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)

UNIKLINIK RWTH AACHEN

Klinik für Neurologie

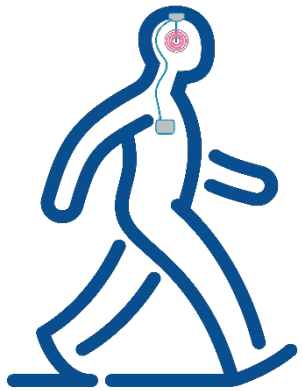
JARA|BRAIN AN INITIATIVE OF RWTH AACHEN UNIVERSITY JÜLICH FORSCHUNGSZENTRUM

Webinar – 12th September 2023

‘Friedreich Ataxia’

by Kathrin Reetz,

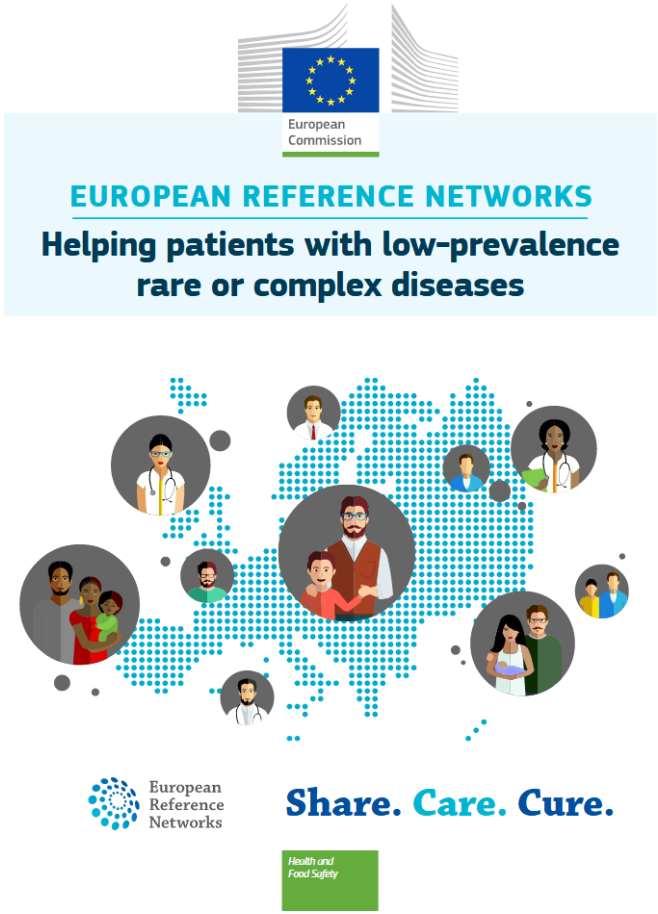
RWTH-University Hospital Aachen, Germany



European Reference Networks (ERNs)

- Networks of healthcare providers
- Established in 2017
- 24 different ERNs
- > 300 hospitals in 26 EU countries

- Goal: intensify collaboration and bundle expertise beyond borders to improve the quality of care for the patients.



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European Reference Network for Rare Neurological Diseases (ERN-RND)

- Coordination: University Hospital Tübingen
- 64 Full Members + 4 Affiliated Partners
- 10 patient representatives
- 1 secure telemedicine platform (CPMS)
- 6 Disease Groups:

1. Ataxia and HSP
2. Leukodystrophies
3. Dystonias /NBIA/Paroxysmal disorders
4. Chorea and Huntington's Disease
5. Frontotemporal Dementia
6. Atypical Parkinsonian Syndromes

Educational Webinars

Aim

Gather the scarce knowledge from experts and share it.

Focus

- RARE neurological, neuromuscular and movement disorders
- Neurorehabilitation
- Advanced therapies
- *Clinical studies (NEW)*
- Adult and pediatric topics
- Target audience: clinicians, physiotherapists and other medical personnel

Participants

- 296 registrants for this webinar
- Feedback: PostWebinar Survey
- Certificate of Attendance on request to: Christine.Diaite-Hecht@med.uni-tuebingen.de

Format

- 45min presentation and 15min Q&A
- Recorded webinars: http://www.ern-rnd.eu/education-training/past-webinars/
- Full programme: http://www.ern-rnd.eu/education-training/webinars/

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Speaker

Kathrin Reetz

- Training: MD Neurologist
- Current position at the Department of Neurology, RWTH Aachen University in Germany:
  - Section Head of Translational Neurodegeneration
  - Head of Neurological Study Centre
  - Managing senior physician
  - Group leader Translational Neurodegeneration at the JARA-BRAIN Institute Molecular Neuroscience and Neuroimaging at the Research Centre Jülich
- Research focus: Neurodegenerative Diseases (Dementia & Movement Disorders)
- Other key activities: Vice-President of the German Brain Foundation

Question 1

What is your professional background? (Single choice)

a. Neurologist
b. Neuropediatrician
c. Neurology resident
d. Psychiatrist
e. Nurse
f. Physiotherapist
g. Geneticist
h. Psychologist
i. Patient or patient representative
j. Other

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Learning objectives

1) How to measure ataxia?

2) Gain deeper knowledge about Friedreich ataxia

3) Major clinical symptoms and signs including diagnosis and treatment recommendations

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Webinar outline

'Friedreich Ataxia'

1

Background

Epidemiology
Pathology
Genetics

2

Clinical Phenotype / Symptoms and Signs

Ataxia
Heart
Scoliosis and Foot deformities
Dysphagia & Dysarthria
Endocrine & metabolism
Vision, Oculomotor and Auditory function

3

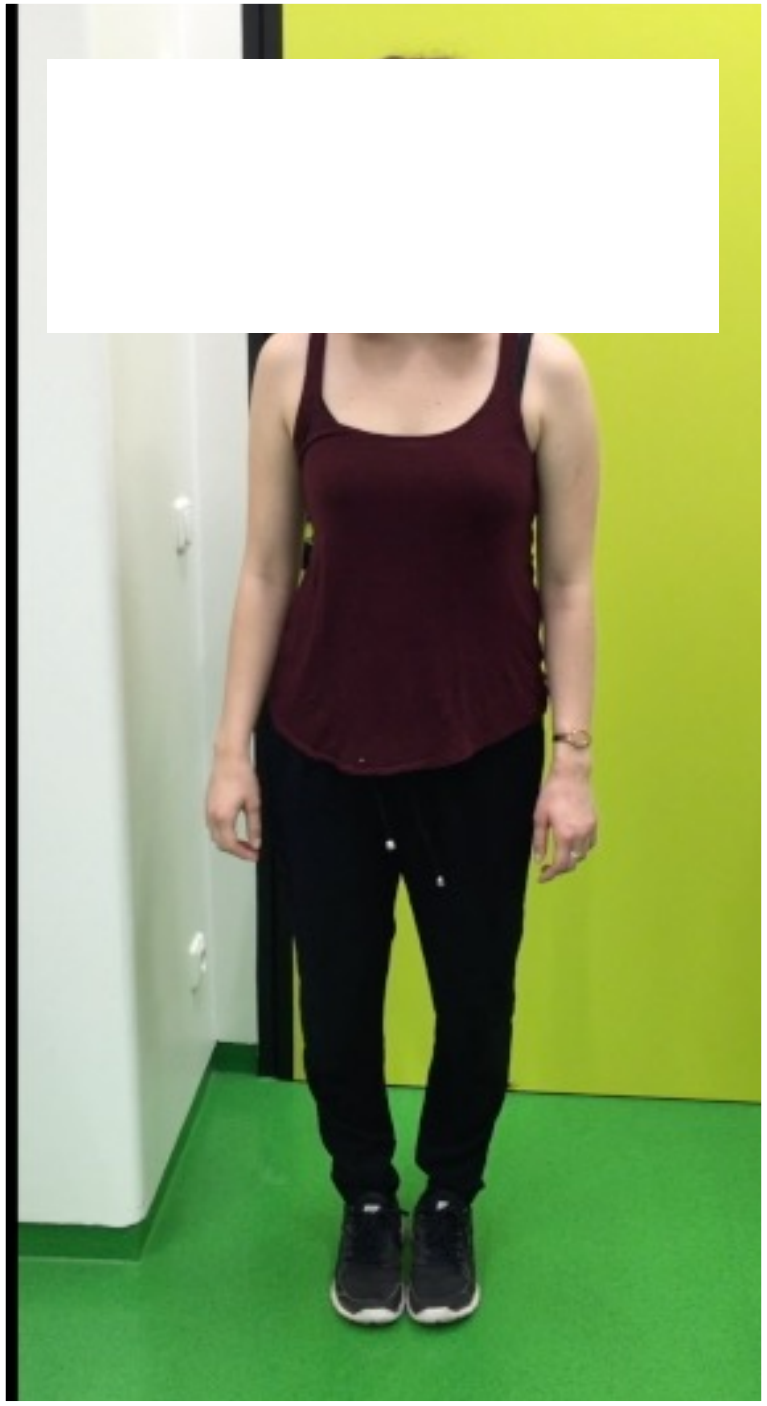
Research

Natural History Studies
Imaging

4

Treatment / best practice

Non-pharmacological treatments
Pharmacological treatments
Clinical Trial Pipeline



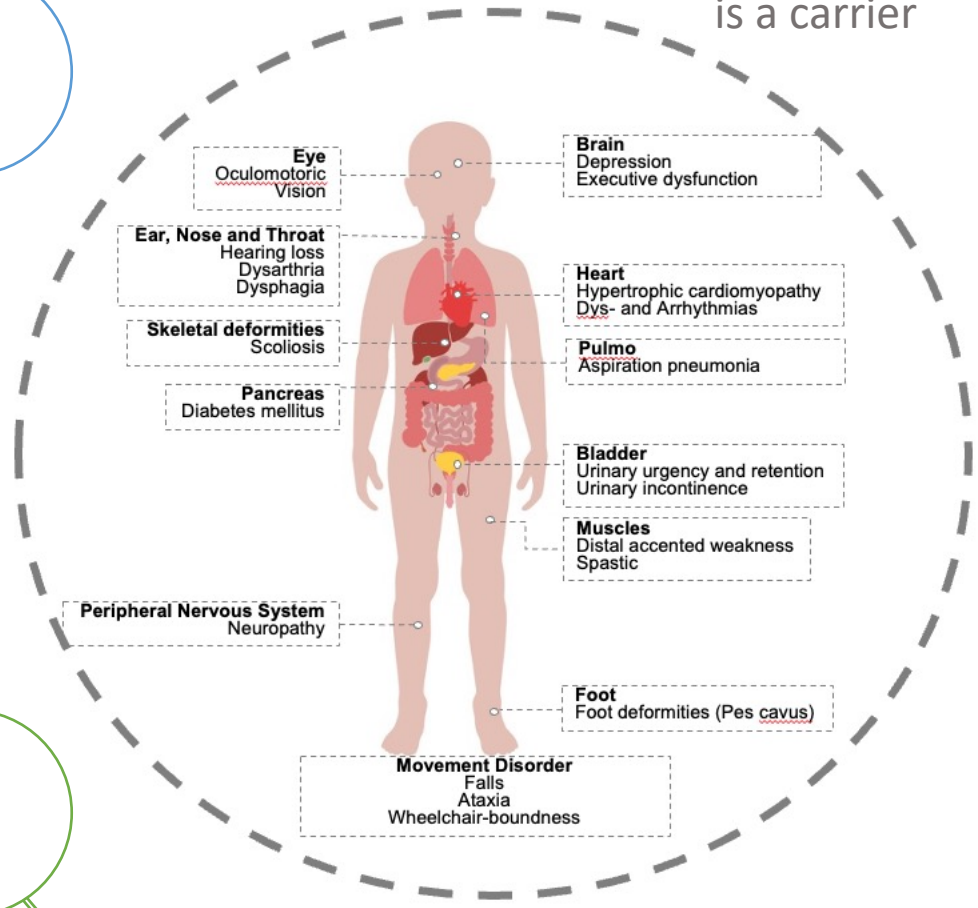
Friedreich Ataxia

The most common autosomal recessive ataxia

1 in 50.000
born with Friedreich ataxia

1 in 100
is a carrier

- Monogenic cause
- Begins around puberty
- Slowly progressive
- Multisystem and complex

