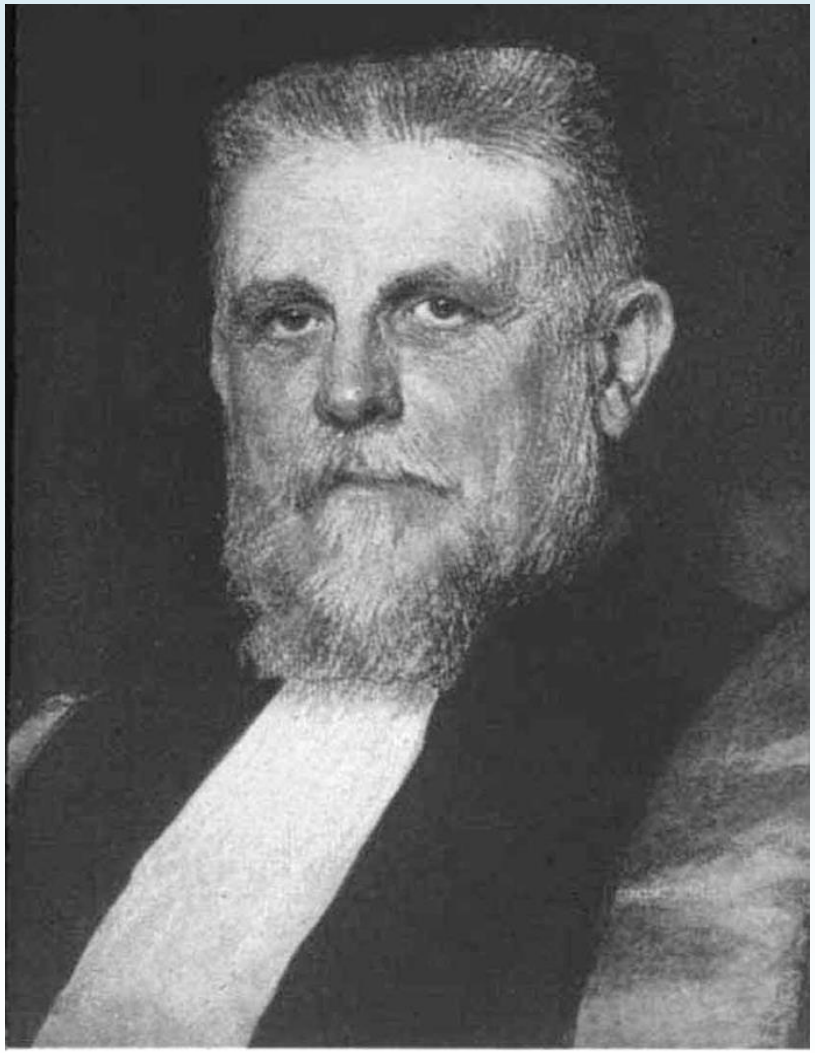
Autosomal dominant and recessive cerebellar ataxias

Group of degenerative disorders clinically and genetically heterogeneous



Dominant ataxias (1893)

(1853-1940)



Autosomal dominant cerebellar ataxias

ADCA - Clinical classification

A.E.Harding

	ADCA I	ADCA II	ADCA III
Clinical Presentation	Cerebellar syndrome with ophthalmoplegia / pyramidal / extrapyramidal signs / cognitive impairment / peripheral neuropathy	Cerebellar syndrome with pigmentary maculopathy	“Pure” cerebellar syndrome
Clinical Presentation			

Epidemiological studies found prevalence between 0.9 - 3.0:100.000

In some geographically isolated regions the frequency is much higher due to a “**founder effect**” like in Cuba, the Azorean island Flores and in Calabria (south of Italy) respectively for SCA 2, 3 and 1.

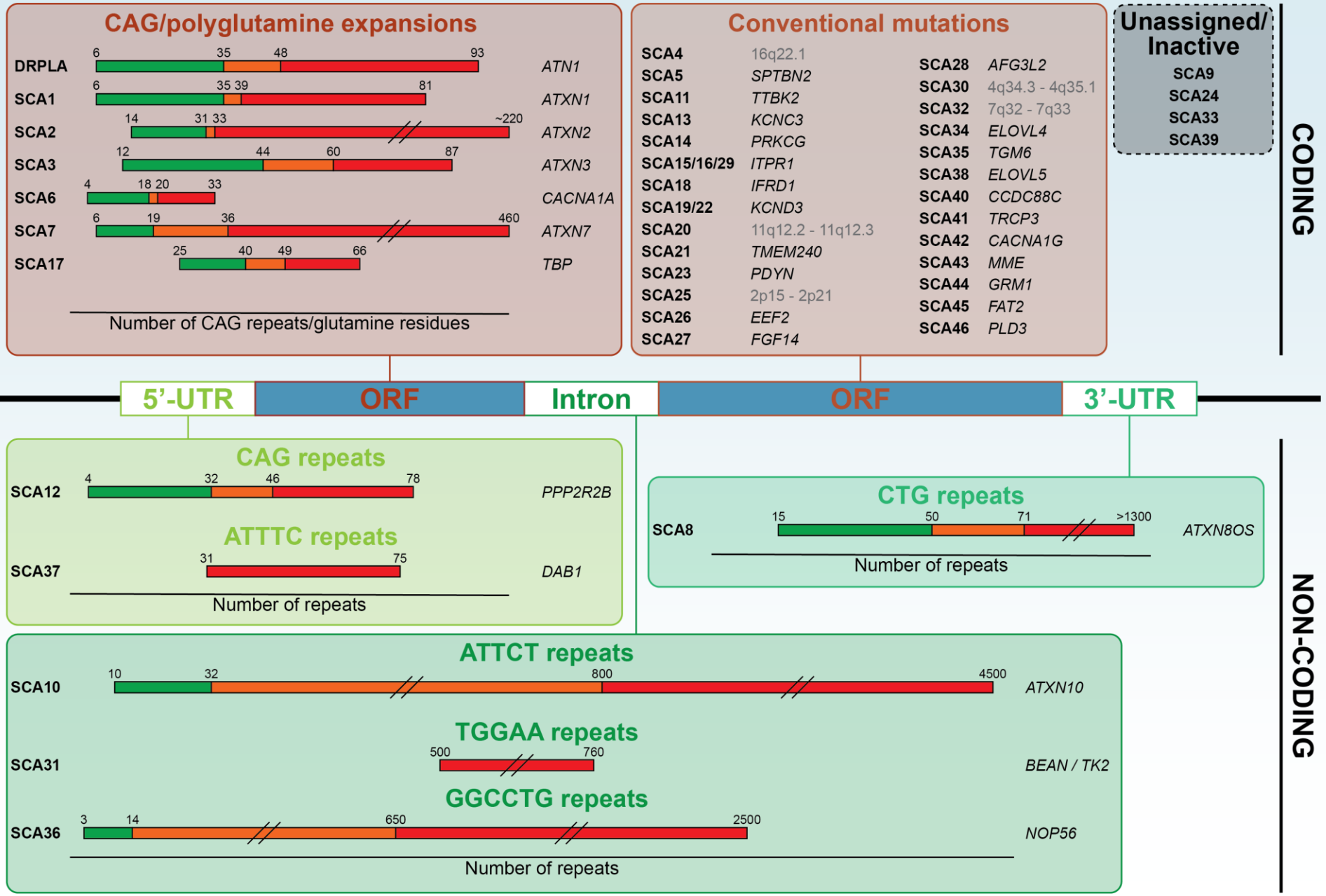
SCA /ADCA mutations

- Polyglutamine expansion in the coding region
  - **SCA 1, 2, 3, 6, 7, 17, DRPLA**

- Non-coding expansion
  - **SCA8*, 10, 12, 31, 36**

- Conventional mutations
  - **SCA 5, 11, 13, 14, 15/16/29, 19, 20, 21, 23, 27, 28, 34, 35, 38, 40, 41, 42, 43, 44,45,46**

AD SCA genes


CAG/polyglutamine expansions
DRPLA 6 35 48 93 ATN1
SCA1 6 35 39 81 ATXN1
SCA2 14 31 33 ~220 ATXN2
SCA3 12 44 60 87 ATXN3
SCA6 4 18 20 33 CACNA1A
SCA7 6 19 36 460 ATXN7
SCA17 25 40 49 66 TBP
Number of CAG repeats/glutamine residues
Conventional mutations
SCA4 16q22.1
SCA5 SPTBN2
SCA11 TTBK2
SCA13 KCNC3
SCA14 PRKCG
SCA15/16/29 ITPR1
SCA18 IFRD1
SCA19/22 KCND3
SCA20 11q12.2 - 11q12.3
SCA21 TMEM240
SCA23 PDYN
SCA25 2p15 - 2p21
SCA26 EEF2
SCA27 FGF14
SCA28 AFG3L2
SCA30 4q34.3 - 4q35.1
SCA32 7q32 - 7q33
SCA34 ELOVL4
SCA35 TGM6
SCA38 ELOVL5
SCA40 CCDC88C
SCA41 TRCP3
SCA42 CACNA1G
SCA43 MME
SCA44 GRM1
SCA45 FAT2
SCA46 PLD3
Unassigned/ Inactive
SCA9
SCA24
SCA33
SCA39
CODING
5'-UTR
ORF
Intron
ORF
3'-UTR
CAG repeats
SCA12 4 32 46 78 PPP2R2B
ATTTC repeats
SCA37 31 75 DAB1
Number of repeats
CTG repeats
SCA8 15 50 71 >1300 ATXN8OS
Number of repeats
ATTCT repeats
SCA10 10 32 800 4500 ATXN10
TGGAA repeats
SCA31 500 760 BEAN / TK2
GGCCTG repeats
SCA36 3 14 650 2500 NOP56
Number of repeats
NON-CODING

Common clinical and genetic features shared by CAG repeat disorders

- Variable age of onset: usually 3rd-4th decade of life
- Juvenile onset more aggressive disease
- Strong inverse correlation between the age of onset and the size of the CAG repeat – no of CAG repeats causes 88% variability A.O. SCA 7, only 57% in SCA2.
- With very large expansions leading to severe juvenile onset disease there is significant overlap in the phenotypes of these diseases (not SBMA)
- Phenotypic variability within the separate diseases

Common clinical and genetic features shared by CAG repeat disorders

- Anticipation with intergenerational instability. Frequency: 45% in **DRPLA**, 43% in **SCA7**, 35% **SCA2**, 30% in SCA17, 15% in SCA1, and 8% in SCA3.

- Parent of origin effect – expansion via **paternal** descent with somatic CAG instability for HD, SCA1, SCA2, SCA3, DRPLA, SCA7, SCA17, due to **increased number of mitotic division** preceding male gametogenesis, also concentration of **DNA repair proteins**.

- Characteristic selective neuronal degeneration in each disease

Common clinical and genetic features shared by CAG repeat disorders

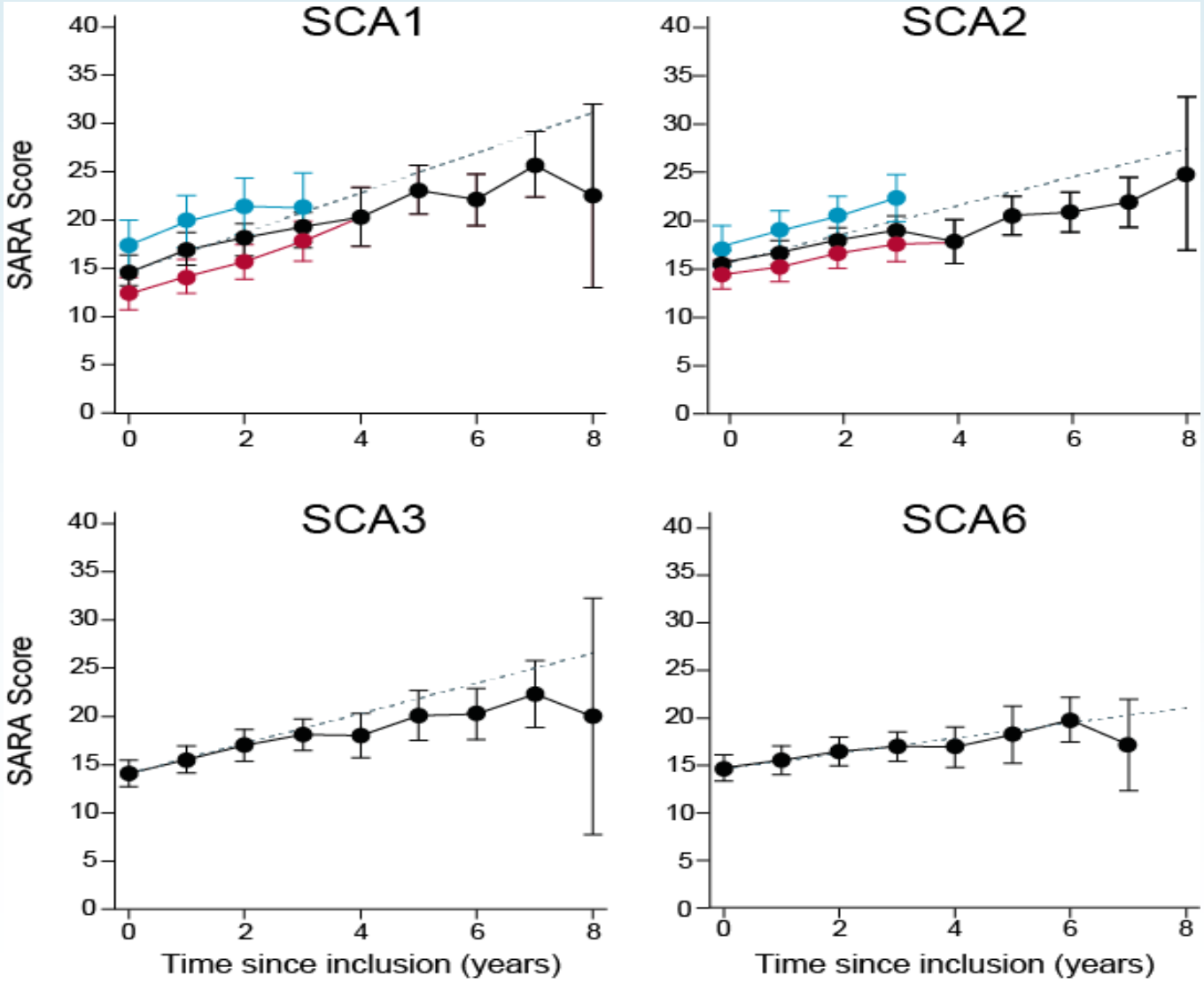
	Small repeat	Medium repeat	Large repeat	Very large repeat
SCA1	..	Cerebellar ataxia, pyramidal syndrome	Amyotrophic lateral sclerosis-like disorders	Developmental delay
SCA2	Postural tremor	Cerebellar ataxia, decreased reflexes	Cerebellar ataxia, chorea, dementia	Myoclonus, dystonia, cardiac failure, retinal degeneration
SCA3	Axonal neuropathy, dopa-responsive parkinsonism	Cerebellar ataxia, diplopia	Dystonia, pyramidal signs	Rare cases, predominant dystonia
SCA6	Episodic ataxia	..	Few associated signs after 10-years of disease course	..
SCA7	Cerebellar ataxia without visual loss	Cerebellar ataxia, macular degeneration	Visual loss before cerebellar syndrome	Cardiac failure
SCA17	Huntington's disease-like phenotype, parkinsonism	Ataxia, dementia, chorea and dystonia, pyramidal signs	Ataxia, dementia, spasticity, epilepsy	Growth retardation
DRPLA	Chorea, ataxia, psychiatric manifestations	..	Progressive myoclonus, epilepsy, developmental delay, mild ataxia	Myoclonic epilepsy, chorea, cognitive impairment

..=unknown. SCA=spinocerebellar ataxia. DRPLA=dentatorubro-pallidoluysian atropy.

