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)
### ADCA - Clinical classification

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>ADCA I</th>
<th>ADCA II</th>
<th>ADCA III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cerebellar syndrome with ophthalmoplegia / pyramidal / extrapyramidal signs / cognitive impairment / peripheral neuropathy</td>
<td>Cerebellar syndrome with pigmentary maculopathy</td>
<td>“Pure” cerebellar syndrome</td>
</tr>
</tbody>
</table>

**Autosomal dominant cerebellar ataxias**

A.E. Harding
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

<table>
<thead>
<tr>
<th>Gene</th>
<th>Positions</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRPLA</td>
<td>6-35-48-93</td>
</tr>
<tr>
<td>SCA1</td>
<td>6-35-39-81</td>
</tr>
<tr>
<td>SCA2</td>
<td>14-31-33-87</td>
</tr>
<tr>
<td>SCA3</td>
<td>12-44-60-87</td>
</tr>
<tr>
<td>SCA6</td>
<td>4-18-20-33</td>
</tr>
<tr>
<td>SCA7</td>
<td>6-19-36-66</td>
</tr>
<tr>
<td>SCA17</td>
<td>25-40-49-66</td>
</tr>
</tbody>
</table>

Conventional mutations

<table>
<thead>
<tr>
<th>Gene</th>
<th>Allele</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCA4</td>
<td>16q22.1</td>
</tr>
<tr>
<td>SCA5</td>
<td>SPTBN2</td>
</tr>
<tr>
<td>SCA11</td>
<td>TTBK2</td>
</tr>
<tr>
<td>SCA13</td>
<td>KCNC3</td>
</tr>
<tr>
<td>SCA14</td>
<td>PRKCG</td>
</tr>
<tr>
<td>SCA15/16/29</td>
<td>ITPR1</td>
</tr>
<tr>
<td>SCA18</td>
<td>IFRD1</td>
</tr>
<tr>
<td>SCA19/22</td>
<td>KCND3</td>
</tr>
<tr>
<td>SCA20</td>
<td>11q12.2 - 11q12.3</td>
</tr>
<tr>
<td>SCA21</td>
<td>TMEM240</td>
</tr>
<tr>
<td>SCA23</td>
<td>PDYN</td>
</tr>
<tr>
<td>SCA25</td>
<td>2p15 - 2p21</td>
</tr>
<tr>
<td>SCA26</td>
<td>EEF2</td>
</tr>
<tr>
<td>SCA27</td>
<td>FGF14</td>
</tr>
</tbody>
</table>

Unassigned/Inactive

<table>
<thead>
<tr>
<th>Gene</th>
<th>Allele</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCA9</td>
<td>AFG3L2</td>
</tr>
<tr>
<td>SCA24</td>
<td>4q34.3 - 4q35.1</td>
</tr>
<tr>
<td>SCA33</td>
<td>7q32 - 7q33</td>
</tr>
<tr>
<td>SCA39</td>
<td>ELOVL4</td>
</tr>
<tr>
<td>SCA35</td>
<td>TGM6</td>
</tr>
<tr>
<td>SCA38</td>
<td>ELOVL5</td>
</tr>
<tr>
<td>SCA40</td>
<td>CCDC88C</td>
</tr>
<tr>
<td>SCA41</td>
<td>TRCP3</td>
</tr>
<tr>
<td>SCA42</td>
<td>CACNA1G</td>
</tr>
<tr>
<td>SCA43</td>
<td>MME</td>
</tr>
<tr>
<td>SCA44</td>
<td>GRM1</td>
</tr>
<tr>
<td>SCA45</td>
<td>FAT2</td>
</tr>
<tr>
<td>SCA46</td>
<td>PLD3</td>
</tr>
</tbody>
</table>

5’-UTR  ORF  Intron  ORF  3’-UTR

CAG repeats

<table>
<thead>
<tr>
<th>Gene</th>
<th>Positions</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCA12</td>
<td>4-32-46-78</td>
</tr>
<tr>
<td>SCA37</td>
<td>31-75</td>
</tr>
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</table>

ATTTC repeats

<table>
<thead>
<tr>
<th>Gene</th>
<th>Positions</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPP2R2B</td>
<td></td>
</tr>
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</table>

DAB1

CTG repeats

<table>
<thead>
<tr>
<th>Gene</th>
<th>Positions</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCA8</td>
<td>15-50-71-1300</td>
</tr>
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</table>

ATTCT repeats

<table>
<thead>
<tr>
<th>Gene</th>
<th>Positions</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCA10</td>
<td>10-32-800</td>
</tr>
</tbody>
</table>

TGGAA repeats

<table>
<thead>
<tr>
<th>Gene</th>
<th>Positions</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCA31</td>
<td>500-760</td>
</tr>
</tbody>
</table>

GGCCTG repeats

<table>
<thead>
<tr>
<th>Gene</th>
<th>Positions</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCA36</td>
<td>3-14-650</td>
</tr>
</tbody>
</table>

ATXN10

BEAN / TK2

NOP56
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

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

---unknown. SCA—spinocerebellar ataxia. DRPLA—dentatorubro-pallidoluysian atrophy.