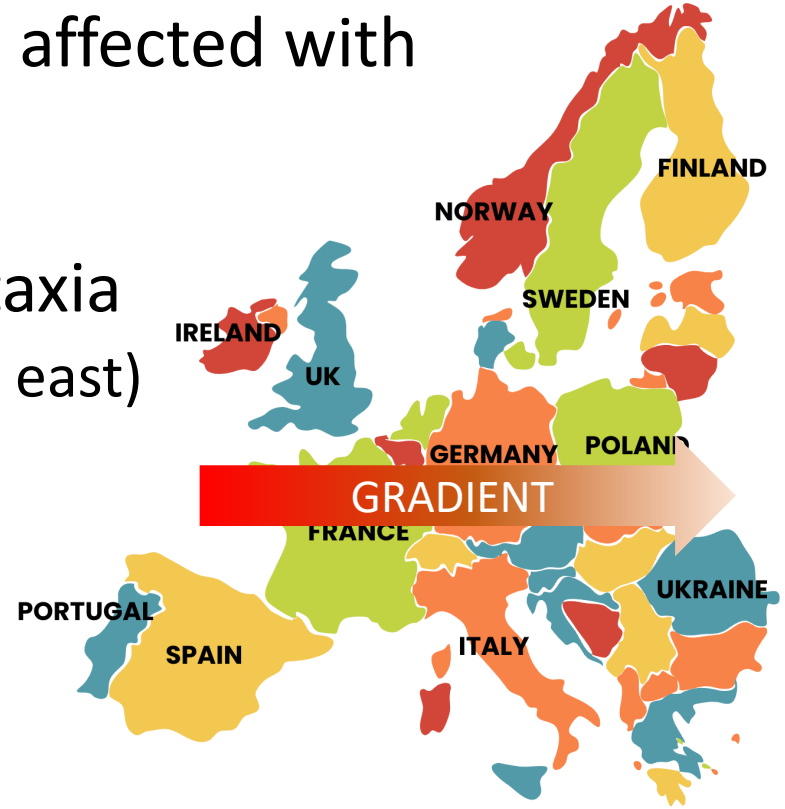


Reetz et al., Lancet Neurology 2015; Reetz et al., Lancet Neurology 2016; ; Reetz et al., Neurology 2018; Reetz et al., Lancet Neurology 2021

Epidemiology

- Most common autosomal recessive ataxia.
- Worldwide about 15.000 individuals are affected with Friedreich ataxia.

- 1 in 20.000 to 1 in 50.000 born with Friedreich ataxia
  - Regional differences in Europe (gradient from west to east)
  - In Germany gradient from south to north
- 1 in 100 is carrier



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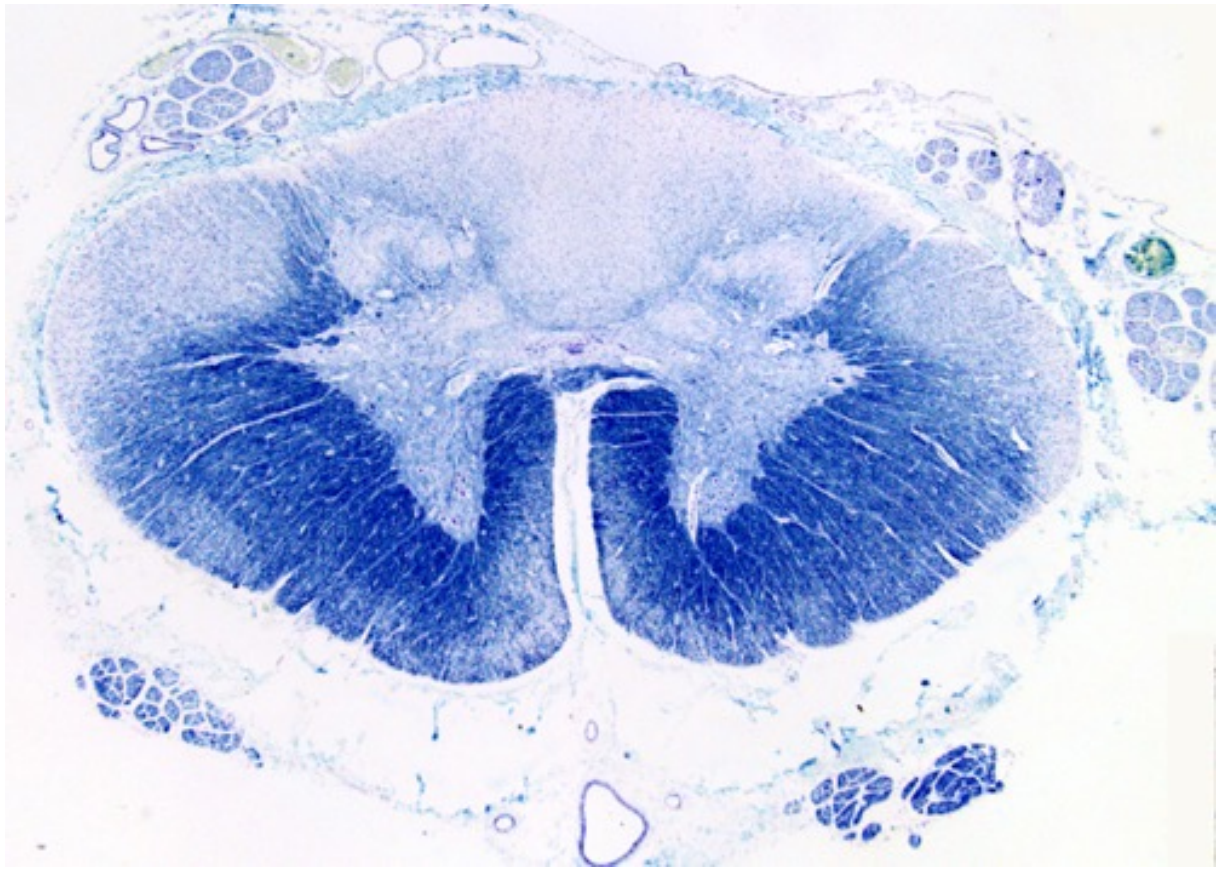
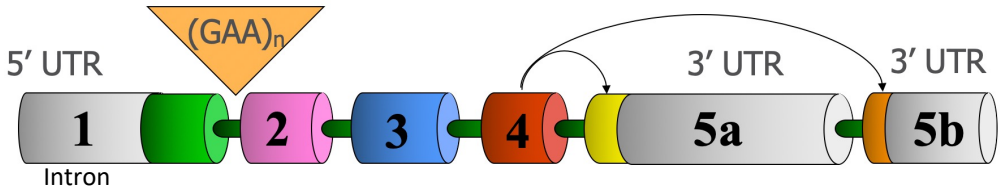
Neuropathology

Nikolaus Friedreich (1825-1882)



Spinal cord (myelin stain) from a patient with Friedreich ataxia – degeneration of the posterior columns, spinocerebellar and corticospinal tracts.

Genetics

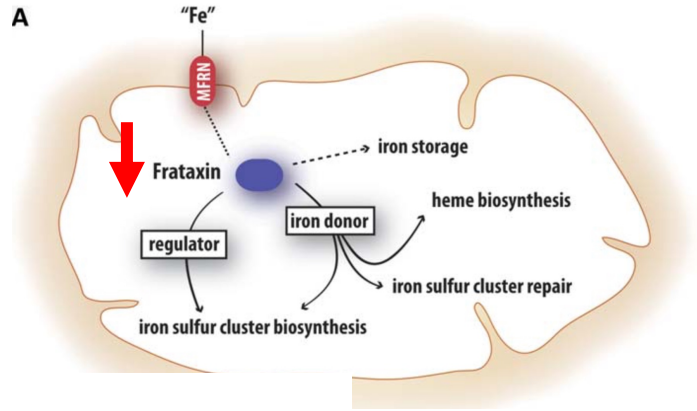


Chr.9q13-21

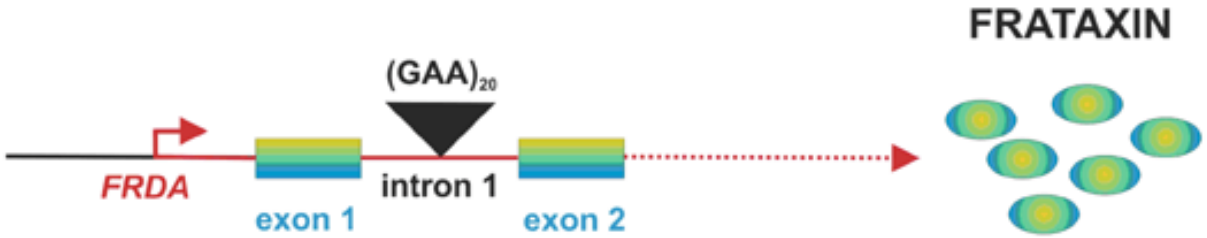
Normal Allele: 6-36 GAA
Expanded Allele: 100-1500 GAA

- Mutation in Frataxin Gene
- 98% homozygote GAA-Expansions in the first intron
- 1-2% heterozygote ((point) mutations/ GAA Expansion)