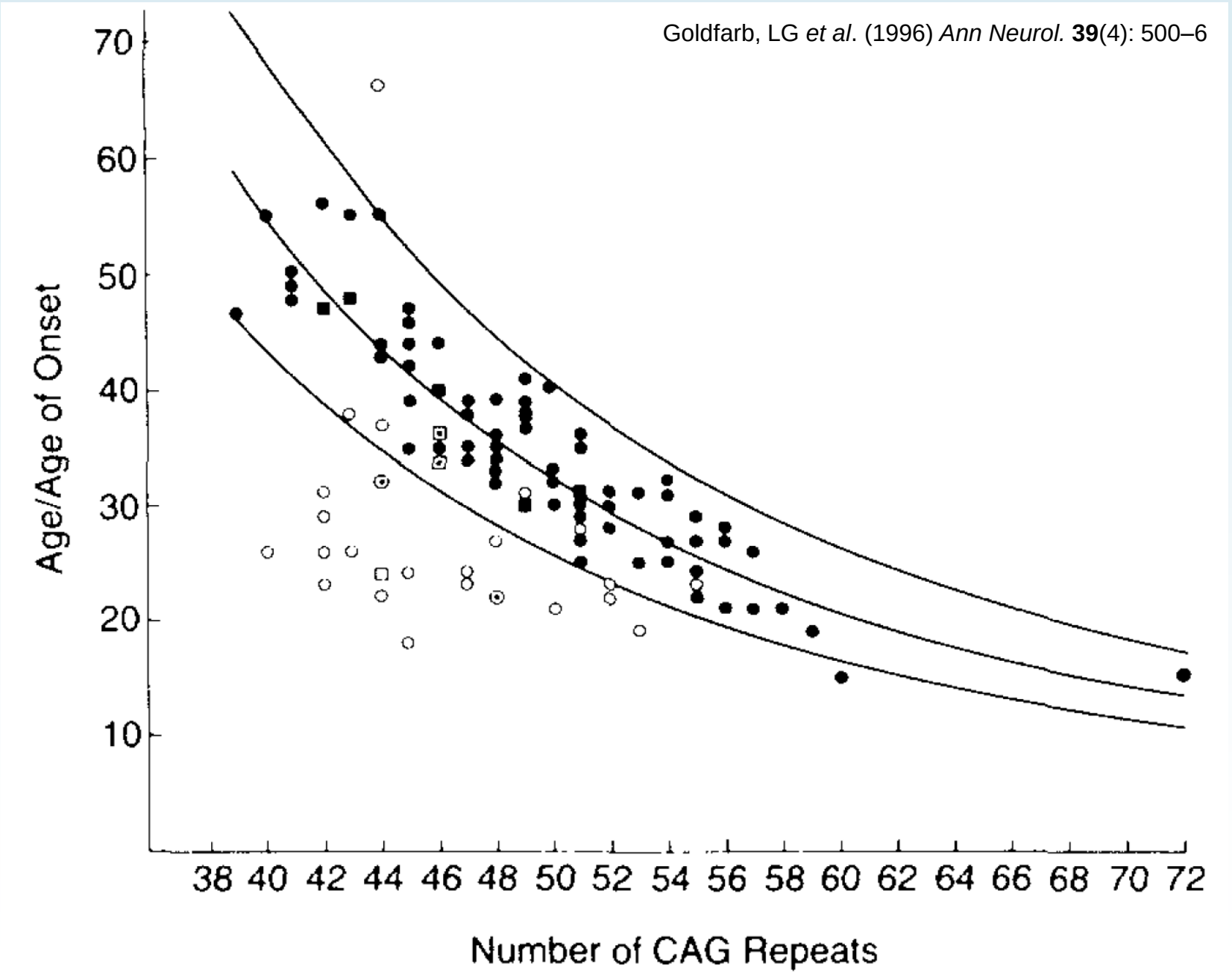
Table 2: **Clinical features in polyglutamine expansion SCAs, according to size of CAG repeat**

Durr, 2010

- **Long-term disease evolution in spinocerebellar ataxia type 1, 2, 3, and 6: a longitudinal cohort study of 536 patients**
- Heike Jacobi, et al. ***Lancet of Neurology Sep,2015***



CAG_n- Age at onset correlation



CAG repeat interruptions in alleles

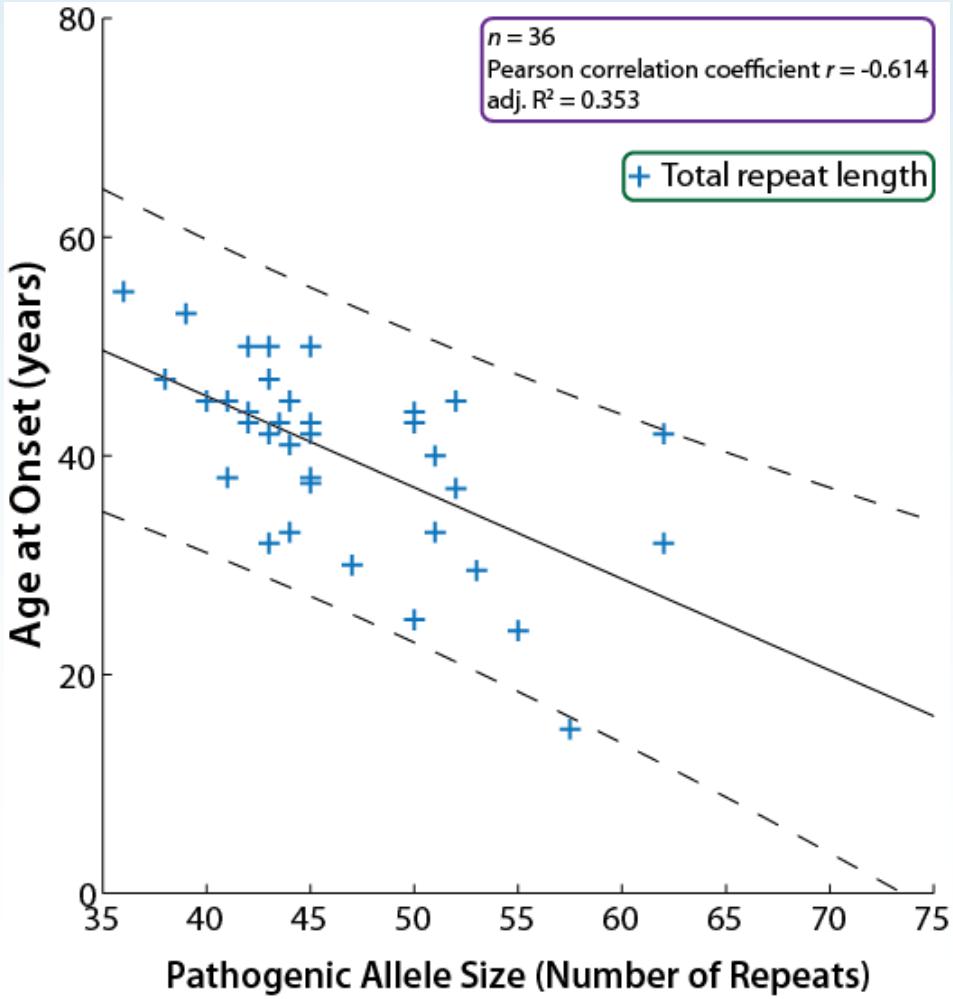
SCA	Gene	Locus	Repeat Configuration
SCA1	*ATXN1*	6p22.36	$(CAG)_n(CAT)(CAG)(CAT)(CAG)_n$
SCA2	*ATXN2*	12q24.13	$(CAG)_n(CAA)(CAG)_4(CAA)(CAG)_n$
SCA3	*ATXN3*	14q32.12	$(CAG)_2(CAA)(AAG)(CAG)(CAA)(CAG)_n$
SCA17	*TBP*	6q27	$(CAG)_3(CAA)_3(CAG)_n(CAA)(CAG)(CAA)(CAG)_n(CAA)(CAG)$

CAG repeat alleles

SCA	Gene	Locus	Repeat Configuration
SCA1	*ATXN1*	6p22.36	$(CAG)_n(CAT)(CAG)(CAT)(CAG)_n$
SCA2	*ATXN2*	12q24.13	$(CAG)_n(CAA)(CAG)_4(CAA)(CAG)_n$
SCA3	*ATXN3*	14q32.12	$(CAG)_2(CAA)(AAG)(CAG)(CAA)(CAG)_n$
SCA17	*TBP*	6q27	$(CAG)_3(CAA)_3(CAG)_n(CAA)(CAG)(CAA)(CAG)_n(CAA)(CAG)$

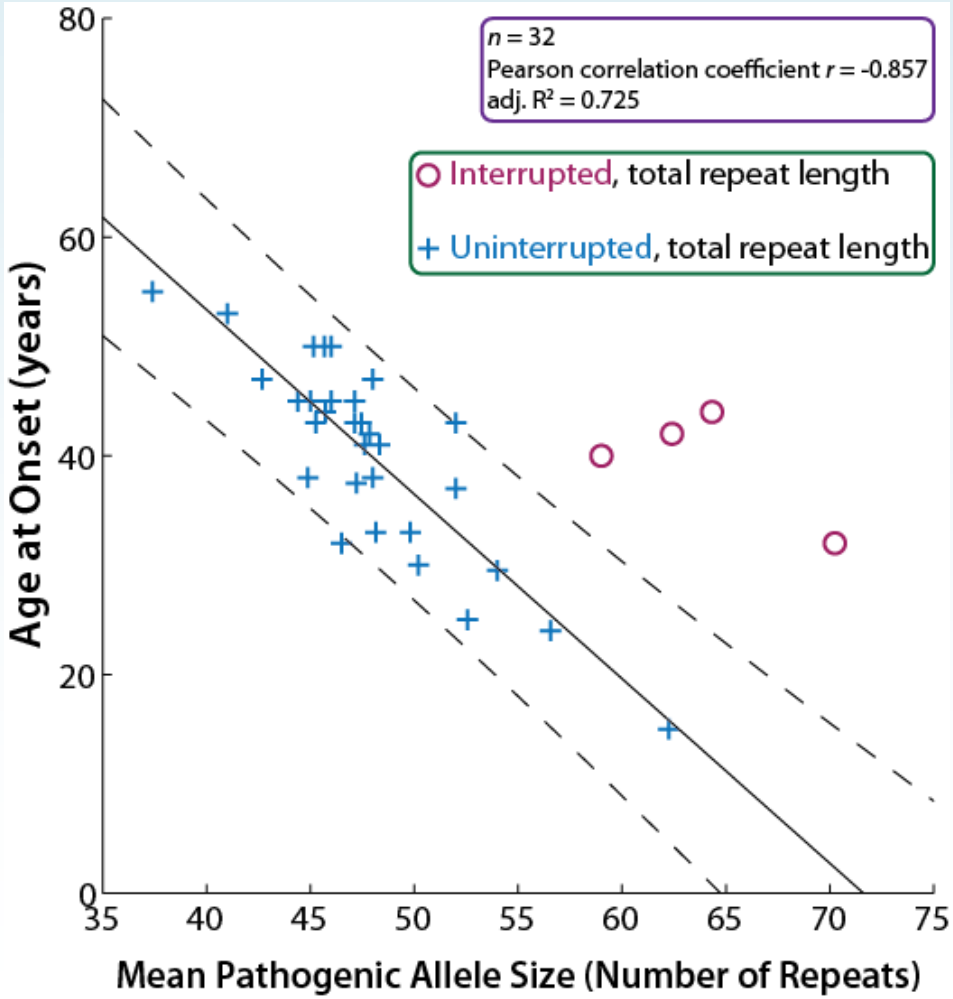
What is the role of the interruption/s in modulating disease pathology?

Age at Onset vs Size of Expanded Allele Fragment Sizing



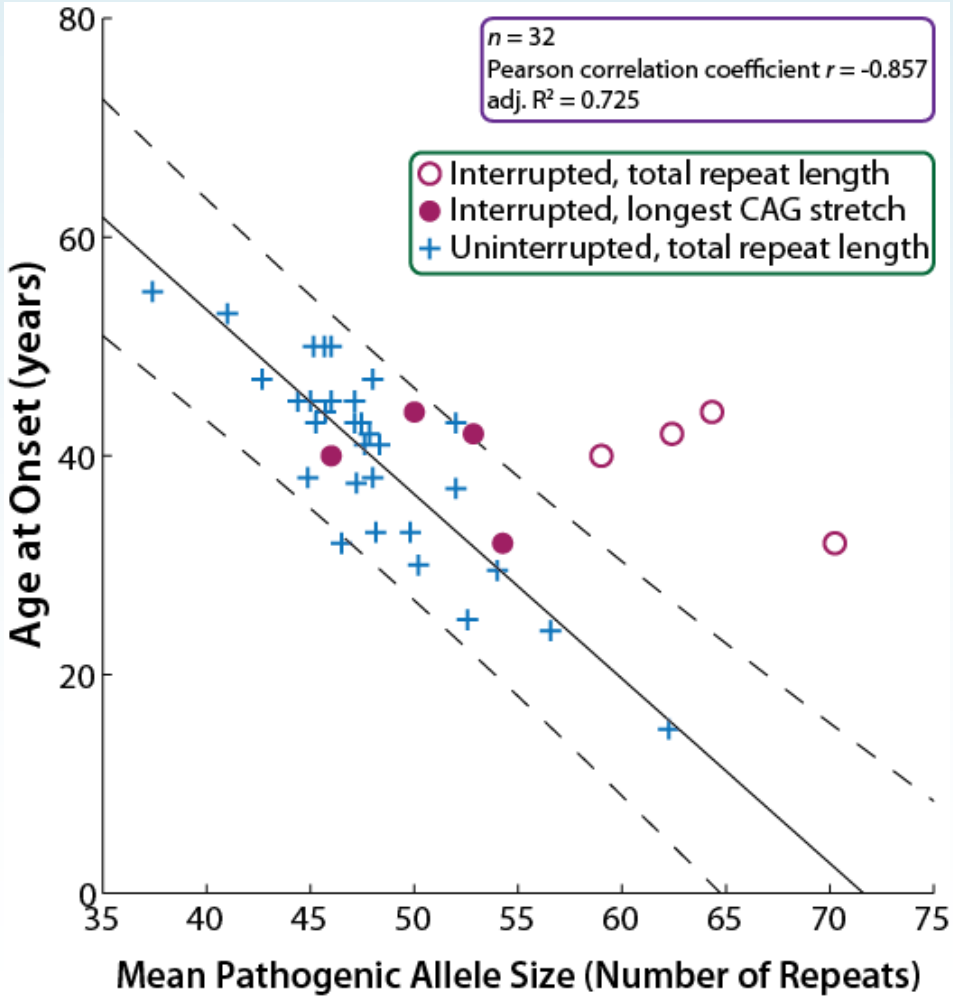
Menon, Nethisinghe et al. Jul 2013, PLOS Genetics