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
CAG$_n$ - Age at onset correlation

CAG repeat interruptions in alleles

<table>
<thead>
<tr>
<th>SCA</th>
<th>Gene</th>
<th>Locus</th>
<th>Repeat Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCA1</td>
<td>ATXN1</td>
<td>6p22.36</td>
<td>(CAG)$_n$(CAT)(CAG)(CAT)(CAG)$_n$</td>
</tr>
<tr>
<td>SCA2</td>
<td>ATXN2</td>
<td>12q24.13</td>
<td>(CAG)$_n$(CAA)(CAG)$_4$(CAA)(CAG)$_n$</td>
</tr>
<tr>
<td>SCA3</td>
<td>ATXN3</td>
<td>14q32.12</td>
<td>(CAG)$_2$(CAA)(AAG)(CAG)(CAA)(CAG)$_n$</td>
</tr>
<tr>
<td>SCA17</td>
<td>TBP</td>
<td>6q27</td>
<td>(CAG)$_3$(CAA)$_3$(CAG)$_n$(CAA)(CAG)(CAA)(CAG)$_n$(CAA)(CAG)</td>
</tr>
</tbody>
</table>
## CAG repeat alleles

<table>
<thead>
<tr>
<th>SCA</th>
<th>Gene</th>
<th>Locus</th>
<th>Repeat Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCA1</td>
<td>ATXN1</td>
<td>6p22.36</td>
<td>(CAG)$_n$(CAT)(CAG)(CAT)(CAG)$_n$</td>
</tr>
<tr>
<td>SCA2</td>
<td>ATXN2</td>
<td>12q24.13</td>
<td>(CAG)$_n$(CAA)(CAG)$_4$(CAA)(CAG)$_n$</td>
</tr>
<tr>
<td>SCA3</td>
<td>ATXN3</td>
<td>14q32.12</td>
<td>(CAG)$_2$(CAA)(AAG)(CAG)(CAA)(CAG)$_n$</td>
</tr>
<tr>
<td>SCA17</td>
<td>TBP</td>
<td>6q27</td>
<td>(CAG)$_3$(CAA)$_3$(CAG)$_n$(CAA)(CAG)(CAA)(CAG)$_n$(CAA)(CAG)</td>
</tr>
</tbody>
</table>
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

\[ n = 32 \]

Pearson correlation coefficient \( r = -0.857 \)
Adjudged \( R^2 = 0.725 \)

- **Interrupted**, total repeat length
- **Uninterrupted**, total repeat length

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

$n = 32$
Pearson correlation coefficient $r = -0.857$
adj. $R^2 = 0.725$
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

(A) Pathogenic Allele Size (Number of Repeats) vs Age at Onset (Years)

(B) Mean Pathogenic Allele Size (Number of Repeats) vs Age at Onset (Years)

(C) Fragment Analysis (Allele Size, Repeats) vs Clone Sequencing (Number of Repeats)
Phenotype Distribution

Dementia

Chorea

Ataxia

Parkinsonism

5
(2, 5, 6, 19, 20)

3
(18, 21, 27)

2
(13, 22, 15)

3
(9, 24, 26)

1
(1, 4, 8, 14, 16, 17, 28, 29, 30)

2
(7, 12)

1
(11)

1
(3)

1
(10)
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
Friedreich's ataxia is an autosomal recessive neurodegenerative disorder characterized by the progressive loss of voluntary movement coordination (ataxia) and heart enlargement.