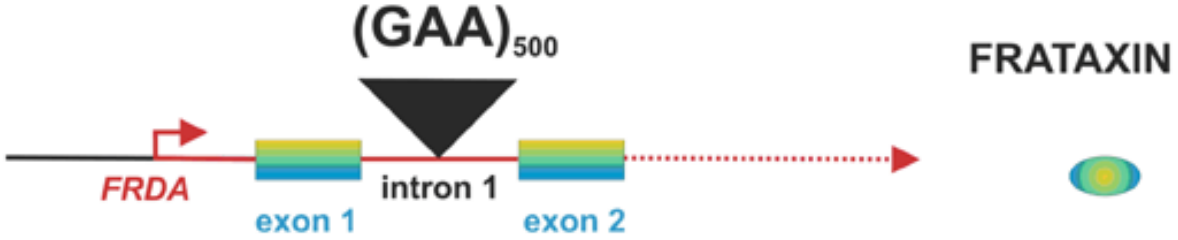
Frataxin deficieny in Friedreich ataxia
frataxin level is <30% that of healthy controls



normal state

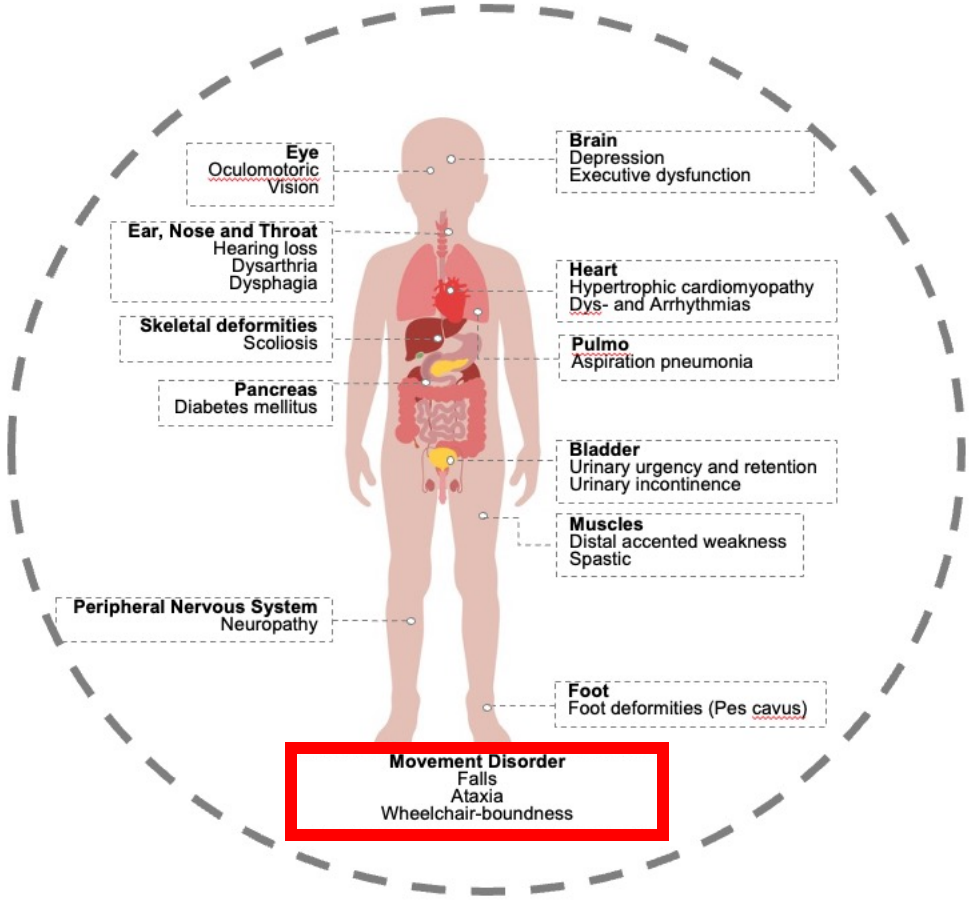


Friedreich Ataxie



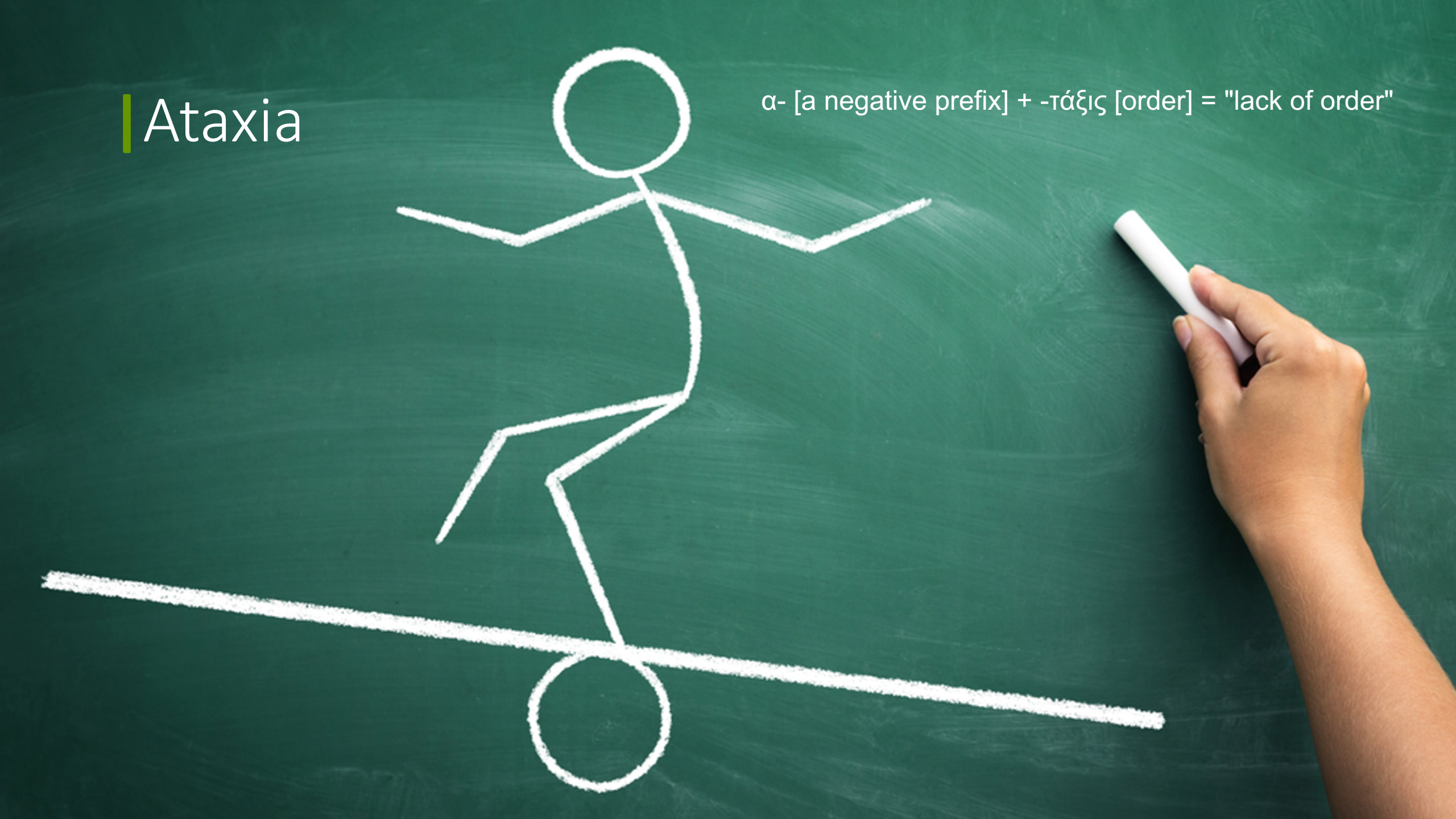
Campuzano et al. *Science* 1996

Multisystem complex disease



Ataxia

α- [a negative prefix] + -τάξις [order] = "lack of order"



Ataxia

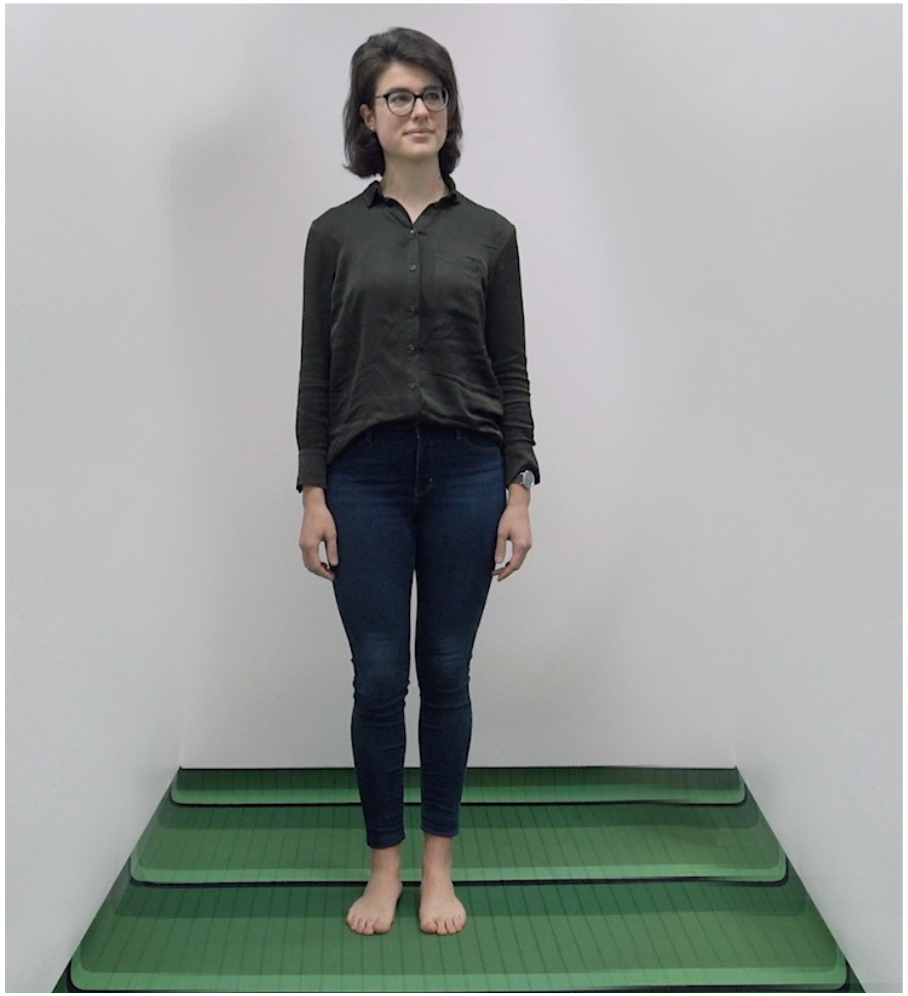
- Gait
- Stance
- Speech
- Coordination
  (Finger-Nose; Heel-Shin)

Ataxia

Item **1**	**Gait**
Task	• Proband is asked (**1**) to walk at a safe distance parallel to a wall including a half-turn and (**2**) to walk in tandem (heels to toes) without support.
Note	• Proband is wearing shoes • Rate what you see! • 10 meter walking distance one way • Sticks, strollers or an accompanying person are not allowed during tandem walk

Ataxia

Item 2	Stance
Task	• Proband is asked to stand (**1**) in natural position, (**2**) with feet together in parallel (big toes touching each other) and (**3**) in tandem (both feet on one line, no space between heel and toe).
Note	• Three trials per condition allowed • Best trial is rated • Balancing movements are not allowed • Pay attention to sway • No shoes, avoid socks • Eyes are open • Additional support or misstep ends one trial