Age at Onset vs Size of Expanded Allele Sequencing Sizing



Menon, Nethisinghe et al. Jul 2013, PLOS Genetics

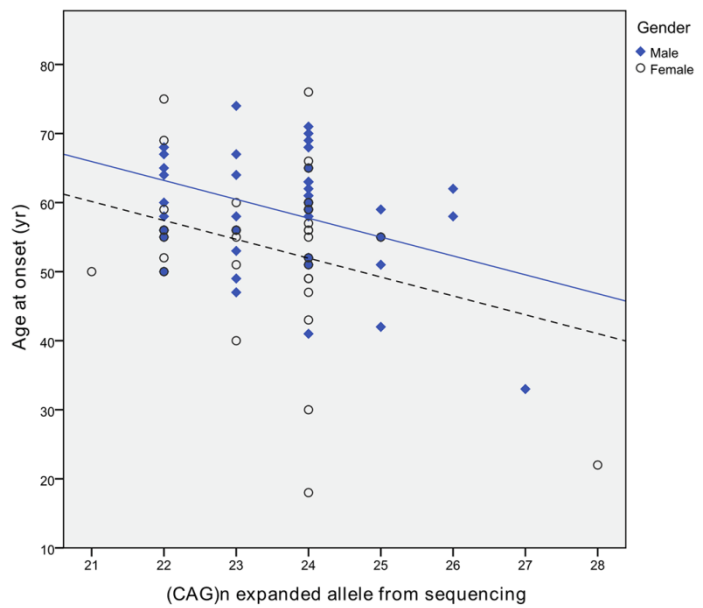
Age at Onset vs Size of Expanded Allele Sequencing Sizing



Menon, Nethisinghe et al. Jul 2013, PLOS Genetics

SCA6

- Very little anticipation and instability
- Expanded repeats - 20-33 CAGs
- No interruptions, so variability seen in some families due to epigenetic factors



Weithoff *et al.* 2018 JNNP doi: 10.1136/jnnp-2017-317253

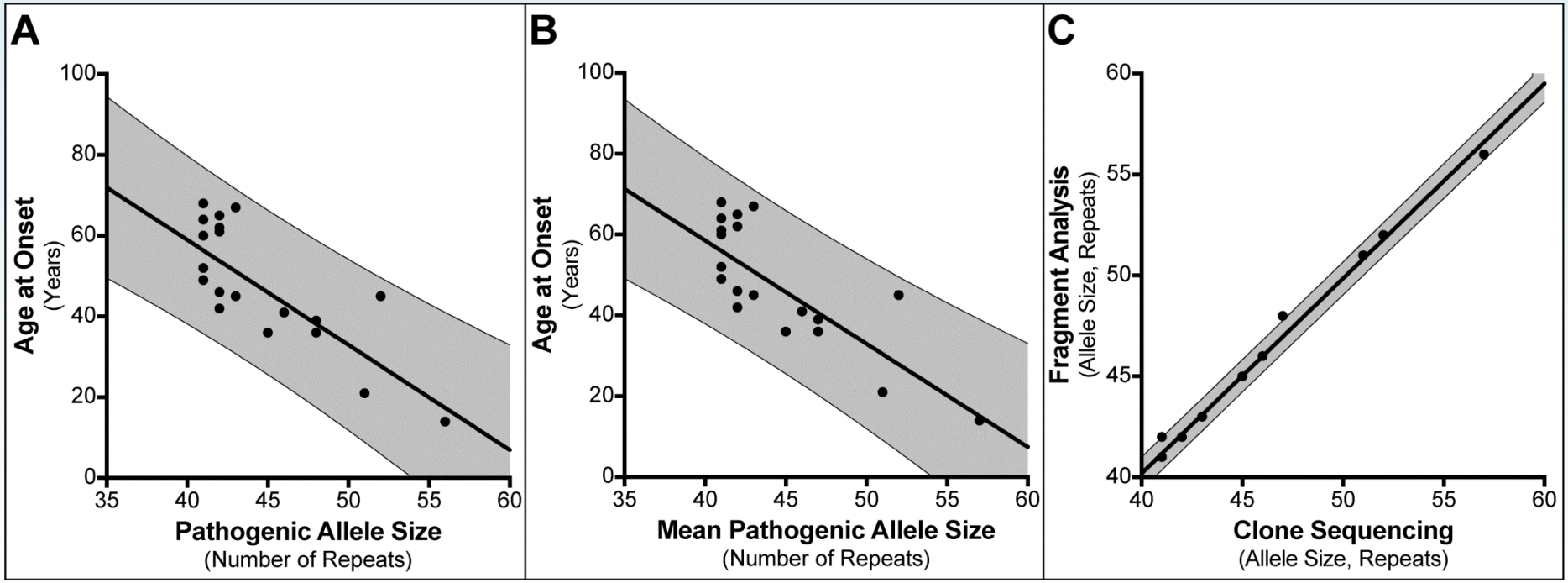
SCA17

- Autosomal dominant cerebellar ataxia
- Characterised by:
    - Ataxia
    - Pyramidal and extrapyramidal signs
    - Cognitive impairments
    - Psychosis
    - Seizures
- Also known as Huntington's Disease-like 4 (HDL-4)
- Caused by polyQ expansion in the TATA box-binding protein
    - *TBP*; 6q27

SCA17 Cohort

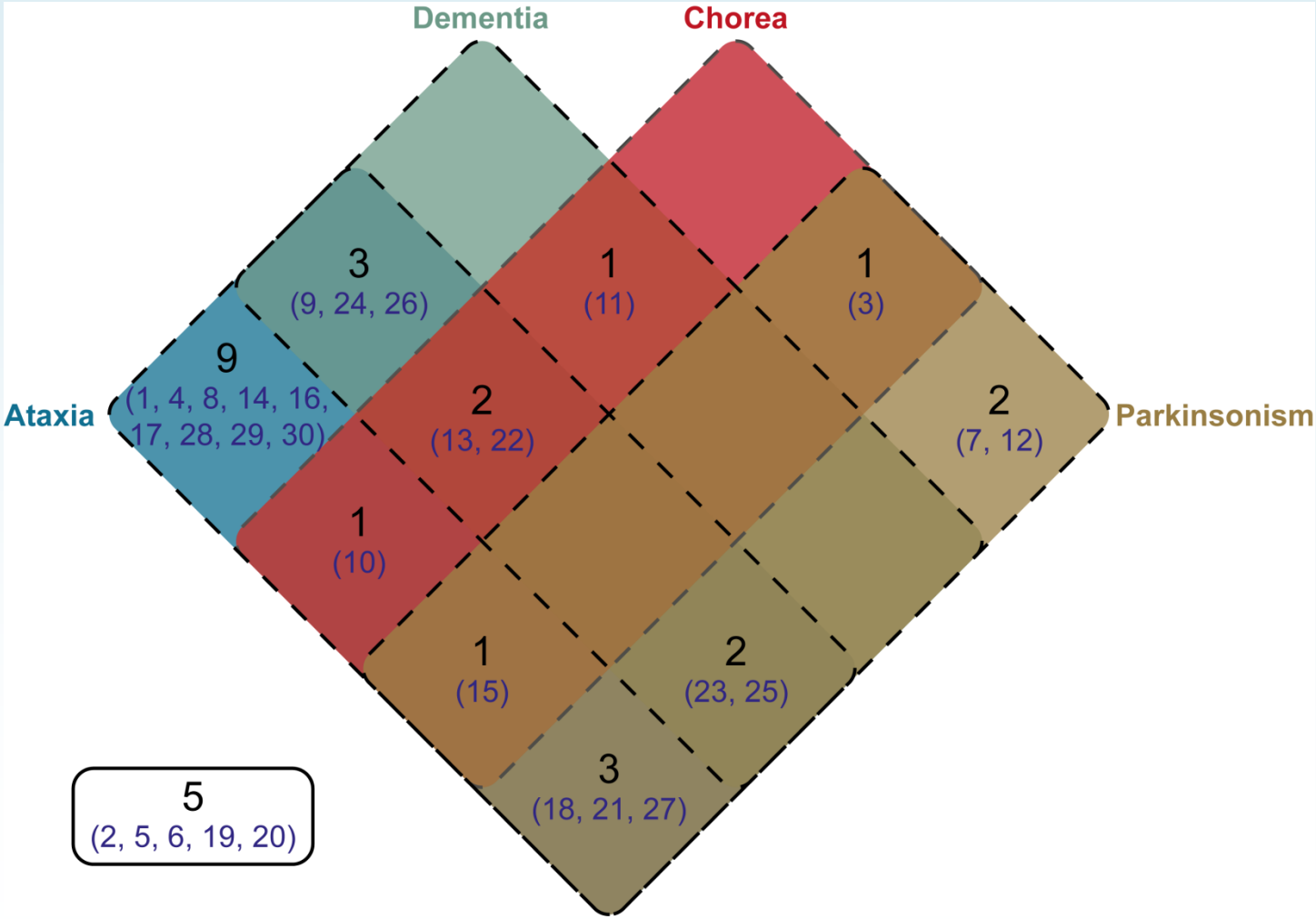
- 467 clones from 30 individuals
  - Most frequent allele (10% of clones) had 38 repeats
    - $(CAG)_3(CAA)_3(CAG)_9(CAA)(CAG)(CAA)(CAG)_{18}(CAA)(CAG)$
  - Most frequent pathogenic allele (2% of clones) had 51 repeats
    - $(CAG)_3(CAA)_3(CAG)_9(CAA)(CAG)(CAA)(CAG)_{31}(CAA)(CAG)$
- Age at onset information for 21 individuals

SCA17 Repeat Size vs Age at Onset



Nethisinghe et al 2018 Front Cell Neurosci

Phenotype Distribution



CONCLUSIONS

- SCA1,2,3,7,17 sharing some common clinical genetic features
- SCA1 shows the most rapid progression as the opposite SCA6
- Expanded allele can be interrupted in all the above conditions
- We found interruption in 11% of the SCA1 expanded allele
- Interruptions in the expanded allele delay age at onset in SCA1
- Longest uninterrupted CAG stretch should be considered rather than the total repeat length when predicting age at disease onset in SCA1
- Repeat instability can occur even in the presence of CAG interruptions in SCA1

Menon, Nethisinghe et al. Jul 2013, PLOS Genetics

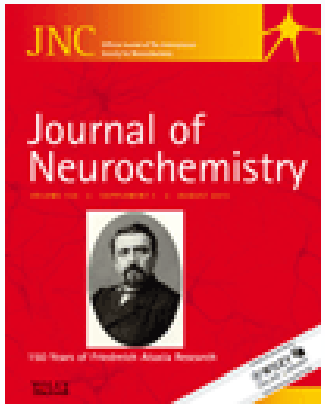
Conclusions

- Despite sharing clinical and genetic aspects, we continue to identify different features that characterise polyQ diseases further.
- SCA1 – repeat configuration is important
  - 11% of SCA1 patients have an interrupted polyQ, reducing severity of their symptoms
  - So far, only translational modifier in the polyQ diseases
- SCA6 – no interruptions
  - variability in age at onset more related to epigenetic factors intrinsic to the mutation
- SCA17 – interruptions present in expanded allele
  - Interruptions not modifiers
  - No particular repeat configuration associated with a particular phenotype

Autosomal recessive cerebellar ataxias

Nikolaus Friedreich (1822-1888)

Friedreich's ataxia is an autosomal recessive neurodegenerative disorder characterized by the progressive loss of voluntary movement coordination (ataxia) and heart enlargement.



Friedreich N (1863). "Ueber Degenerative Atrophie der Spinalen Hinterstränge". *Arch Pathol Anat Phys Klin Med* **26** (3–4): 391–419

Differential diagnosis with FRDA

Genetic:	AR Genetic: DNA repair disorders	AR Genetic: Metabolic
Charcot-Marie-Tooth	ATM	Ataxia with vitamin E deficiency
ARSACS	AOA1	Abetalipoproteinemia
SPG7	AOA2	Refsum Disease
	SCAN1 (spinocerebellar ataxia with axonal neuropathy).	

Friedreich's Ataxia: typical phenotype

- **Inheritance: AR** neurodegenerative disease: onset <25.

- **Prevalence:** 1:50.000; heterozygote frequency 1:70-90.

- **Clinical features:**
- **1. Neurological** Progressive **gait and limb ataxia** from age 5-15, **dysartria**, **pyramidal weakness** and **Babinski sign**, sensory loss and **sensory neuropathy** (absent DTR).
    - NS hearing loss, optic atrophy, distal amyotrophy.
- 2. **Extraneurological manifestations**:
    1. Kypho-scoliosis, pes cavus
    2. Hypertrophic/dilated cardiomyopathy (70%).
    3. Diabetes or glucose intolerance (10-30%)
- **Degeneration :** DRG large neurons, spinocerebellar, pyramidal, cuneate, gracile tracts, with relative sparing of the cerebellum

RESEARCH Open Access

Urinary, bowel and sexual symptoms in a cohort of patients with Friedreich's ataxia

Meher Lad[1,2], Michael H. Parkinson[1], Myriam Rai[3], Massimo Pandolfo[3], Petya Bogdanova-Mihaylova[4], Richard A. Walsh[4,5], Sinéad Murphy[4], Anton Emmanuel[6], Jalesh Panicker[2†] and Paola Giunti[1*†]

Abstract

Background: Pelvic symptoms are distressing symptoms experienced by patients with Friedreich's Ataxia (FRDA).

The aim of this study was to describe the prevalence of lower urinary tract symptoms (LUTS), bowel and sexual
symptoms in FRDA.

Methods: Questionnaire scores measuring LUTS, bowel and sexual symptoms were analysed with descriptive statistics as a cohort and as subgroups (Early/Late-onset and Early/Late-stage FRDA) They were also correlated with validated measures of disease severity including those of ataxia severity, non-ataxic symptoms and activities of daily living.

Results: 80% (n = 46/56) of patients reported LUTS, 64% (n = 38/59) reported bowel symptoms and 83% (n = 30/36)reported sexual symptoms. Urinary and bowel or sexual symptoms were significantly likely to co-exist among patients.

Late-onset FRDA patients were also more likely to report LUTS than early-onset ones. Patients with a longer disease duration reported higher LUTS scores and poorer quality of life scores related to urinary symptoms.

Conclusions: A high proportion of FRDA have symptoms suggestive of LUTS, bowel and sexual dysfunction. This is more marked with greater disease duration and later disease onset. These symptoms need to be addressed by clinicians as they can have a detrimental effect on patients.