Differential diagnosis with FRDA

<table>
<thead>
<tr>
<th>Genetic:</th>
<th>AR Genetic: DNA repair disorders</th>
<th>AR Genetic: Metabolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charcot-Marie-Tooth</td>
<td>ATM</td>
<td>Ataxia with vitamin E deficiency</td>
</tr>
<tr>
<td>ARSACS</td>
<td>AOA1</td>
<td>Abetalipoproteinemia</td>
</tr>
<tr>
<td>SPG7</td>
<td>AOA2</td>
<td>Refsum Disease</td>
</tr>
<tr>
<td></td>
<td>SCAN1 (spinocerebellar ataxia with axonal neuropathy).</td>
<td></td>
</tr>
</tbody>
</table>
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, *dysarthria*, *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
Urinary, bowel and sexual symptoms in a cohort of patients with Friedreich’s ataxia

Meher Lad1,2, Michael H. Parkinson1, Myriam Rai3, Massimo Pandolfo3, Petya Bogdanova-Mihaylova4, Richard A. Walsh4,5, Sinéad Murphy4, Anton Emmanuel6, Jalesh Panicker2† and Paola Giunti1†

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
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**

(GAA)$_n$ controls 6-33 premutation 34-65 patients 66-1700

5’ UTR

1

2

3

4

5a

5b

3’ UTR

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

L106X
D122Y
Y118X*
L156P

I154F
G130V

R165C
L182F
L182H
H183R
R165P

W173G

Campuzano et al, 1996
Forrest et al, 1998
Cossée et al, 1999
De Michele et al, 2000
Gellera et al 2007

Filla et al, 1996

Galea et al 2017
FRDA Disease Mechanism

Unaffected

FXN

FRDA

DISEASE EFFECTS
Epigenetic & Neurological Effects of Nicotinamide in FRDA
Heterochromatinization induced by GAA-repeat hyperexpansion in Friedreich's ataxia can be reduced upon HDAC inhibition by vitamin B3

Ping K. Chan1†, Raul Torres1†, Cihangir Yandim1, Pui P. Law1, Sanjay Khadayate2, Marta Mauri1, Crina Grosan3, Nadine Chapman-Rothel1, Paola Giunti5, Mark Pook4 and Richard Festenstein1,*
Phase II Open Label Trial of Nicotinamide in FRDA Patients

**Enrolment**

Assessed for eligibility (n=18)

Excluded (n=6)
- Not meeting inclusion/exclusion criteria (n=6)

**Analysis**

Part 1: Dose escalation (n=10)

Analysed (n=10)

Drop outs (n=2)
- Discontinued due to SAE unlikely related to the study (n=1)
- Patient unwilling to participate to part 2 (n=1)

**Allocation**

Part 2: Single Dose (n=10)

- Entered straight to part 2 and received no drug (n=2)

Analysed (n=10)

Follow-up

Part 3: Once daily dosing for 2 months
- Allocated (n=10)

Part 3: followed up (n=10)
- Completed (n=10)

Analysed (n=10)

June 2012-June 2013

• 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
• 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.
Frataxin (FRDA) is associated with oxidative stress. The diagram illustrates the deregulation of the membrane potential (∆Ψm) and the disruption of the mitochondrial electron transport chain. Frataxin is involved in the localization of 2Fe-2S clusters, which are crucial for enzymatic reactions. The inner membrane shows the presence of complexes I (CI), II (CII), III (CIII), and IV (CIV), and the outer membrane has complex V (CV) and 2Fe-2S clusters. ATP is produced, leading to H+ efflux, which results in oxidative stress (ROS) and lipid peroxidation. Abeti et al., 2015.
Frataxin (FRDA) is involved in oxidative stress. Frataxin deregulation leads to a decrease in the ΔΨm of the inner membrane. This affects the function of Complexes I, II, III, and IV, leading to lipid peroxidation.

Nicotinamide and clinical phase II study: Frataxin levels are elevated in clinical phase II.

Oxidative stress and lipid peroxidation are increased.

d4-PUFA and clinical phase II-III study: Lipid peroxidation and oxidative stress are reduced.

Clinical phase III study: Omav shows an increase in Frataxin levels.

Abeti et al., 2015
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.
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
- 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
Retinal Nerve Fibre Layer Thickening

Luis E Pablo Molecular Vision 2011; 17:1871-1876
Retinal Nerve Fibre Layer Thickening by OCT

Parkinson et al. Brain 2018
Recessive
Results

191 patients and 101 controls

Normal: $97.2 \pm 9.7 \mu m$

Box plots showing RNFL thickness for different groups:
- ARSACS
- ARSACS carriers
- FRDA
- SCA
- Other ataxias
- iCA

The mean RNFL thickness for the Recessive group is $119 \mu m$. 
Results: ROC Plot with 119µm cut-off

<table>
<thead>
<tr>
<th>RNFL:</th>
<th>ARSACS</th>
<th>other</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 119µm</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>&lt; 119µm</td>
<td>0</td>
<td>174</td>
</tr>
</tbody>
</table>

Sensitivity = 100%
Specificity = 99.4%

ROC plot
AUC ≈ 1.0
[95%CI 0.999-1.000]
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, paraplechin
# Table 2: Phenotypic description of the patients with SPG7 mutations