Ataxia

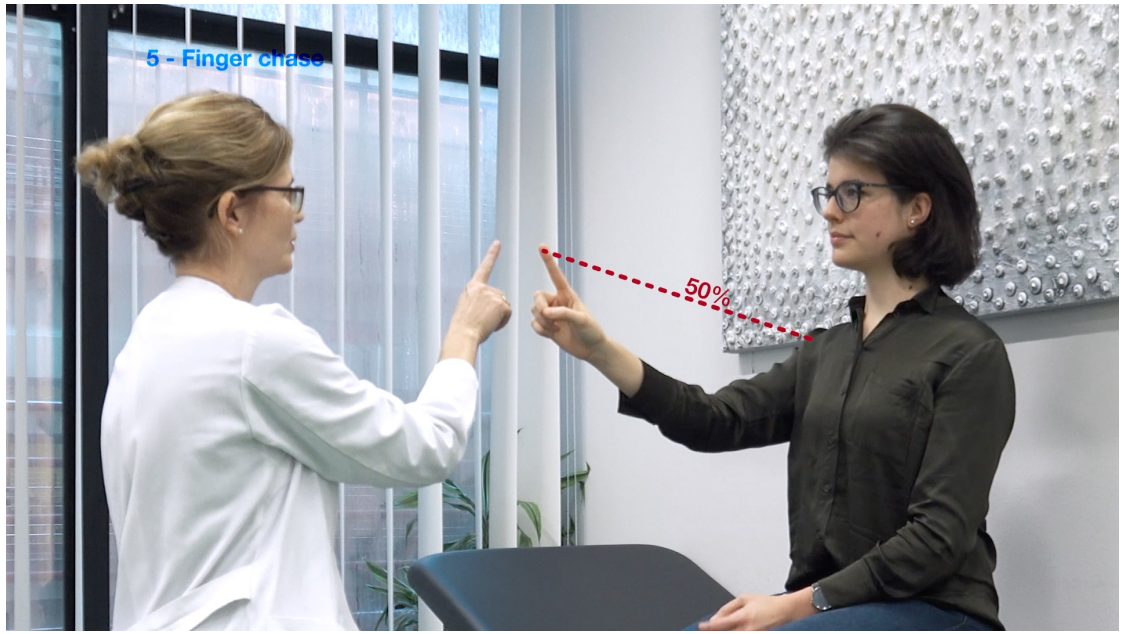
Item 3	Sitting
Task	• Proband is asked to sit on an examination bed without support of feet, eyes open and arms outstretched to the front.
Note	• Do not rate movements of the arms or tremor of the hands!

Ataxia

Item 4	Speech
Task	• Speech is assessed during normal conversation.
Note	• Rate how many words you understand if there is a substantial speech impairment

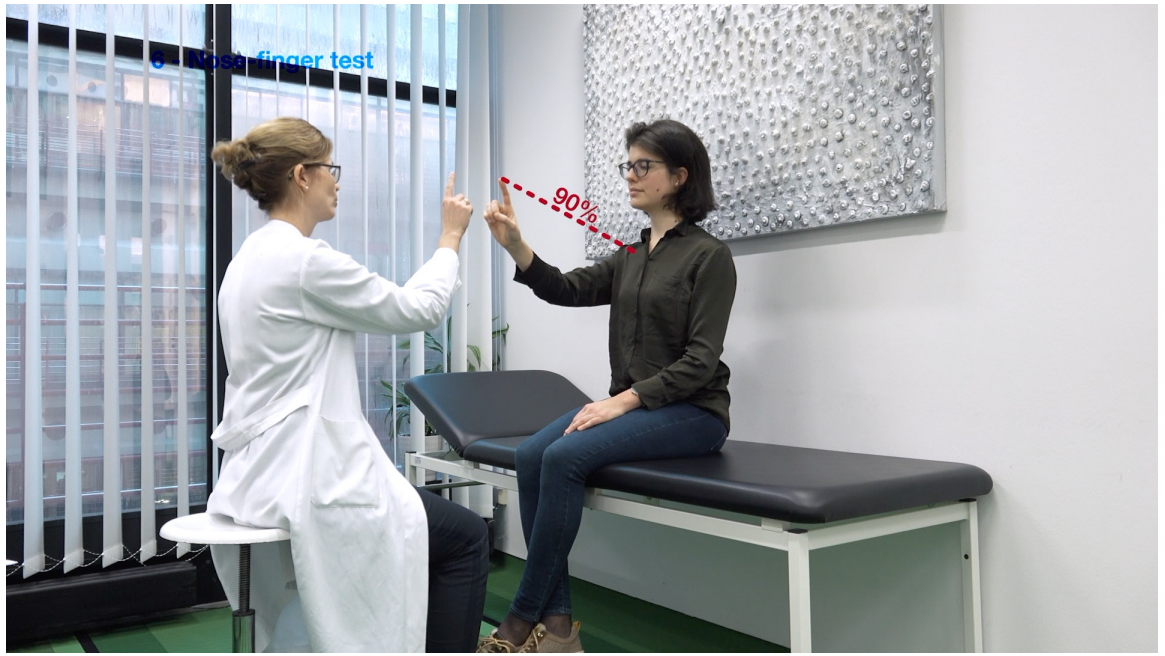
Ataxia

Item 5	Finger chase
Task	Examiner sits in front of proband and performs 5 consecutive sudden and fast pointing movements in unpredictable directions in a frontal plane, at about 50 % of proband's reach. Proband is asked to follow the movements with his index finger, as fast and precisely as possible.
Note	• Movements have an amplitude of 30 cm • 1 movement every 2 s • Make sure movements are in one plane • Average performance of last 3 movements is rated



Ataxia

Item 6	Nose-finger test
Task	Proband is asked to point repeatedly with his index finger from his nose to examiner's finger which is in front of the proband at about 90 % of proband's reach.
Note	• Movements are performed at moderate speed to not mask an intention tremor • Amplitude of tremor is rated • Dysmetria should not be rated!



Ataxia

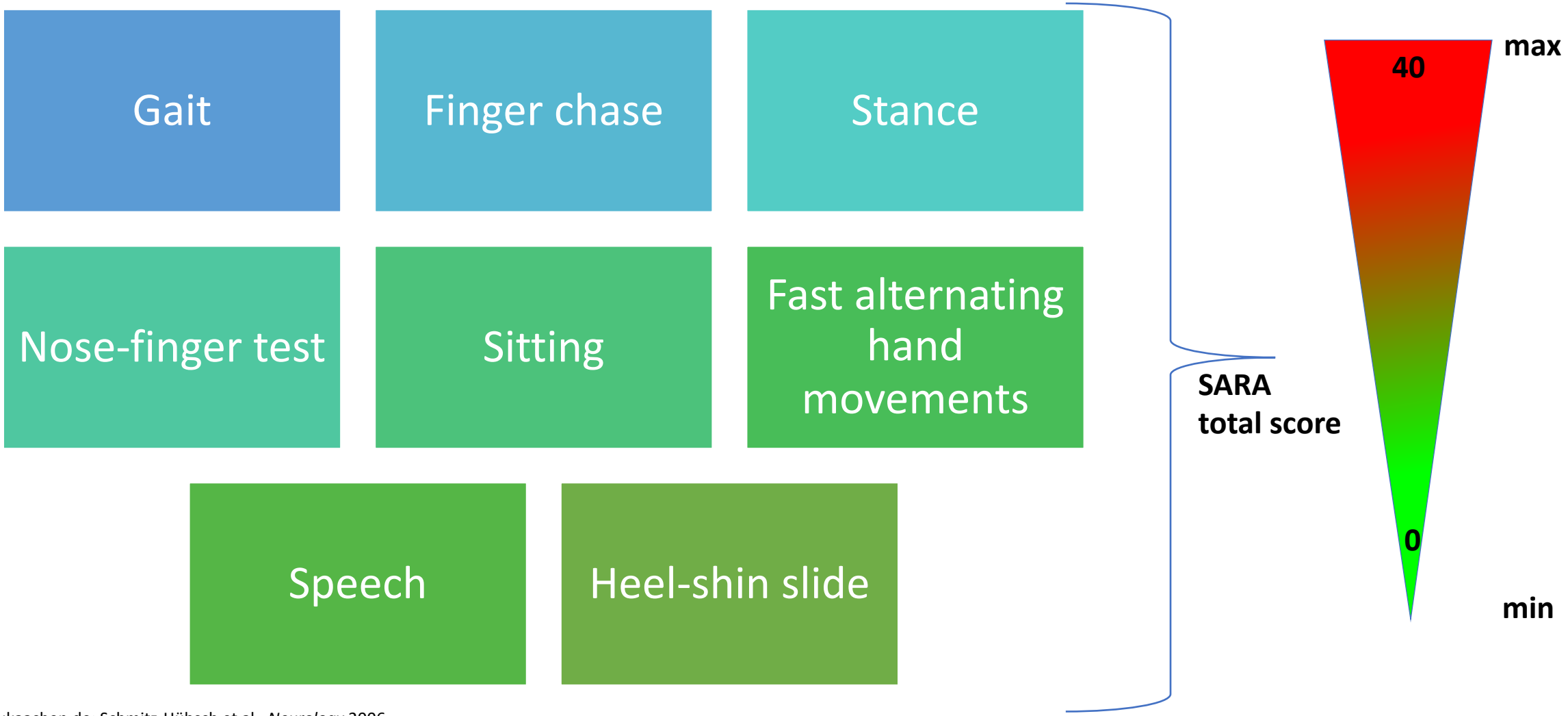
Item 7	Fast alternating hand movements
Task	• Proband is asked to perform 10 cycles of repetitive alternation of pro- and supinations of the hand on his/her thigh as fast and as precise as possible.
Note	• Movements are performed at <u>maximum speed</u> • Average performance is rated • Hands have to be lifted up for each cycle

Ataxia

Item 8	Heel-shin slide
Task	• Proband is asked to lift one leg, point with the heel to the opposite knee, slide down along the shin to the ankle, and lay the leg back on the examination bed.
Note	• Slide-down movements should be performed within 1 s • Pants, shoes and socks are not allowed • Make sure rolled up pants are not restricting the range of motion • Count how many times the heel loses contact to the shin • The heel must touch the shin • Sliding down with the side of the foot is rated as loss of contact

Ataxia

Scale for the assessment and rating of ataxia (SARA)



www.neurologie.ukaachen.de; Schmitz-Hübsch et al., *Neurology* 2006

Natural History Studies

EFACTS Research For a Better Future

EUROPEAN FRIEDREICH'S ATAXIA CONSORTIUM FOR TRANSLATIONAL STUDIES

www.e-facts.eu

Natural History Data

EFACTS Research For a Better Future

EUROPEAN FRIEDREICH'S ATAXIA CONSORTIUM FOR TRANSLATIONAL STUDIES

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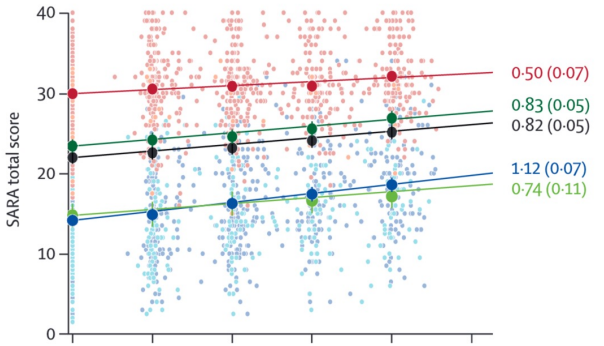
Registry > 1.100 Friedreich Ataxia