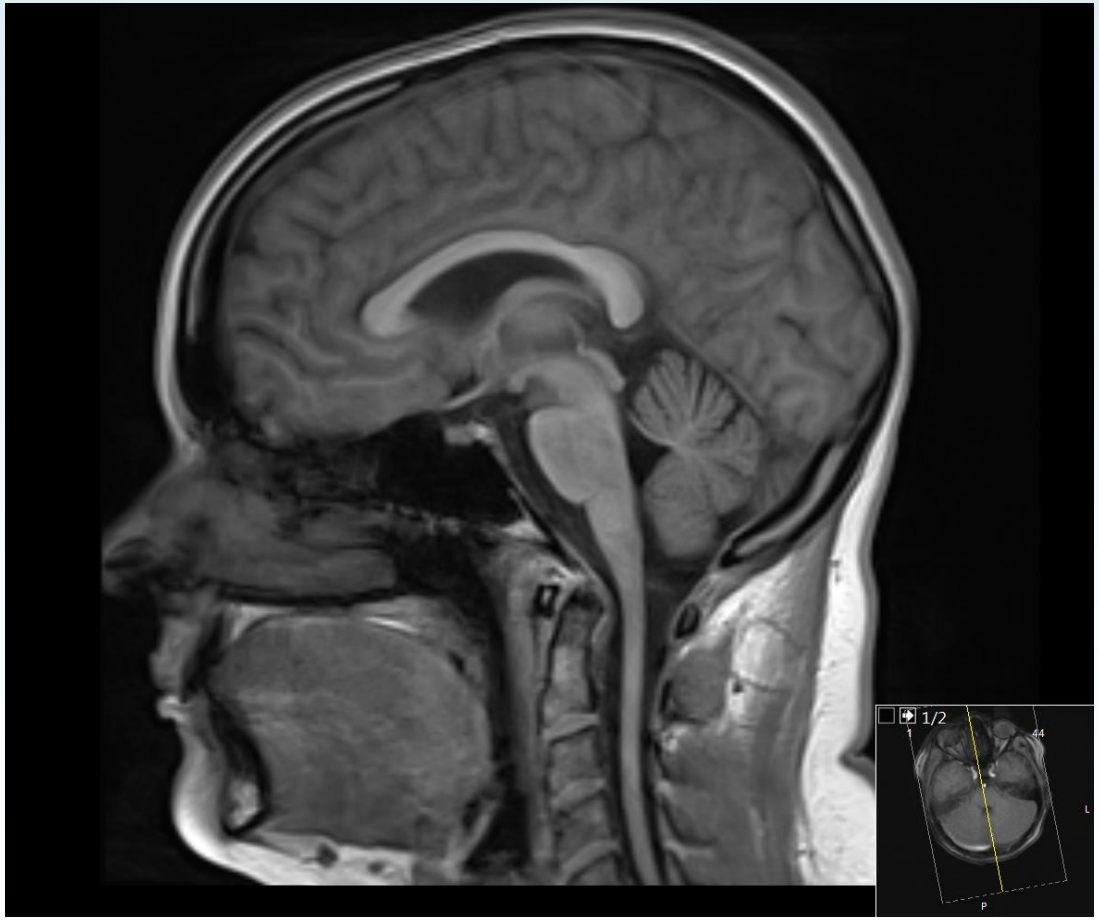
Keywords: Friedreich's ataxia, Urinary, Bladder, Bowel, Sexual function

Lad et al. Orphanet Journal of Rare Diseases (2017) 12:158
DOI 10.1186/s13023-017-0709-y

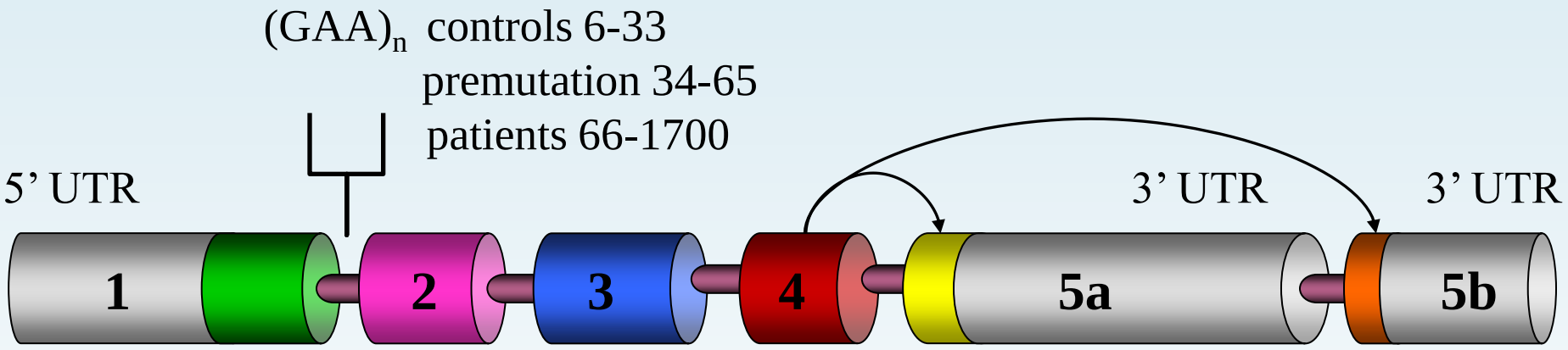
Friedreich's Ataxia: "atypical phenotypes"

- FARR: Friedreich's ataxia with retained DTR
- LOFA : late-onset Friedreich's ataxia (> 25, to 60 yrs)
- Very rare Pure Spastic phenotype, Dystonic, "Chorea", Neuropathic Variants of Friedreich's ataxia

FRDA



Frataxin Gene and Mutations in Friedreich Ataxia Patients



M1 incorrect initiation
L33 fs → 76X*
P34 fs → 76X*
P52 fs → 76X*

Campuzano et al, 1996

Filla et al, 1996

Bidichandani et al, 1997

Galea et al 2017

L106X
D122Y
Y118X*
ex3/IVS3del13*

Forrest et al, 1998

Cossée et al, 1999

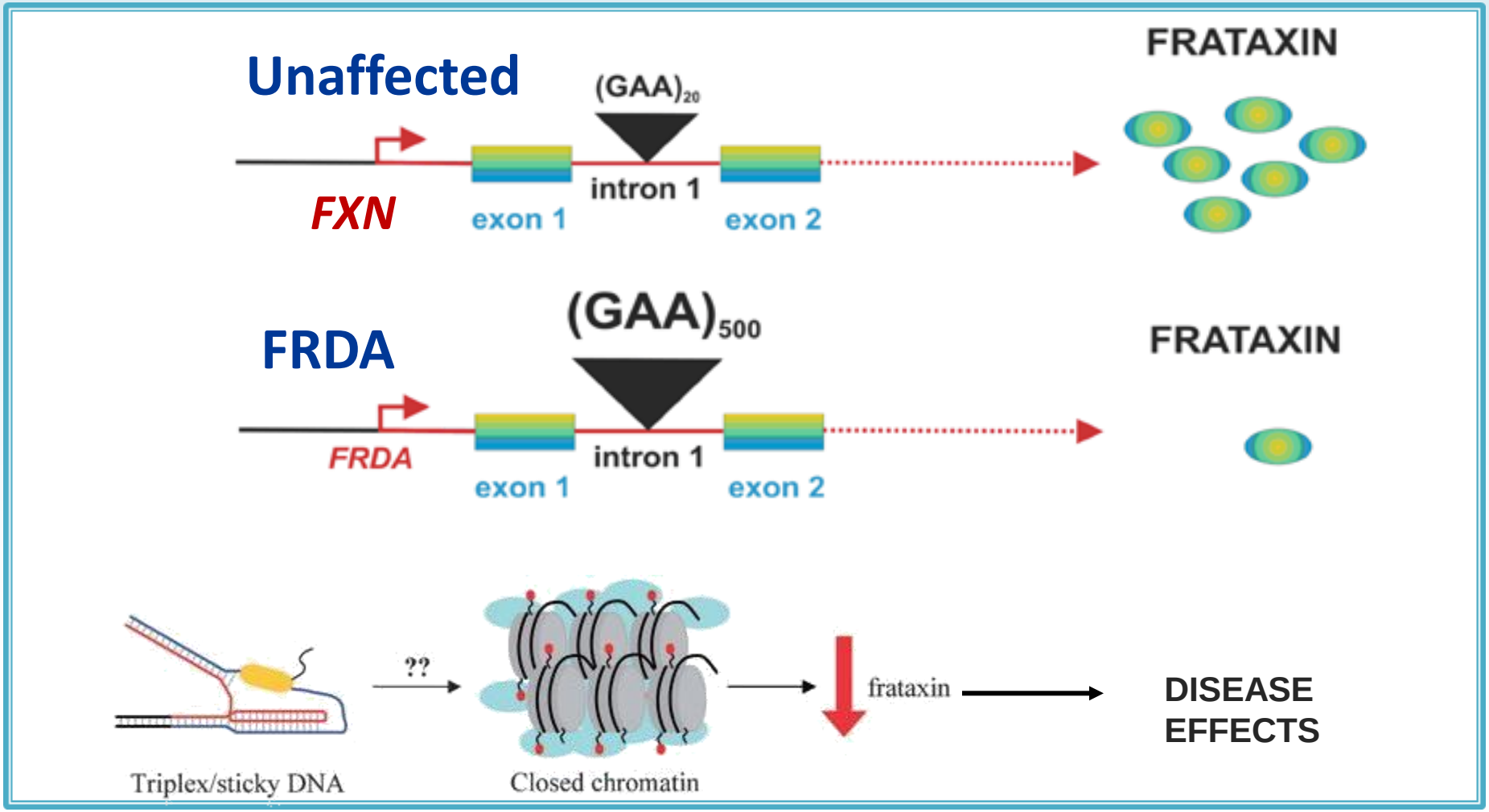
De Michele et al, 2000

I154F
G130V
L156P

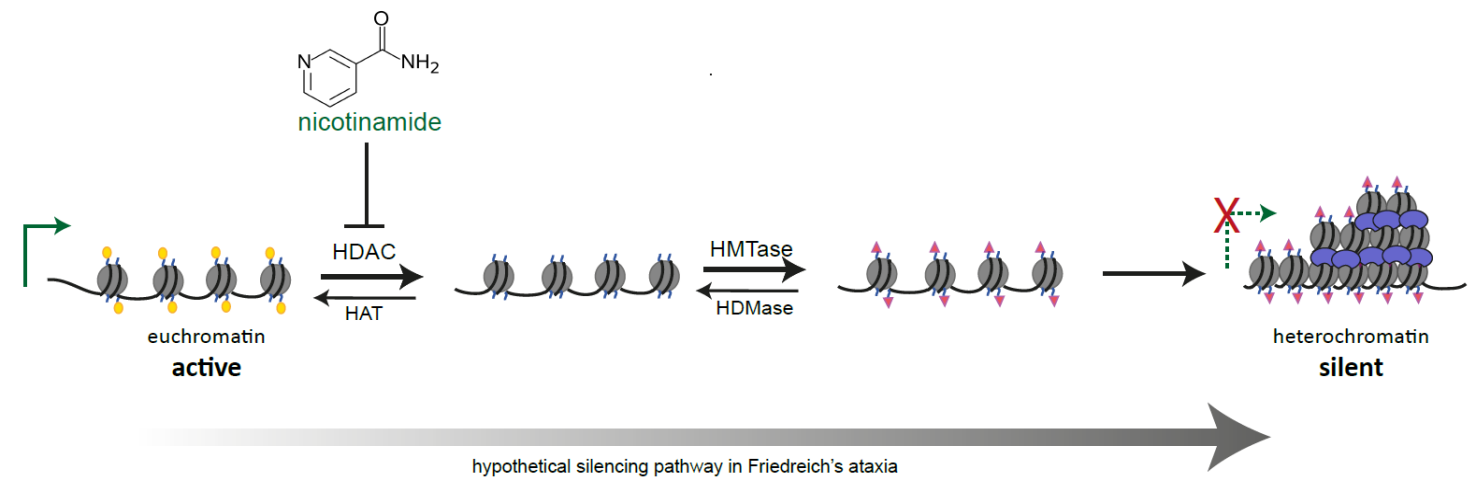
R165C
L182F
L182H
H183R
R165P
W173G

Gellera et al 2007

FRDA Disease Mechanism



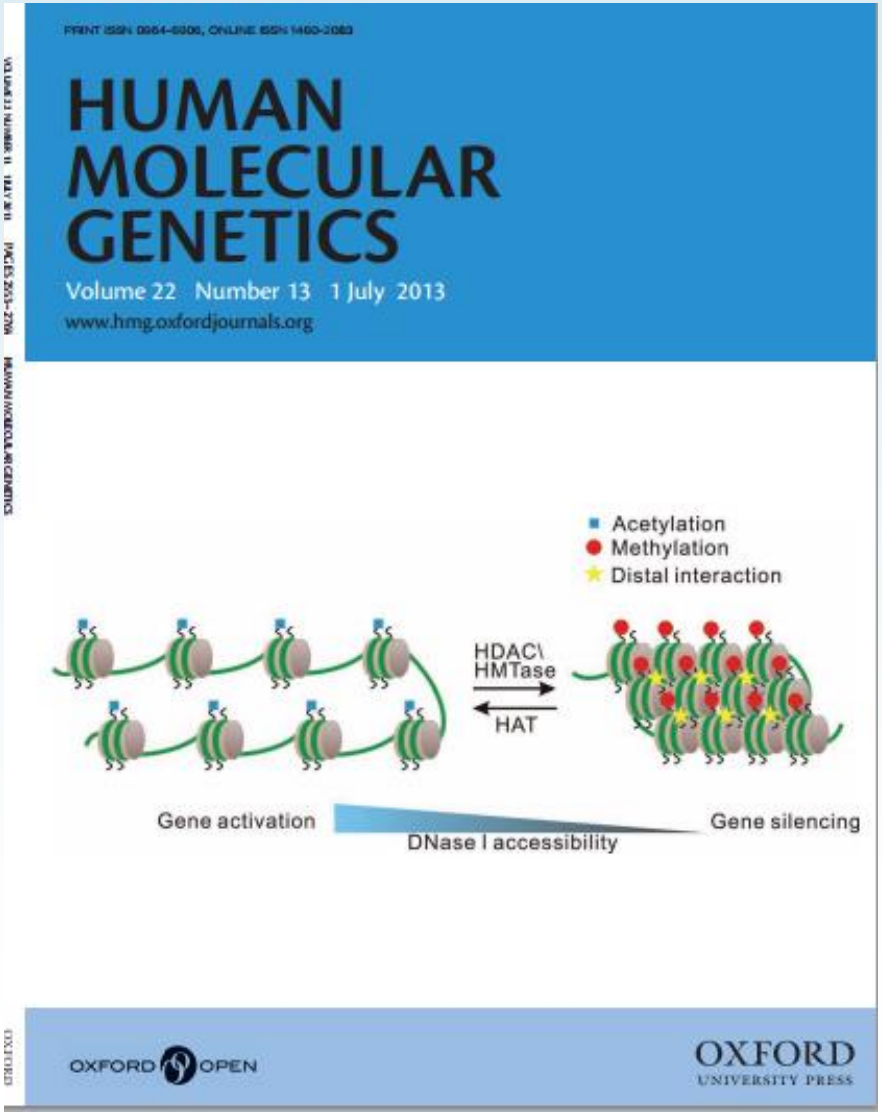
Epigenetic & Neurological Effects of Nicotinamide in FRDA



lysine acetylation lysine methylation (e.g. H3K9me3) heterochromatin proteins (e.g. HP1)