<table>
<thead>
<tr>
<th>Features</th>
<th>Index cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male:female ratio</td>
<td>35:7</td>
</tr>
<tr>
<td>Mean age at onset (SD), y</td>
<td>41.7 (±11)</td>
</tr>
<tr>
<td>Mean age at onset for males (SD), y</td>
<td>46.6 (±10)</td>
</tr>
<tr>
<td>Mean age at onset for females (SD), y</td>
<td>38.5 (±15)</td>
</tr>
<tr>
<td>Mean disease duration at examination (range), y</td>
<td>9.2 (3-20)</td>
</tr>
</tbody>
</table>

## Symptoms at presentation

<table>
<thead>
<tr>
<th></th>
<th>Index cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired balance</td>
<td>41/42 (98%)</td>
</tr>
<tr>
<td>Slurred speech</td>
<td>32/42 (78%)</td>
</tr>
<tr>
<td>Stiffness</td>
<td>32/42 (76%)</td>
</tr>
<tr>
<td>Leg weakness</td>
<td>10/42 (24%)</td>
</tr>
</tbody>
</table>

## Upper limbs

<table>
<thead>
<tr>
<th></th>
<th>Index cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>27/42 (63%)</td>
</tr>
<tr>
<td>Increased tone</td>
<td>5/34 (15%)</td>
</tr>
</tbody>
</table>

## Lower limbs

<table>
<thead>
<tr>
<th></th>
<th>Index cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal or reduced</td>
<td>3/42 (7%)</td>
</tr>
<tr>
<td>Increased tone</td>
<td>39/42 (93%)</td>
</tr>
</tbody>
</table>

## Cerebellar signs

<table>
<thead>
<tr>
<th></th>
<th>Index cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysdiadochokinesia</td>
<td>16/35 (48%)</td>
</tr>
<tr>
<td>Finger-nose test impaired</td>
<td>13/35 (39%)</td>
</tr>
<tr>
<td>Heel-shin test impaired</td>
<td>24/35 (67%)</td>
</tr>
<tr>
<td>Cerebellar dysarthria</td>
<td>32/42 (76%)</td>
</tr>
<tr>
<td>Pure spastic gait</td>
<td>2/42 (5%)</td>
</tr>
</tbody>
</table>

## Sensation

<table>
<thead>
<tr>
<th></th>
<th>Index cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vibration</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>31/40 (78%)</td>
</tr>
<tr>
<td>Reduced</td>
<td>9/40 (22%)</td>
</tr>
</tbody>
</table>

## Pin-prick

<table>
<thead>
<tr>
<th></th>
<th>Index cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>32/35 (91%)</td>
</tr>
<tr>
<td>Reduced</td>
<td>3/35 (9%)</td>
</tr>
</tbody>
</table>

## Tendon reflexes

<table>
<thead>
<tr>
<th></th>
<th>Index cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper and lower limbs</td>
<td></td>
</tr>
<tr>
<td>Normal or reduced</td>
<td>3/42 (7%)</td>
</tr>
<tr>
<td>Brisk</td>
<td>39/42 (93%)</td>
</tr>
<tr>
<td>Babinski</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>20/39 (51%)</td>
</tr>
<tr>
<td>Negative</td>
<td>19/39 (49%)</td>
</tr>
</tbody>
</table>

## Gait

<table>
<thead>
<tr>
<th></th>
<th>Index cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spastic ataxia</td>
<td>33/42 (79%)</td>
</tr>
<tr>
<td>Pure cerebellar gait</td>
<td>5/42 (12%)</td>
</tr>
<tr>
<td>Spastic waddling gait</td>
<td>4/42 (10%)</td>
</tr>
</tbody>
</table>

## MRI brain

<table>
<thead>
<tr>
<th></th>
<th>Index cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebellar atrophy</td>
<td>38/40 (95%)</td>
</tr>
<tr>
<td>Mild or no atrophy of the vermis</td>
<td>37/38 (98%)</td>
</tr>
<tr>
<td>Mild or no atrophy of the cerebellar hemispheres</td>
<td>26/38 (71%)</td>
</tr>
<tr>
<td>Severe atrophy</td>
<td>0/38 (0%)</td>
</tr>
</tbody>
</table>

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.
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:

Consensus clinical management guidelines for Friedreich ataxia

Louise A Corben1,2, David Lynch3,4,5, Massimo Pandolfo6, Jörg B Schulz2, Martin B Delatycki1,8,9 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 areflexic 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
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