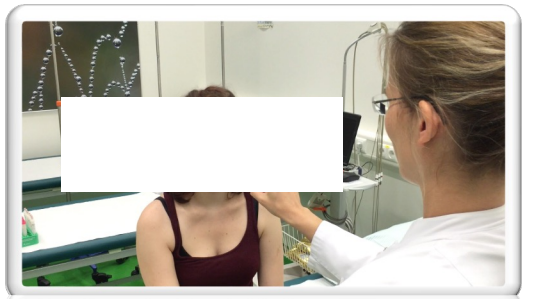
Coordinator: Prof. J.B. Schulz

18 sites, 8 countries

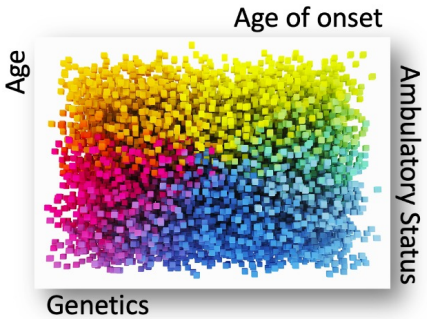
Αθήνα/Athens

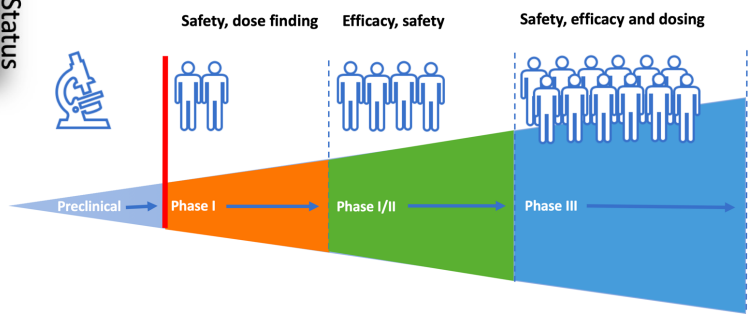
Clinical Rating Scale for Ataxia: SARA



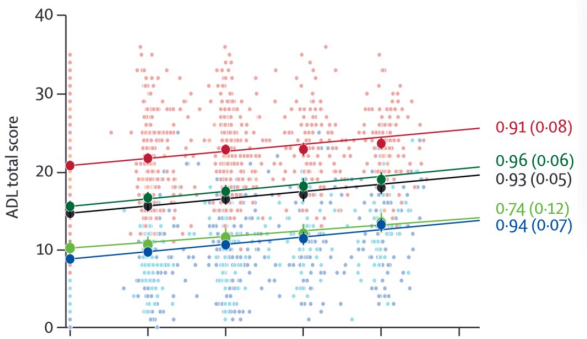


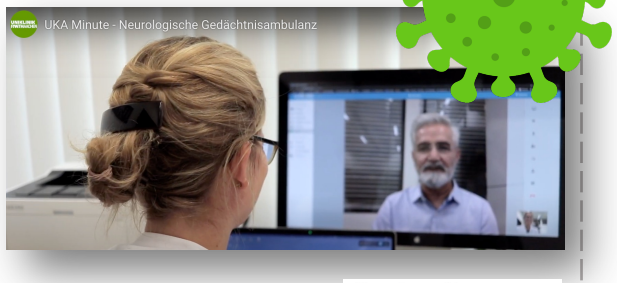
Stratification

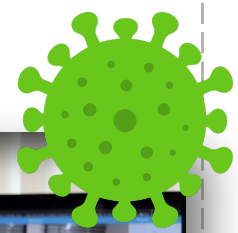


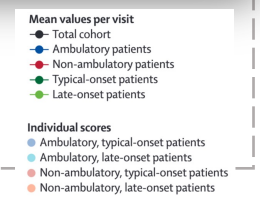


Activities of Daily Living: ADL







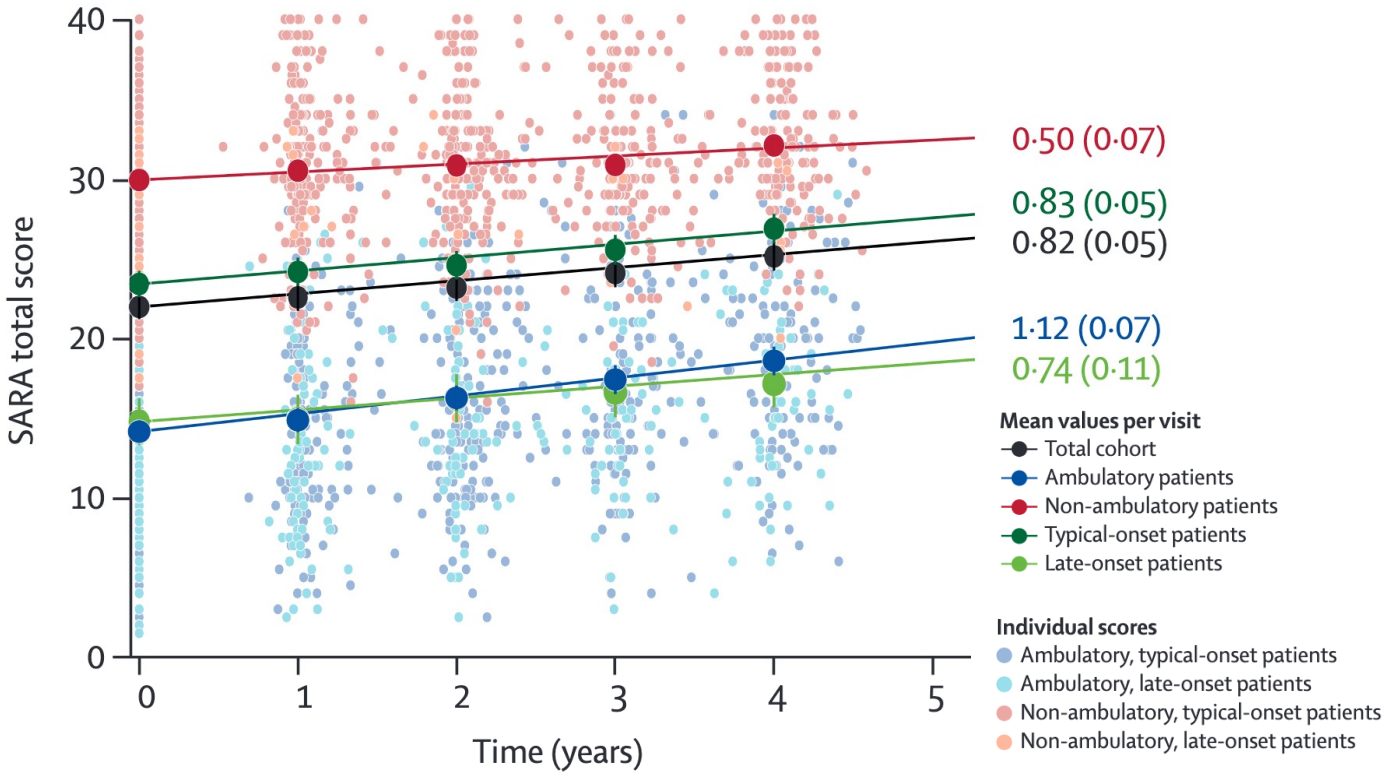


Reetz et al., *Lancet Neurology 2015;* ***Reetz et al.,*** *Lancet Neurology 2016;* ***Reetz et al.,*** *Neurology 2018;* ***Reetz et al.,*** *Lancet Neurology 2021*