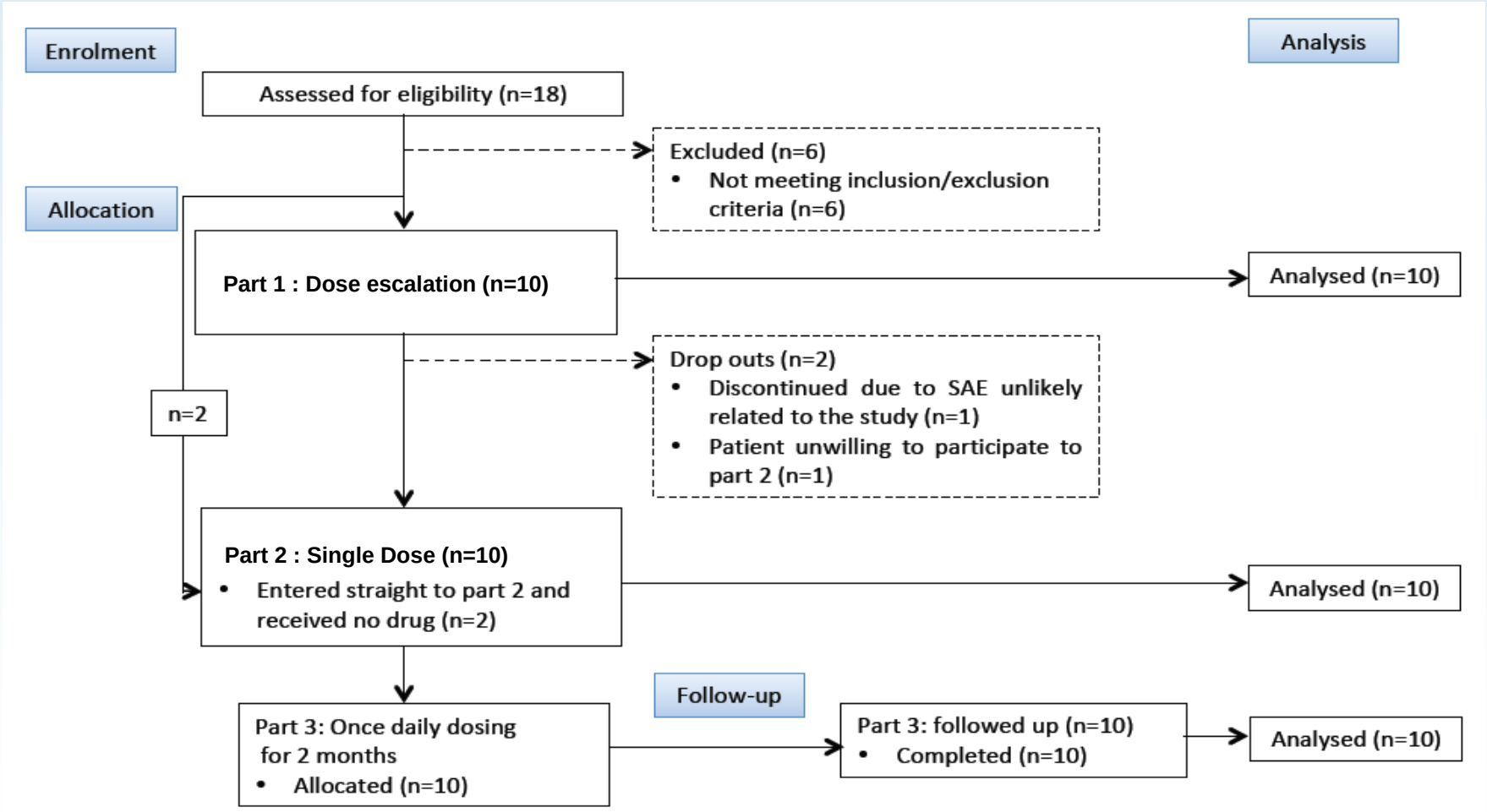
Heterochromatinization induced by GAA-repeat hyperexpansion in Friedreich's ataxia can be reduced upon HDAC inhibition by vitamin B3

Ping K. Chan[1,†], Raul Torres[1,†], Cihangir Yandim[1], Pui P. Law[1], Sanjay Khadayate[2], Marta Mauri[1], Crina Grosan[3], Nadine Chapman-Rothe[1], Paola Giunti[5], Mark Pook[4] and Richard Festenstein[1,*]



Prof R. Festenstein

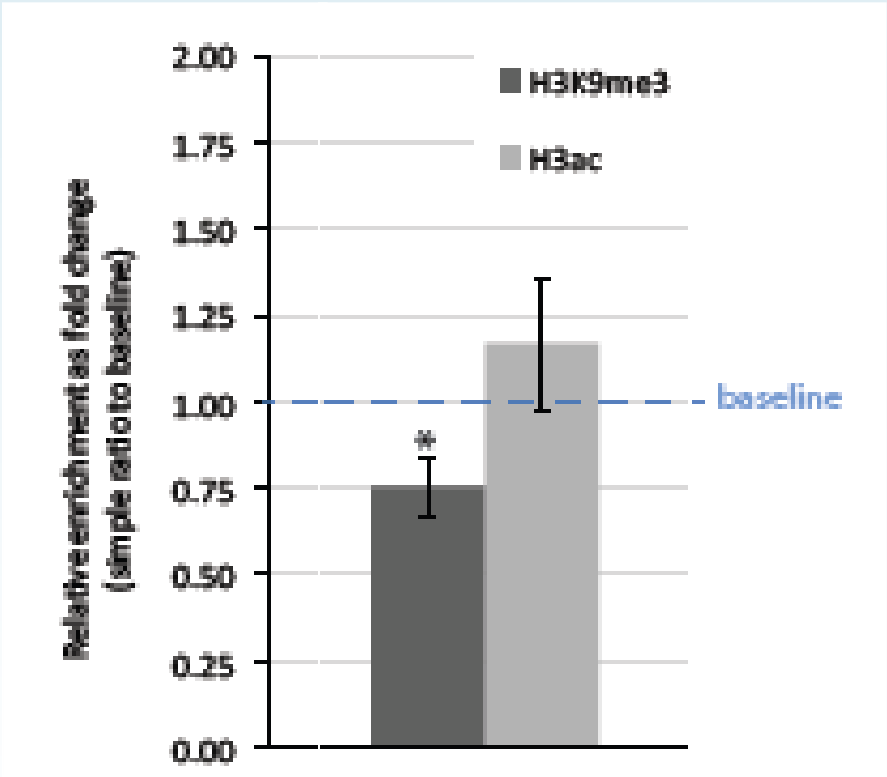
Phase II Open Label Trial of Nicotinamide in FRDA Patients



June 2012-June 2013

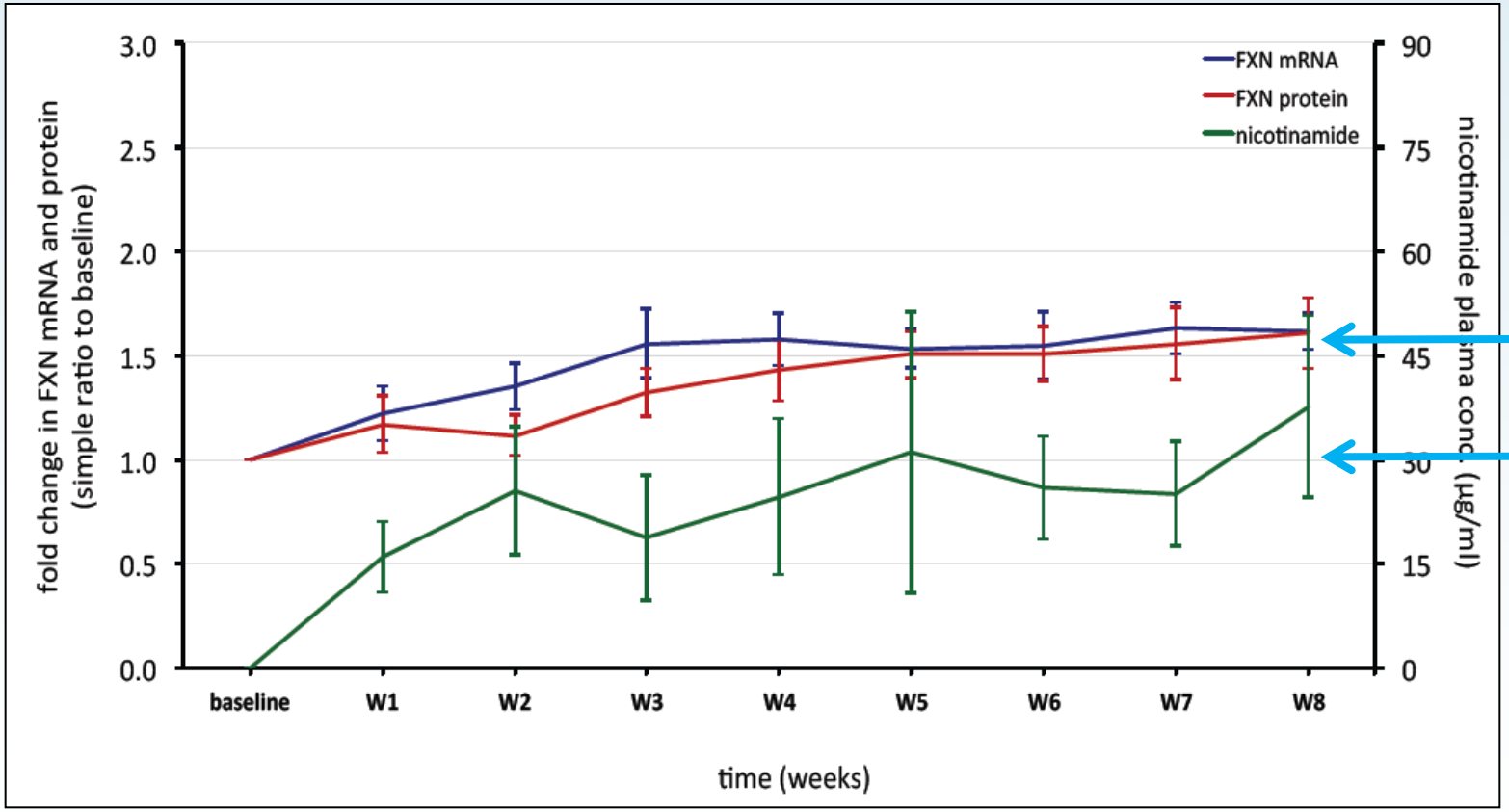
Libri *et al.* Lancet (2014)

- Decrease in DNA methylation (H3K9me3) around GAA expansion
- Increase in histone acetylation (H3ac) (not stat significant)



- Results consistent with hypothesis that nicotinamide can reduce heterochromatinisation at the *FXN* gene

FXN expression upregulated towards levels found in asymptomatic carriers



Epigenetic and neurological effects and safety of high-dose nicotinamide in patients with Friedreich's ataxia: an exploratory, open-label, dose-escalation study

Vincenzo Libri, Cihangir Yandim*, Stavros Athanasopoulos, Naomi Loyse, Theona Natisvili, Pui Pik Law, Ping Kei Chan, Tariq Mohammad, Marta Mauri, Kin Tung Tam, James Leiper, Sophie Piper, Aravind Ramesh, Michael H Parkinson, Les Huson, Paola Giunti, Richard Festenstein*

Lancet, 2014.

- Nicotinamide rapidly absorbed via oral route
- Safe & well-tolerated.
- Nausea treated with anti-emetics.
- Self-limiting rises in LFTs
- No SAEs

NICOFA: a randomized, double-blind, placebo-controlled, parallel group, multi centre study of the efficacy and safety of the nicotinamide in patients with Friedreich's ataxia

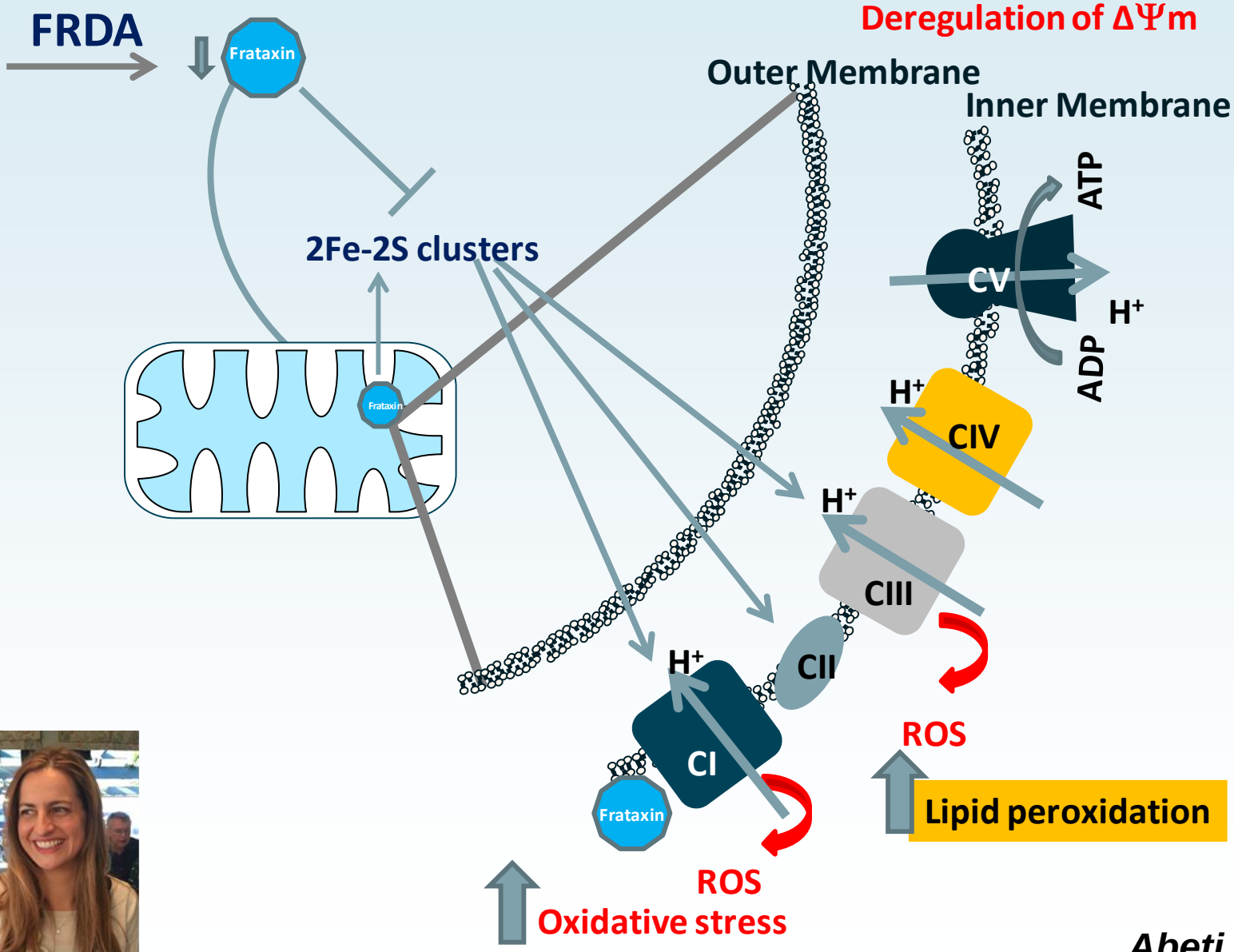
Participants must:

- be aged between 18 and 50
- have a molecular genetic diagnosis of Friedreich's ataxia

There are other specific inclusion and exclusion criteria, which will be discussed with the study team eg: SARA Score >7 and <28