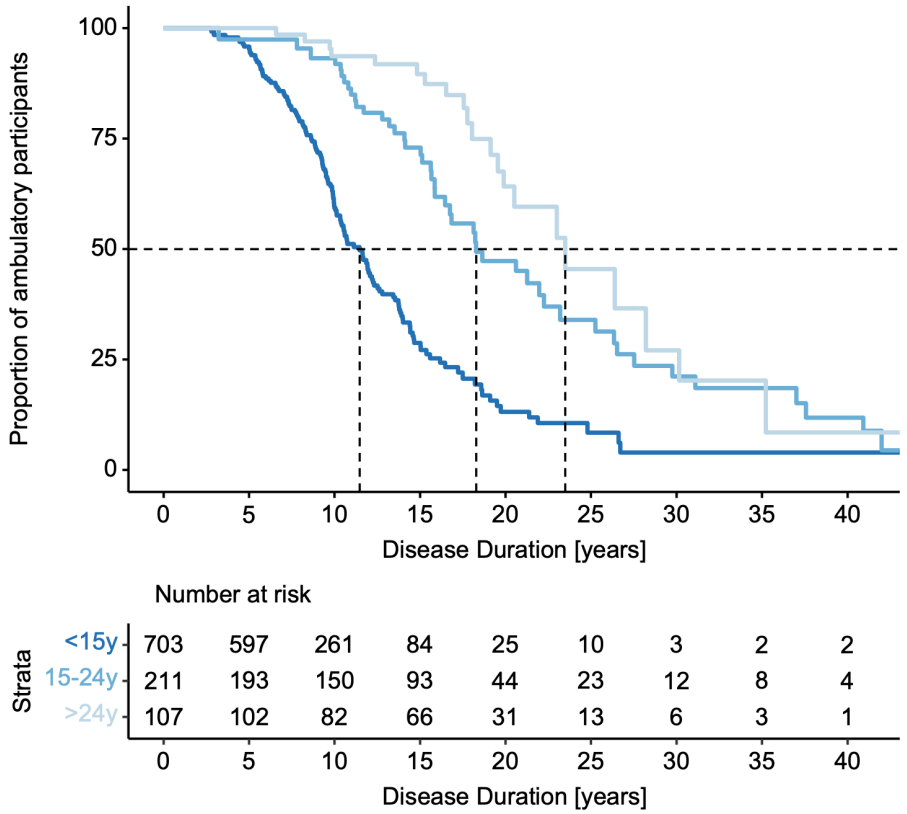
Ataxia

Natural history data from EFACTS and FA-COMS

Annual progression rate

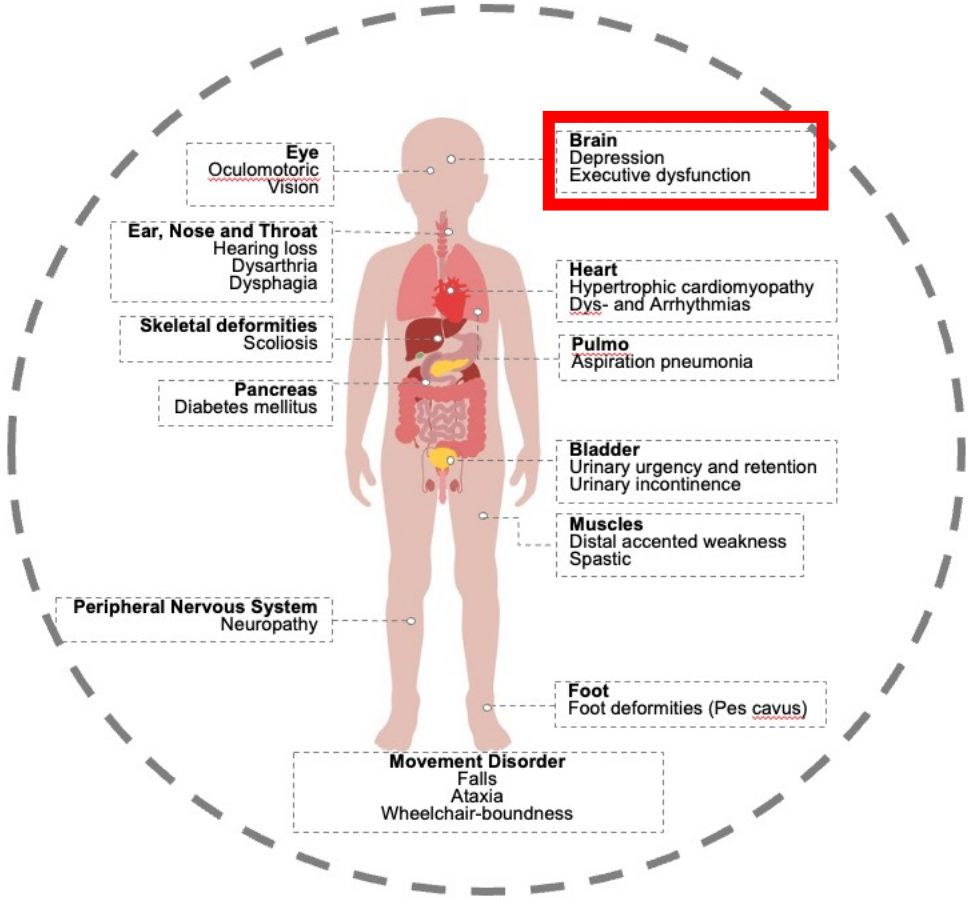


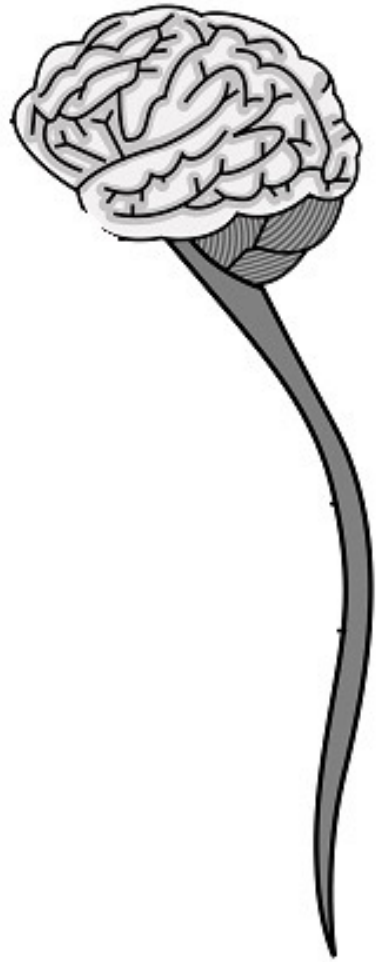
Predictors of loss of ambulation



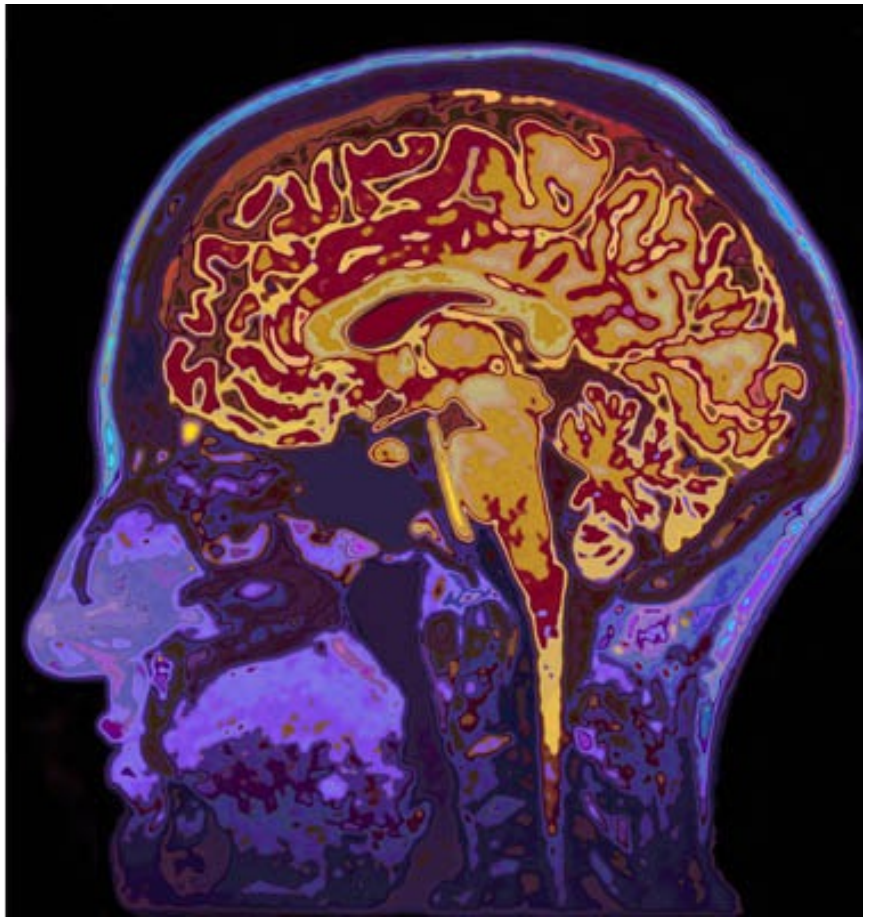
Reetz et al., Lancet Neurology 2021; Rummey et al.; EClinical Medicine 2020

Multisystem complex disease



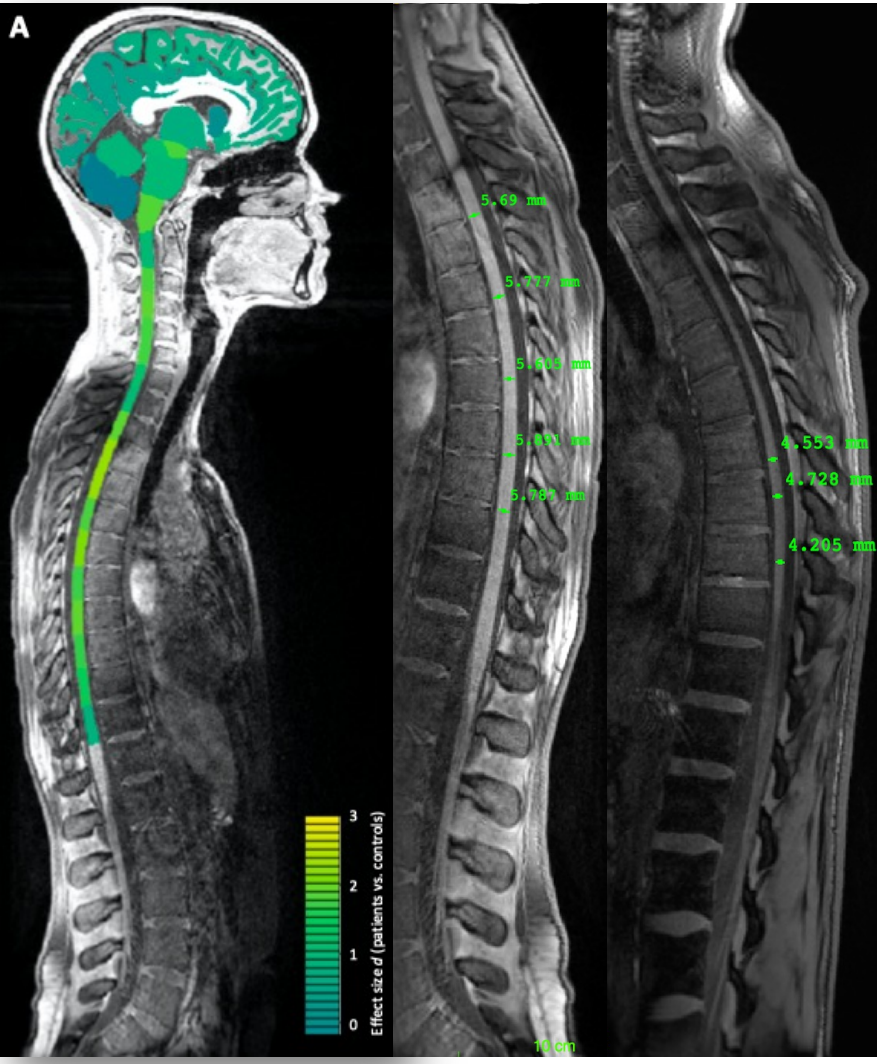


Imaging Research Studies

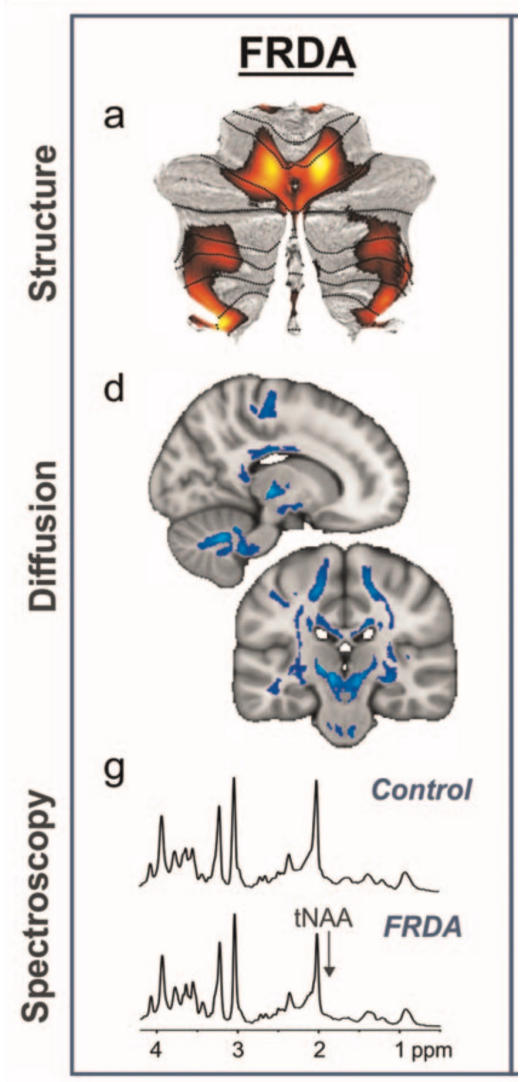


Source: TRACK-FA Study

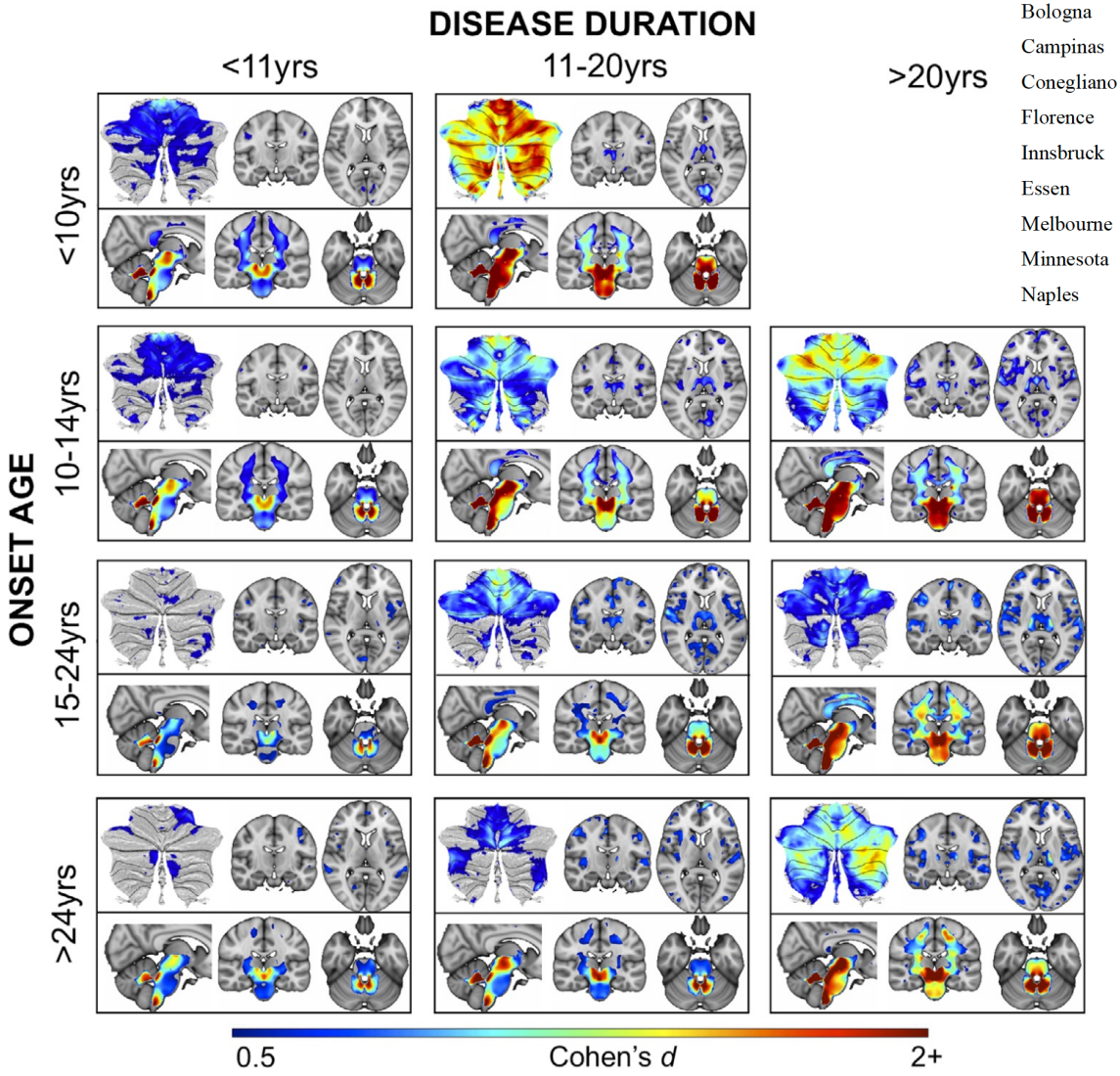
Imaging in Friedreich Ataxia



Dogan et al., *ACTN* 2016; Dogan et Romanzetti *JNNP* 2018



Öz et al., *Curr Opinion* 2020



Aachen
Bologna
Campinas
Conegliano
Florence
Innsbruck
Essen
Melbourne
Minnesota
Naples

Harding et al., *Annals Neurology* 2021

Prospective Imaging Research Study

A Natural History Study to TRACK Brain and Spinal Cord Changes in Individuals With Friedreich Ataxia (TRACK-FA)

NIH U.S. National Library of Medicine
ClinicalTrials.gov

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A Natural History Study to TRACK Brain and Spinal Cord Changes in Individuals With Friedreich Ataxia (TRACK-FA) ((TRACK-FA))

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT04349514

Recruitment Status : Not yet recruiting
First Posted : April 16, 2020
Last Update Posted : July 20, 2020

See Contacts and Locations

Sponsor:
Monash University

Collaborators:
University of Minnesota
RWTH Aachen University
University of Campinas, Brazil
Children's Hospital of Philadelphia
University of Florida
Friedreich's Ataxia Research Alliance

FARA Friedreich's Ataxia Research Alliance

TRACK-FA

MONASH University

UNICAMP

murdoch children's research institute

RWTH AACHEN UNIVERSITY

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Driven to Discover℠

www.clinicaltrials.gov

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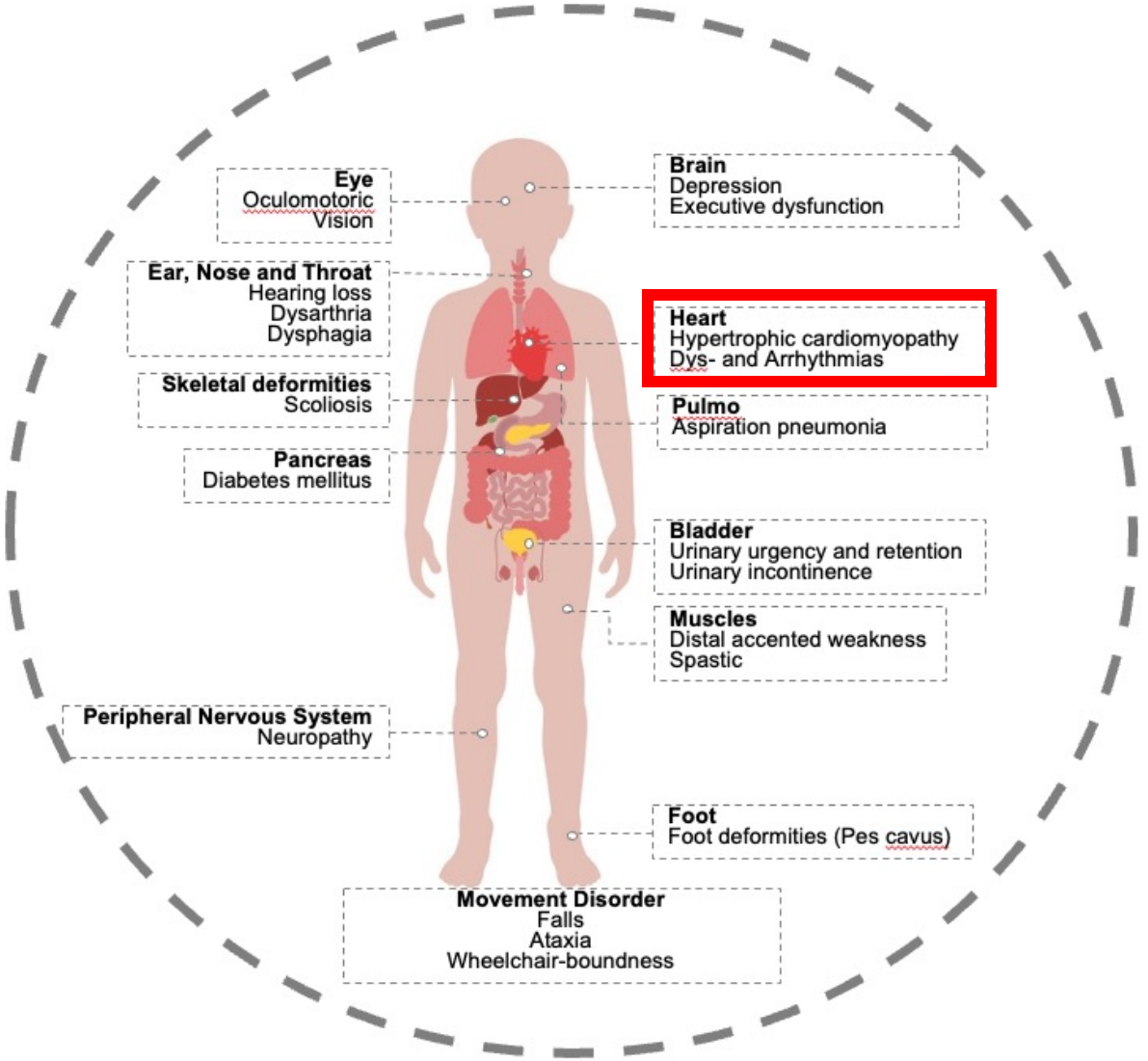
Question 2

Which answers are correct (multiple right)?

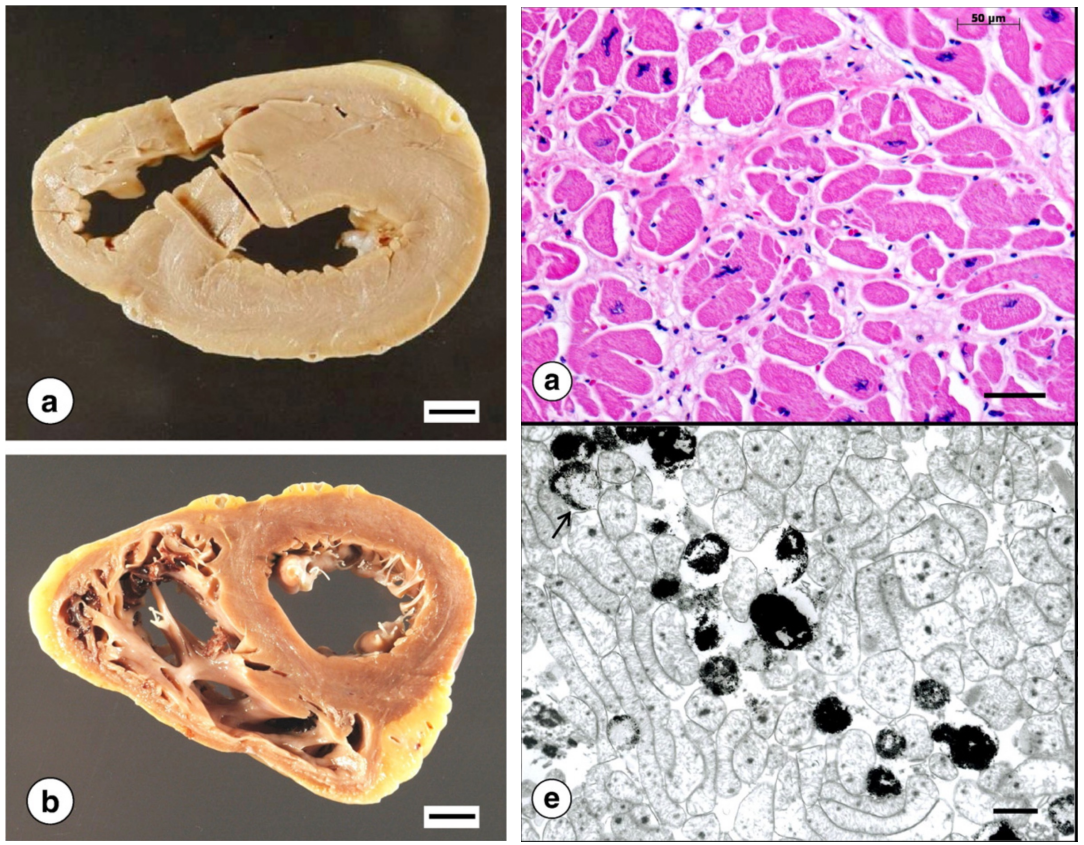
a. Friedreich ataxia is an autosomal-dominant genetic disease.
b. Frataxin is increased in Friedreich ataxia.
c. Structural MR Imaging research data show typically spinocerebellar atrophy.
d. Neuropathological spinal cord samples show degeneration of the posterior columns.
e. Clinical manifestation is typically in late adulthood.