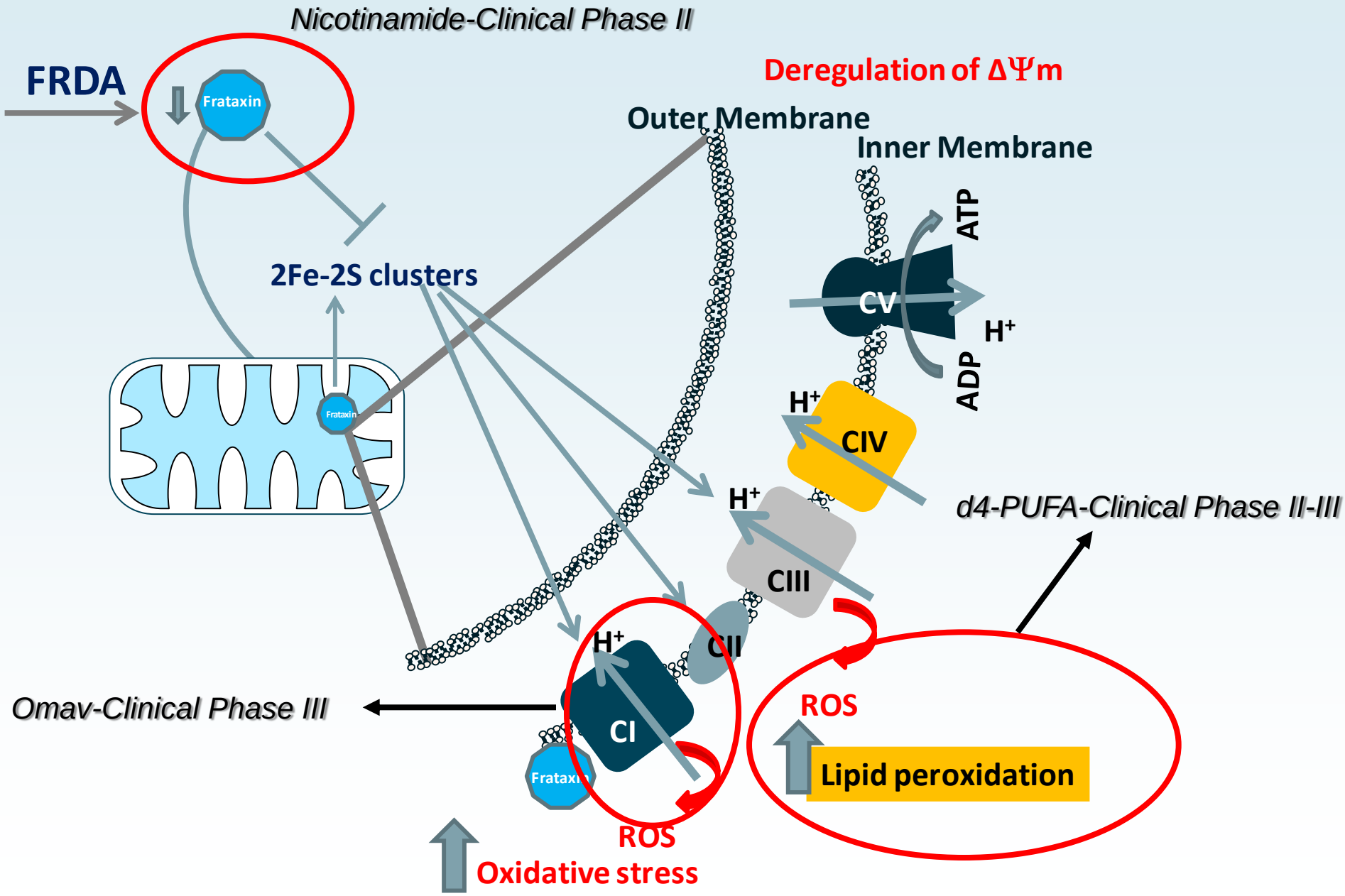
This study will take place in the UK, Germany, Austria, Italy, Spain, and France.

225 patients in total will be included in the study, about 90 of these patients will be recruited in the UK.



Rosella Abeti, PhD

Abeti et al., 2015



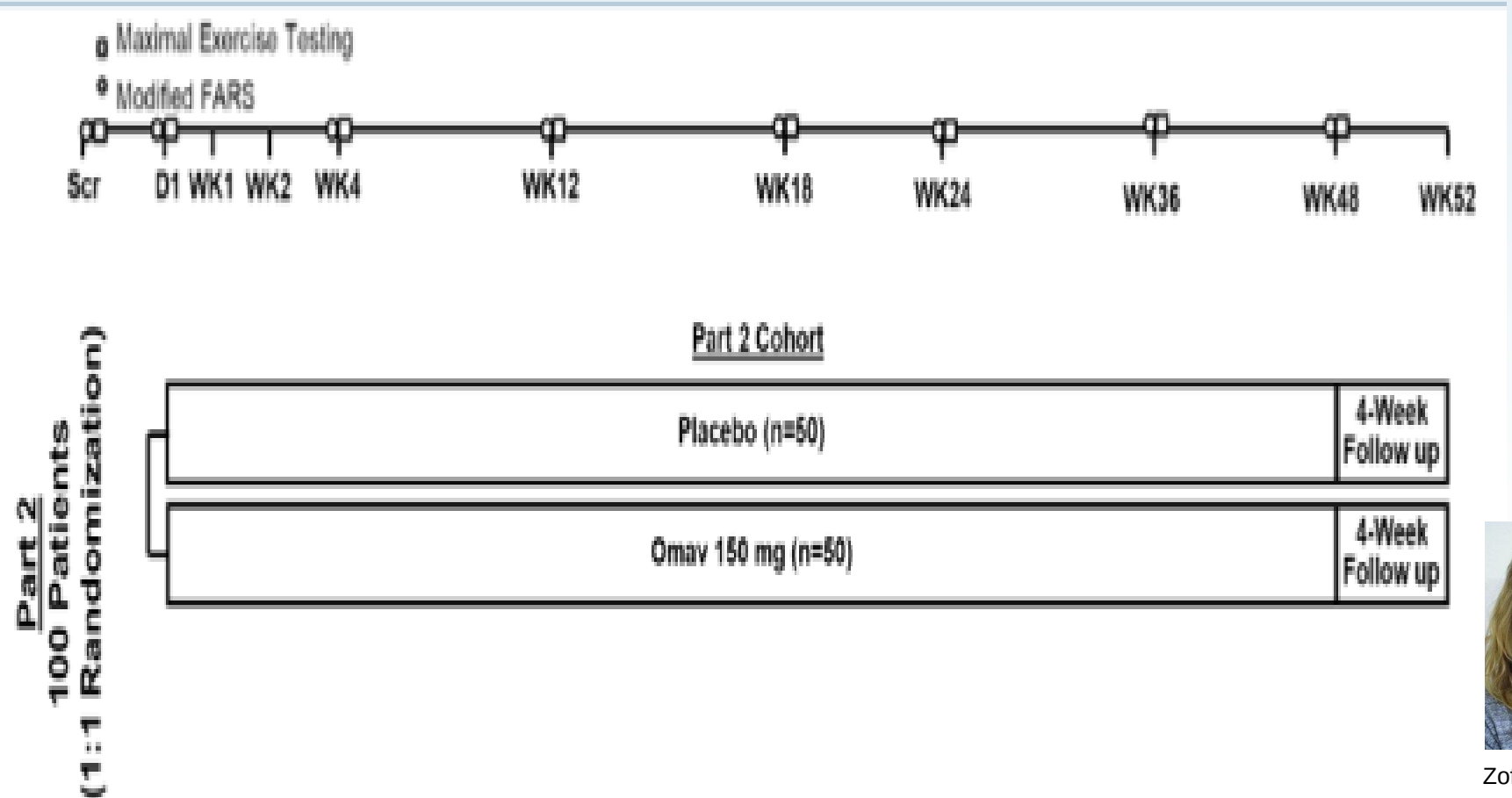
Abeti et.al., 2015

Moxi study Global FA trial

Part 2: The second part of MOXIe is a double-blind, placebo-controlled, randomized, multicenter, international trial designed to assess the efficacy, safety, and tolerability of omaveloxolone in individuals with FA.

-**primary endpoint-** change from baseline in mFARS of omaveloxolone versus placebo at 48 weeks.

Other endpoints -change from baseline in peak work during maximal exercise testing, Patient Global Impression of Change, and the Clinical Global Impression of Change.



Zofia Fleszar, MD

Highlights Moxi trial- Reata press release

ACHIEVED PRIMARY ENDPOINT OF STATISTICALLY SIGNIFICANT IMPROVEMENT IN mFARS COMPARED TO PLACEBO AFTER 48 WEEKS OF TREATMENT

- Phase 2 trial of omaveloxolone in patients with Friedreich's ataxia (FA) met its primary endpoint of change in the modified Friedreich's Ataxia Rating Scale (mFARS) relative to placebo after 48 weeks of treatment.

- Patients treated with omaveloxolone (150 mg/day) demonstrated a statistically significant, placebo-corrected 2.40 point improvement in mFARS after 48 weeks of treatment ($p=0.014$).

- Omaveloxolone treatment was generally reported to be well-tolerated.

- Based on these positive results, and subject to discussions with regulatory authorities, the company plans to proceed with the submission of regulatory filings for marketing approval in the United States and internationally.

Conclusions

FRDA is the most common inherited disorder.

The clinical spectrum encompass EOFA, LOFA & classical presentations

GAA expansion in both alleles of the FXN gene is the most common mutation , in around 4-5% of cases there is a compound heterozygous mutation with classical mutation. Deletion occurs as well but is rarer.

Screening of a large cohort of pts with a non “classical” phenotype
showed that only 3/2000 (0.15%) were positive

Clinical trial MOXI : highlight from the press realise about novel compound OMAV is promising as for the first drug for FRDA.

Clinical trail NICOFA with Nicotinamide is about to start. It is a multi centre, multi national randomised clinical trail.

Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS)

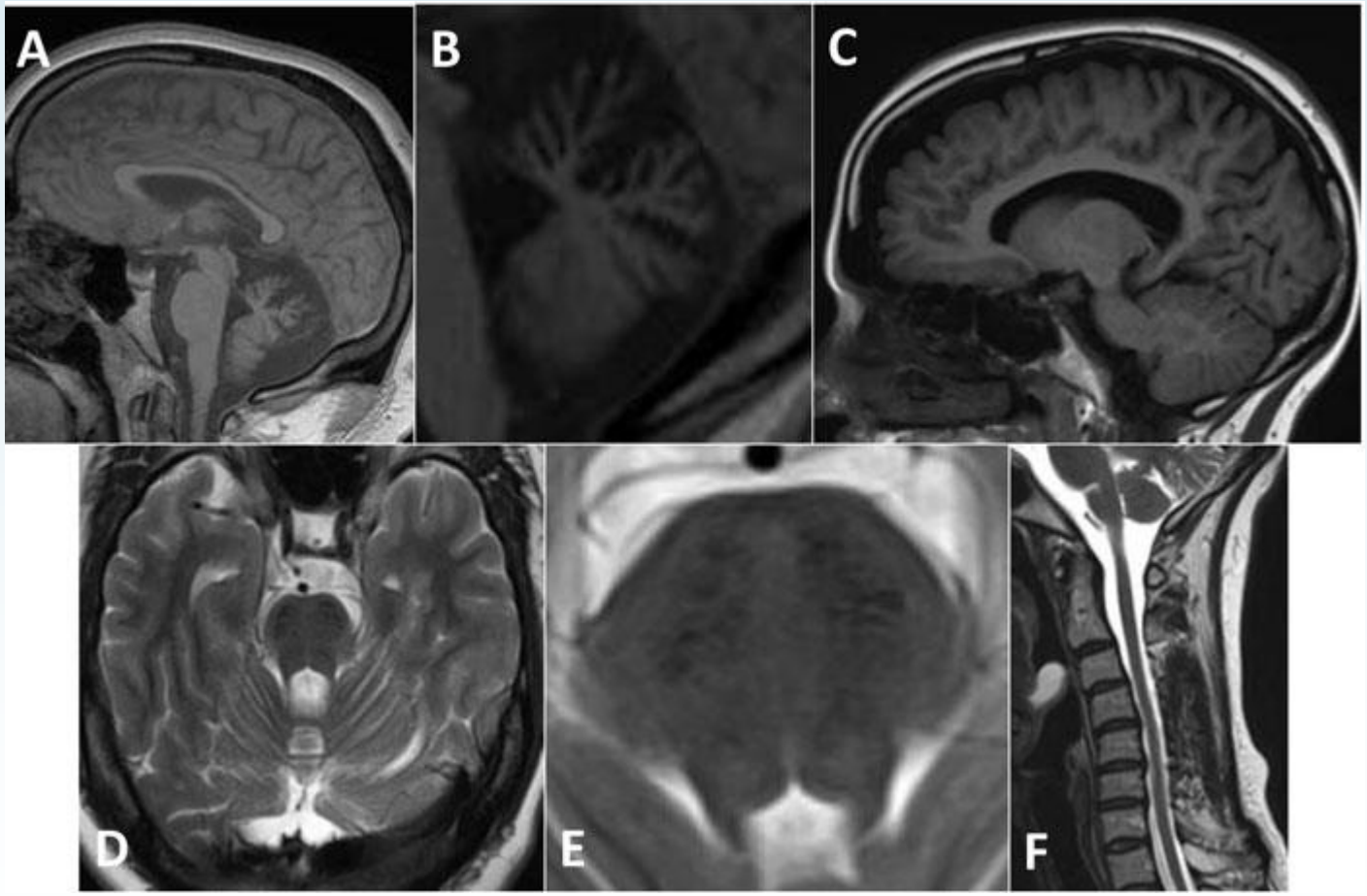
- Spastic ataxia caused by mutations in the *SACS* gene which encodes the protein **sacsin** in early childhood with lower limb spasticity and a gait ataxia
- Slow progression
- First identified in a Canadian population, now known to have a worldwide distribution(Engert, J. C. *et al. Nat. Genet.* (2000) **24**:120-125)
- Typically presents
- Canadian founder mutations
  - c.8844delT
  - c.7504C>T

ARSACS (Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay)

- ***SACS*** gene (13q12.12)→ **sacsin**.
- Macrodeletion, deletion, substitution, duplication.
- Mean AO: **15+/-17.4** y.o. (range 1-51).
- Slowly progressive ataxia, spasticity, neuropathy, skeletal foot abnormalities (**pes cavus**).
- Hearing impairment, bladder symptoms, epilepsy (20%).
- **Demyelinating** sensory-motor neuropathy

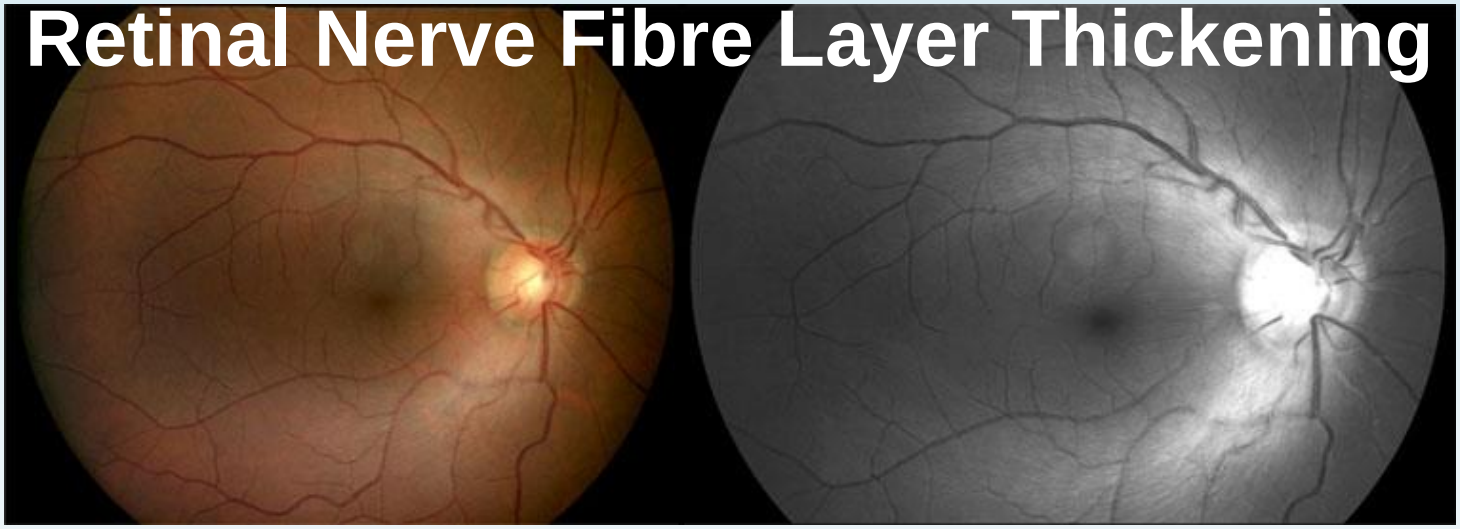
AR /Biomarkers

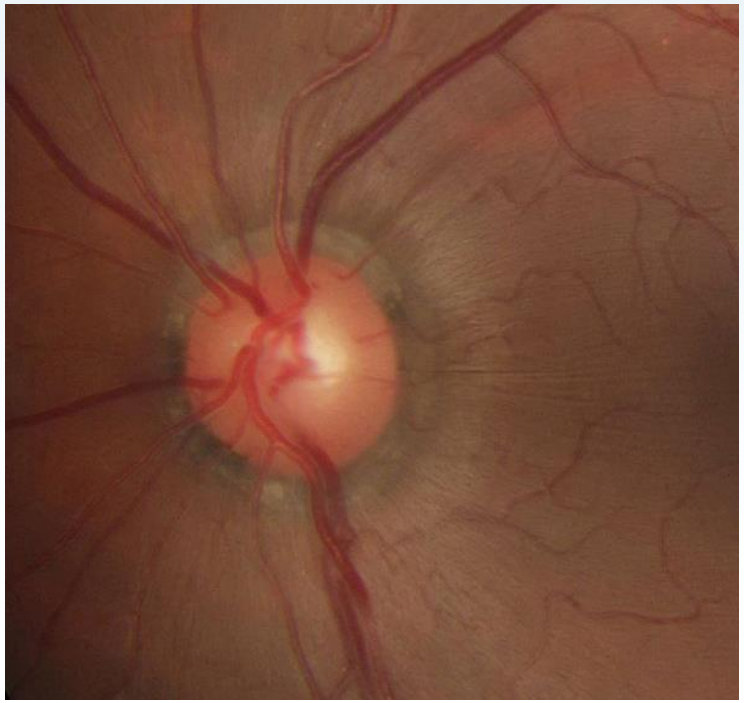
ARSACS

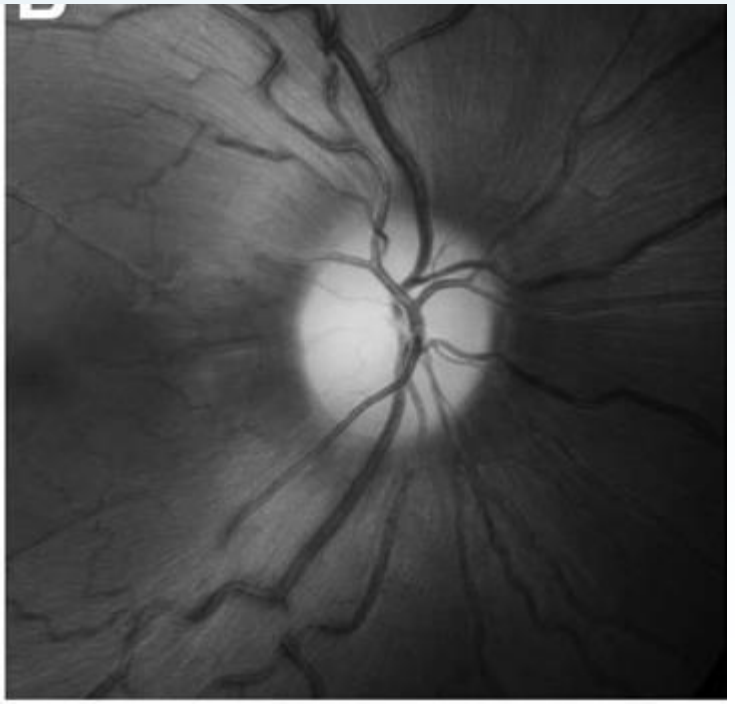


AR/ Biomarkers

Retinal Nerve Fibre Layer Thickening



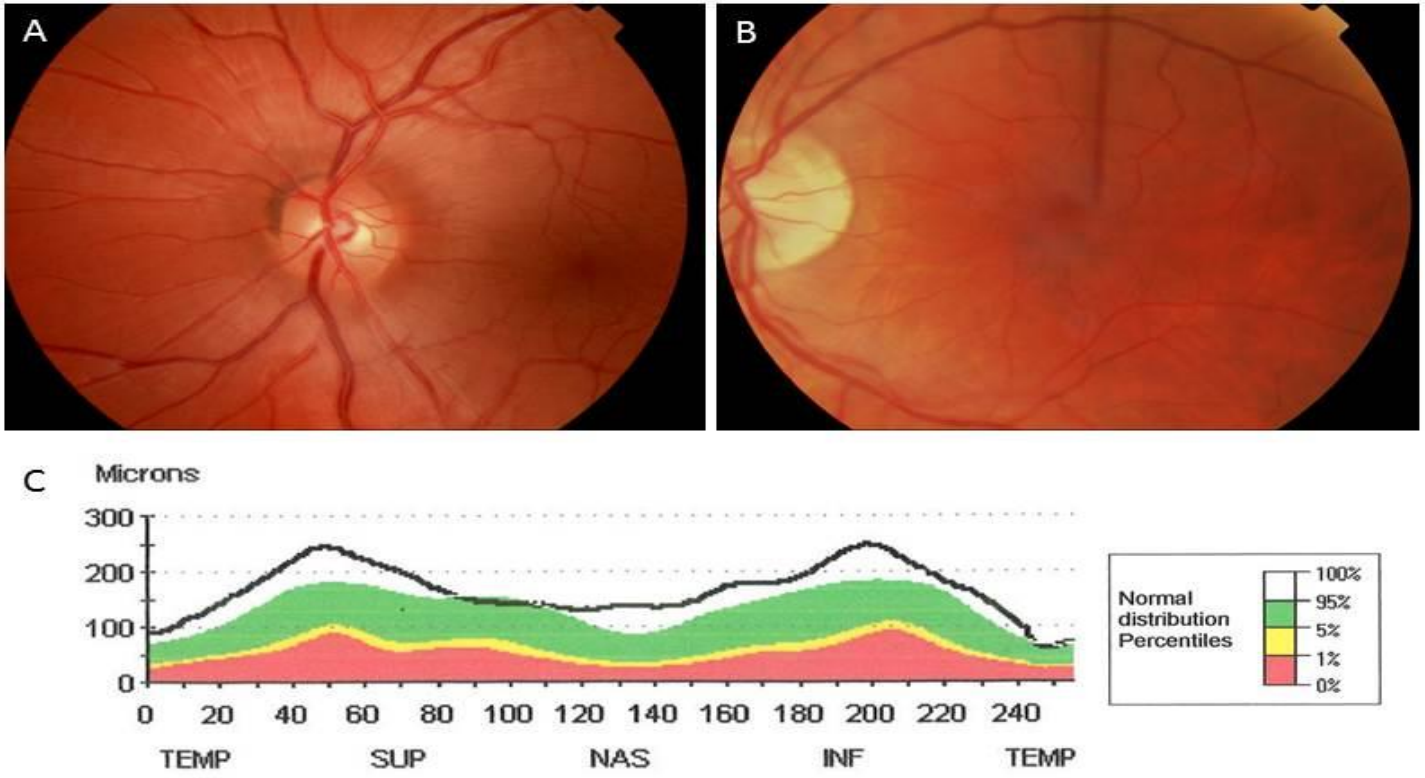




Luis E Pablo *Molecular Vision* 2011; 17:1871-1876

Jeremy Desserre Cerebellum (2011) 10:758–762

Retinal Nerve Fibre Layer Thickening by OCT



Parkinson et al. Brain 2018

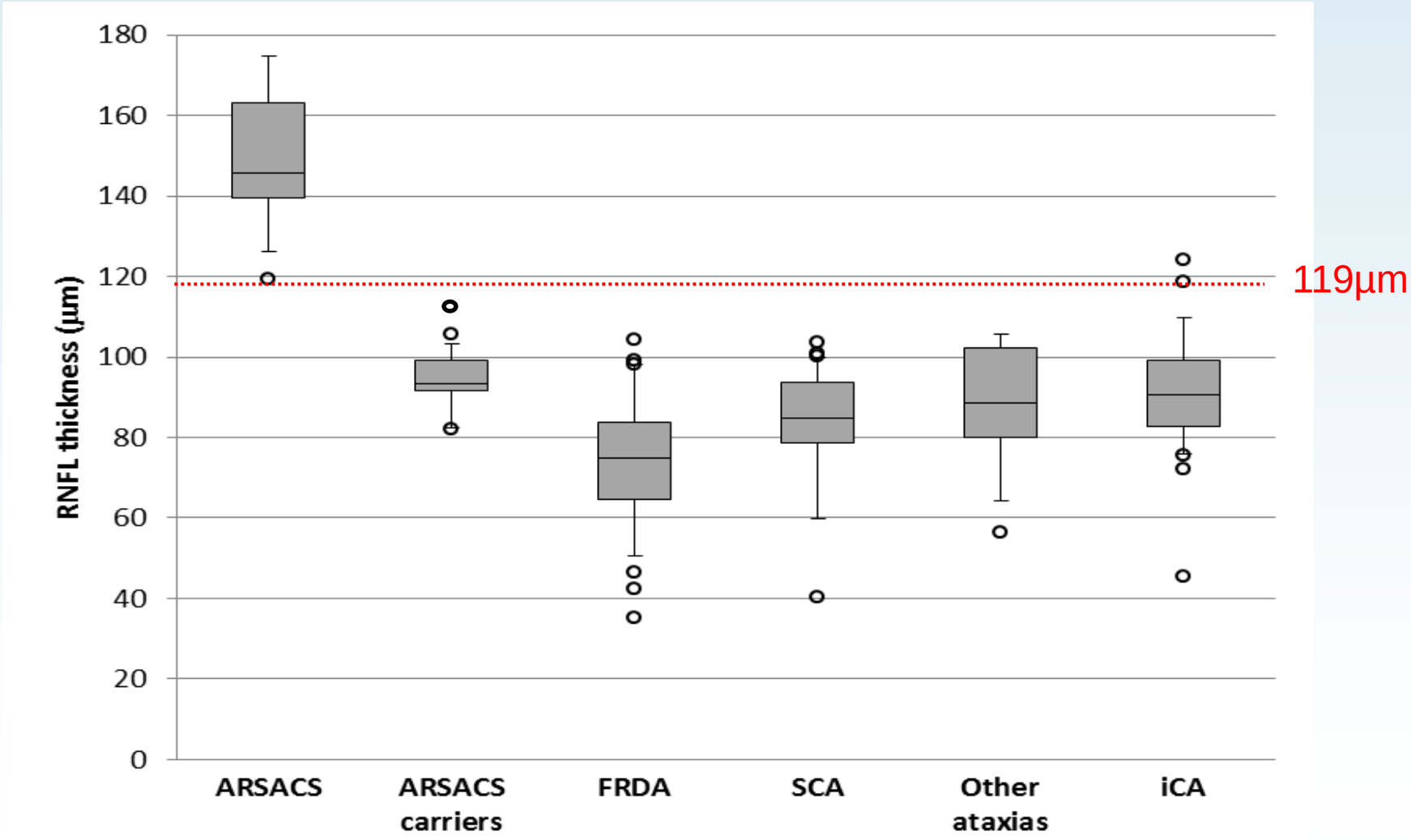
Recessive

Recessive

191 patients and 101 controls

Normal: 97.2 ± 9.7µm

Results

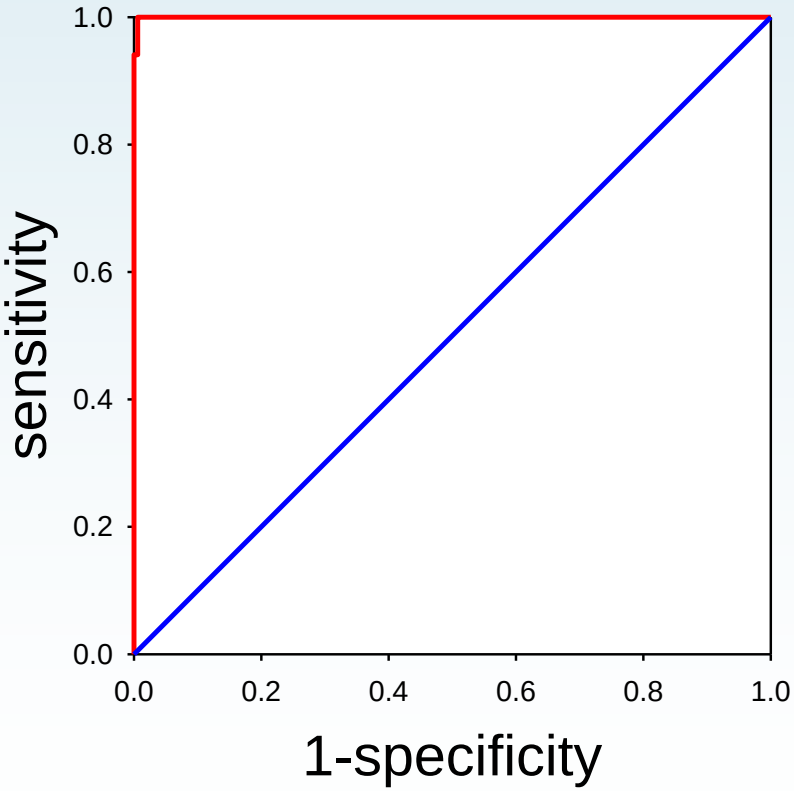


Results : ROC Plot with 119µm cut-off

	diagnosis:	
RNFL:	ARSACS	other
≥ 119µm	17	1
< 119µm	0	174

Sensitivity = 100%

Specificity = 99.4%



ROC plot

AUC ≈ 1.0

[95%CI 0.999-1.000]

Parkinson et al Brain 2018

Conclusions

- RFNL thickening on OCT is a sensitive and specific marker of ARSACS amongst a population of patients with suspected ataxia
- Proposed cut-off of 119µm provides sensitivity of 100% and specificity of 99.4%
- However, caution with carriers of *SACS* gene mutations and idiopathic ataxias
- Other cases of ataxia generally have normal or thinned RNFL, especially FRDA
- ARSACS patients rarely have visual symptoms and do not have other retinal disease
- OCT should be part of routine pre-genetic screening in patients with spastic ataxia/idiopathic recessive ataxia (cheap, rapid, widely available)

SPG7

- Most frequent form of late-onset spastic ataxia
  - Prevalence 1-9 in 100,000 for most countries
- Progressive bilateral leg weakness and spasticity
- Pure cerebellar ataxia +/- peripheral neuropathy
- Caused by autosomal recessive rarely dominant, mutations in *SPG7*
- Phenotype often indistinguishable from many other forms of hereditary spastic paraplegia therefore a multigene panel used for diagnosis.
- Some cases of pes cavus and axonal peripheral neuropathy

SPG7 gene

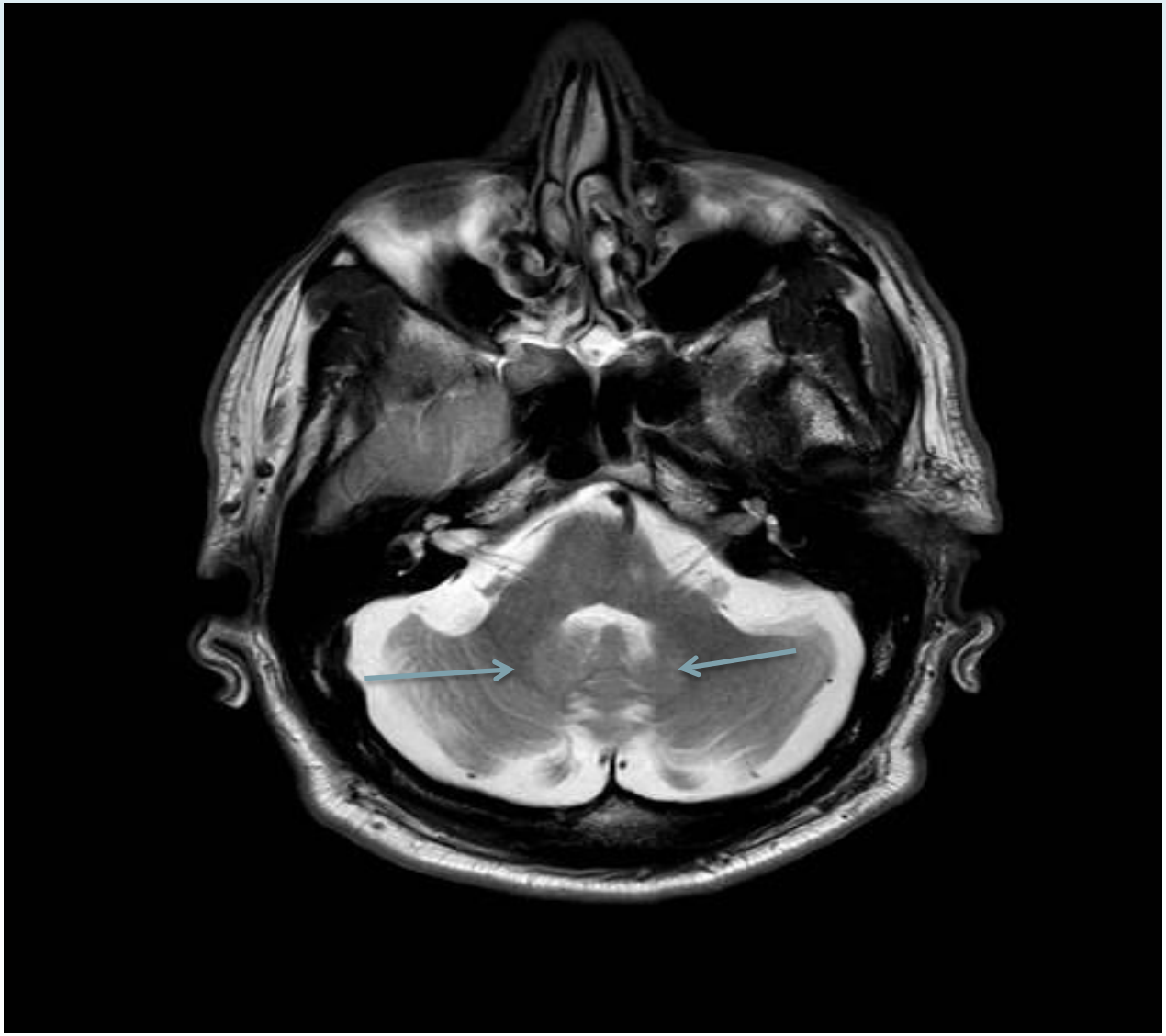
- 49,364 bp gene consisting of 22 exons
- Chr 16q24.3
- 3076 nt mRNA transcript
- Encodes a mitochondrial metalloprotease protein that is a member of the AAA family, paraplegin

Table 2 Phenotypic description of the patients with *SPG7* mutations

Features	Index cases (%)
Male:female ratio	35:7
Mean age at onset (SD), y	41.7 (±11)
Mean age at onset for males (SD), y	46.6 (±10)
Mean age at onset for females (SD), y	38.5 (±15)
Mean disease duration at examination (range), y	9.2 (3–20)
Symptoms at presentation	
Impaired balance	41/42 (98%)
Slurred speech	32/42 (76%)
Stiffness	32/42 (76%)
Leg weakness	10/42 (24%)
Upper limbs	
Normal	27/42 (63%)
Increased tone	5/34 (15%)
Lower limbs	
Normal or reduced	3/42 (7%)
Increased tone	39/42 (93%)
Cerebellar signs	38/42 (90%)
Dysdiadochokinesia	16/35 (48%)
Finger-nose test impaired	13/35 (39%)
Heel-shin test impaired	24/35 (67%)
Cerebellar dysarthria	32/42 (76%)
Pure spastic gait	2/42 (5%)
Sensation	
Vibration	
Normal	31/40 (78%)
Reduced	9/40 (22%)
Pin-prick	
Normal	32/35 (91%)
Reduced	3/35 (9%)
Tendon reflexes	
Upper and lower limbs	
Normal or reduced	3/42 (7%)
Brisk	39/42 (93%)
Babinski	
Positive	20/39 (51%)
Negative	19/39 (49%)
Gait	
Spastic ataxia	33/42 (79%)
Pure cerebellar gait	5/42 (12%)
Spastic waddling gait	4/42 (10%)
MRI brain	
Cerebellar atrophy	38/40 (95%)
Mild or no atrophy of the vermis	37/38 (98%)
Mild or no atrophy of the cerebellar hemispheres	26/38 (71%)
Severe atrophy	0/38 (0%)

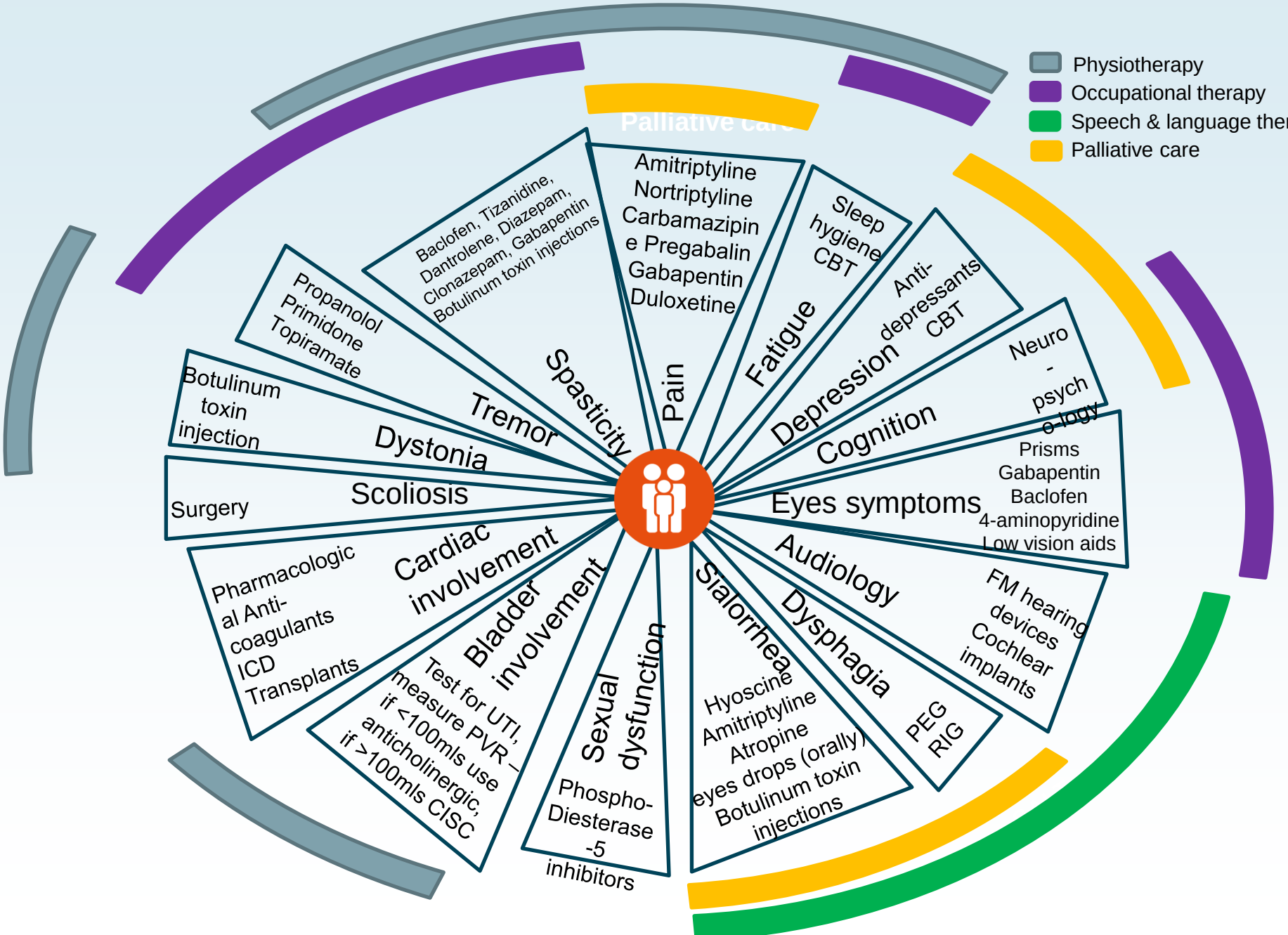
Channa A. Hewamadduma et al, 2018

SPG7



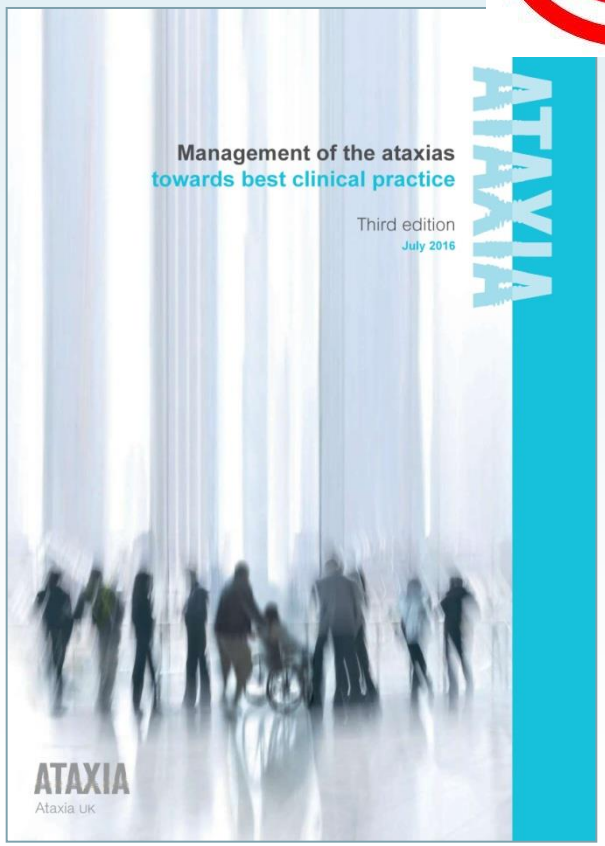
Conclusions

- Mutant *SPG7* is common in sporadic ataxia.
- In patients with British ancestry, c.1529C>T allele represents the most frequent mutation.
- *SPG7* mutations can be clinically predicted when spastic ataxia is present with MRI showing inT2 hyperintensity of the dentate nucleus.


Physiotherapy
Occupational therapy
Speech & language therapy
Palliative care
Spasticity
Baclofen, Tizanidine, Dantrolene, Diazepam, Clonazepam, Gabapentin Botulinum toxin injections
Tremor
Propanolol Primidone Topiramate
Dystonia
Botulinum toxin injection
Scoliosis
Surgery
Cardiac involvement
Pharmacologic al Anti-coagulants ICD Transplants
Bladder involvement
Test for UTI, measure PVR – if <100mls use anticholinergic, if >100mls CISC
Sexual dysfunction
Phospho-Diesterase -5 inhibitors
Sialorrhea
Hyoscine Amitriptyline Atropine eyes drops (orally) Botulinum toxin injections
Dysphagia
PEG RIG
Audiology
FM hearing devices Cochlear implants
Eyes symptoms
Prisms Gabapentin Baclofen 4-aminopyridine Low vision aids
Cognition
Neuro - psych o-logy
Depression
Anti-depressants CBT
Fatigue
Sleep hygiene CBT
Pain
Amitriptyline Nortriptyline Carbamazipin e Pregabalin Gabapentin Duloxetine

Leading contributor to ERN-RND

The London Ataxia Centre has led the development of guidelines that are now adopted around the world.



Recent citations:

The diagnosis and management of progressive ataxia in adults
De Silva et al, Practical Neurology, 2019

Guidelines on the diagnosis and management of the progressive ataxias
De Silva et al, Orphanet Journal of Rare Diseases, 2019

Friedreich's ataxia

Ataxia Centre, member of the Clinical Management Guidelines Working Group:

Corben *et al. Orphanet Journal of Rare Diseases* (2014) 9:184
DOI 10.1186/s13023-014-0184-7

ORPHANET JOURNAL OF RARE DISEASES

REVIEW Open Access

Consensus clinical management guidelines for Friedreich ataxia

Louise A Corben[1,2], David Lynch[3,4,5], Massimo Pandolfo[6], Jörg B Schulz[7], Martin B Delatycki[1,8,9*] and On behalf of the Clinical Management Guidelines Writing Group

Abstract

Friedreich ataxia (FRDA), a multisystem autosomal recessive condition, is the most common inherited ataxia in Caucasians, affecting approximately 1 in 29,000 individuals. The hallmark clinical features of FRDA include progressive afferent and cerebellar ataxia, dysarthria, impaired vibration sense and proprioception, absent tendon reflexes in lower limbs, pyramidal weakness, scoliosis, foot deformity and cardiomyopathy. Despite significant progress in the search for disease modifying agents, the chronic progressive nature of FRDA continues to have a profound impact on the health and well-being of people with FRDA. At present there is no proven treatment that can slow the progression or eventual outcome of this life-shortening condition. Thirty-nine expert clinicians located in Europe, Australia, Canada and USA critically appraised the published evidence related to FRDA clinical care and provided this evidence in a concise manner. Where no published data specific to FRDA existed, recommendations were based on data related to similar conditions and/or expert consensus. There were 146 recommendations developed to ensure best practice in the delivery of health services to people with FRDA. Sixty-two percent of recommendations are based on expert opinion or good practice indicating the paucity of high-level quality clinical studies in this area. Whilst the development of these guidelines provides a critical first step in the provision of appropriate clinical care for people with FRDA, it also highlights the urgency of undertaking high-quality clinical studies that will ensure the delivery of optimum clinical management and intervention for people with FRDA.

Keywords: Friedreich ataxia, Clinical, Guidelines, Evidence, Recommendations

Consensus Clinical Management
Guidelines for Friedreich's ataxia

Guidelines for clinicians, patients and research to ensure better outcomes today, and for the future.

Murdoch Childrens Research Institute · UNIKLINIK RWTH AACHEN · ULB Université Libre de Bruxelles · FARA

What are the key features of ataxia?

- a. Loss of balance with unsteadiness.
- b. Limb movements are irregular, fragmented, and tremulous. Dysdiadochokinesis
- c. Eye movements are interrupted, not calibrated (nystagmus);
- d. Speech is slurred in speed and volume (dysarthria).
- e. Atrophy of cerebellum on MRI.
- f. All the above

How many type of inheritance are in the inherited ataxia

- a. Autosomal dominant,
- b. Autosomal recessive, X-linked
- c. Mitochondrial
- d. All the above