Multisystem complex disease



Heart

Pathology of cardiomyopathy



Koeppen et al., *J Neurol Sci* 2011

Pathology & Epidemiology

- *Gross pathology*: Concentric cardiac hypertrophy of the left ventricular wall and interventricular septum and discoloration of the myocardium[1]
- *Histopathology*: abnormal fiber size variation, fiber splitting, abnormal nuclei, and an excess of endomysial connective tissue[1]
- Reduction of cardiac frataxin levels, iron accumulation, and inflammatory mechanisms[2]
  - progressive continuum of cardiac involvement[3]
- In 650 FA patients of the EFACTS registry[4]
  - about 40% presented with heart disease, mainly left ventricular hypertrophy, associated with earlier age of onset
- Cardiac events have been deemed the primary cause of mortality in over half (~60%) of patients with FA—death typically occurs in those aged < 40 years[5,6]

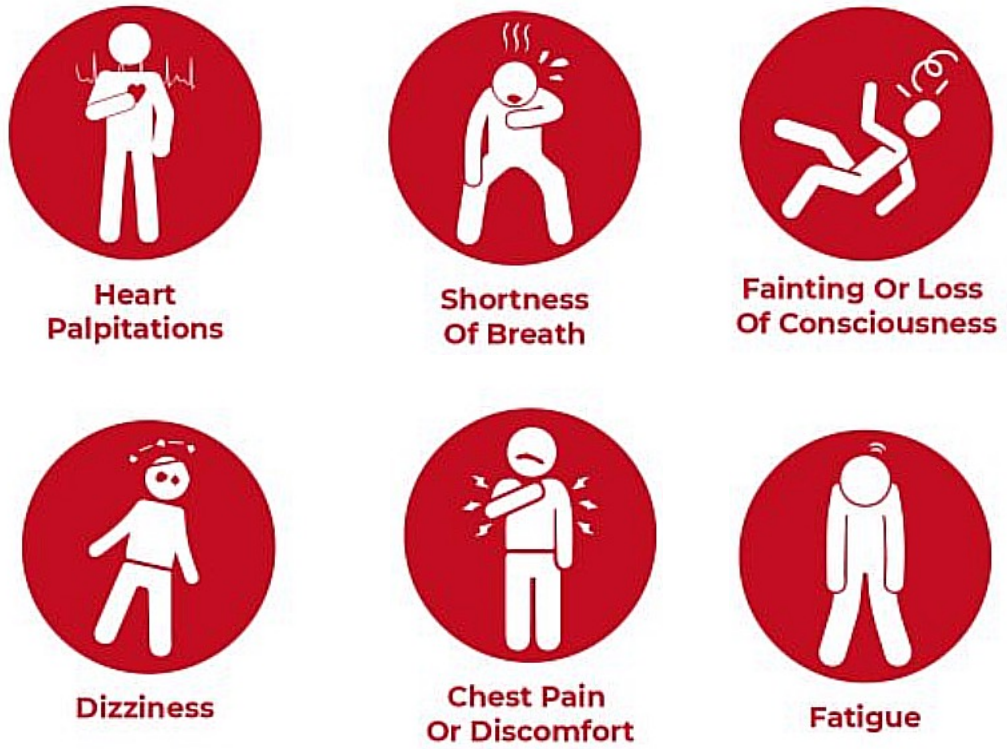
[1]Koeppen et al., *J Neurol Sci* 2011; [2]Weidemann et al., *Int J Cardiol* 2015; [3]Legrand et al.; *Archives of Cardiovasc Dis* 2022; [4]Reetz et al., *Neurology* 2018; [5]Pousset et al., *JAMA Neurol* 2015; [6]Tsou et al., *J Neurol Sci* 2011

Heart

Symptoms of cardiomyopathy

Cardiac affects & Symptoms

- Arrhythmias
- Symptoms
  - **palpitations**
  - dizziness
  - **dyspnoea**
  - **chest discomfort**
  - fainting
  - fatigue



Source: https://www.artemiscardiac.com/arrhythmia/

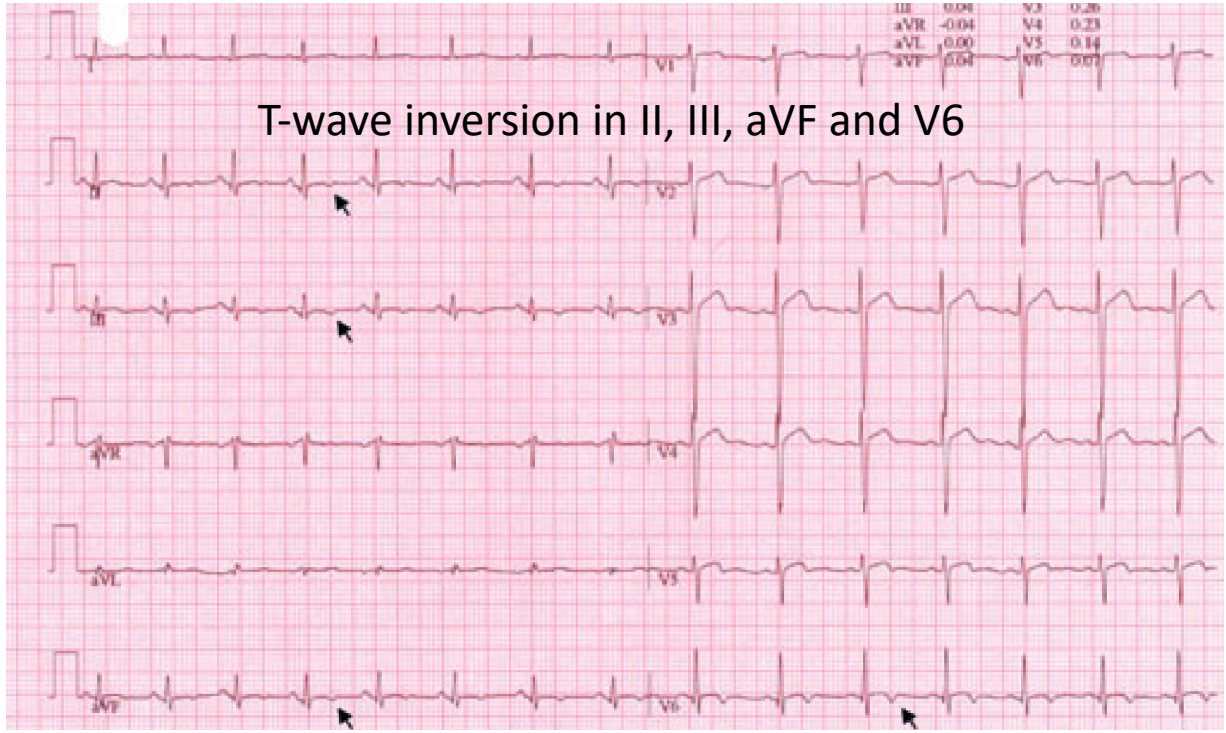
Weidemann et al., *Int J Cardiol* 2015; Corben et al., *Orphanet J Rare Dis 2022;* Clinical Management Guidelines for Friedreich Ataxie (https://www.curefa.org/research/clinical-care-guidelines)

Heart

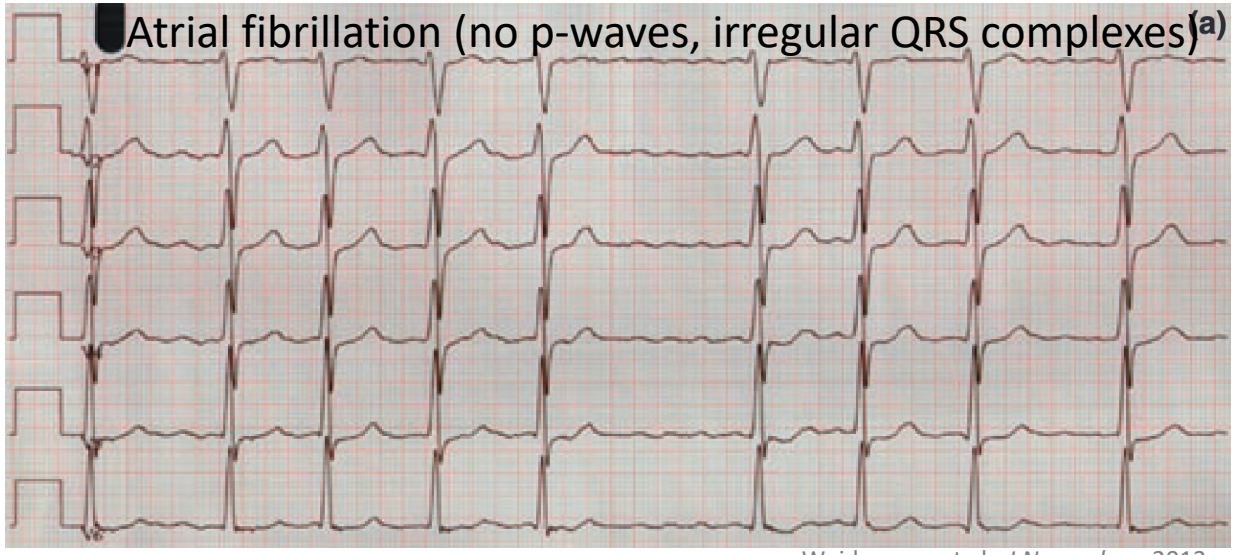
Measures: ECG

Diagnostics - Electrocardiogramm

- Electrocardiogramm:
  - QRS duration often normal
  - abnormal repolarization with T-wave abnormalities (inversion > flattening) -> myocardial involvement even without detectable hypertrophy
  - signs of LV hypertrophy in advanced stages high S-wave in V1 and V2, high R-wave in V5 and V6
- in advanced stages supraventricular tachycardias like atrial fibrillation (a), atrial flutter and atrioventricular reentry tachycardia
  - bundle branch block



T-wave inversion in II, III, aVF and V6



Atrial fibrillation (no p-waves, irregular QRS complexes)[a]

Weidemann et al.; *J Neurochem* 2013

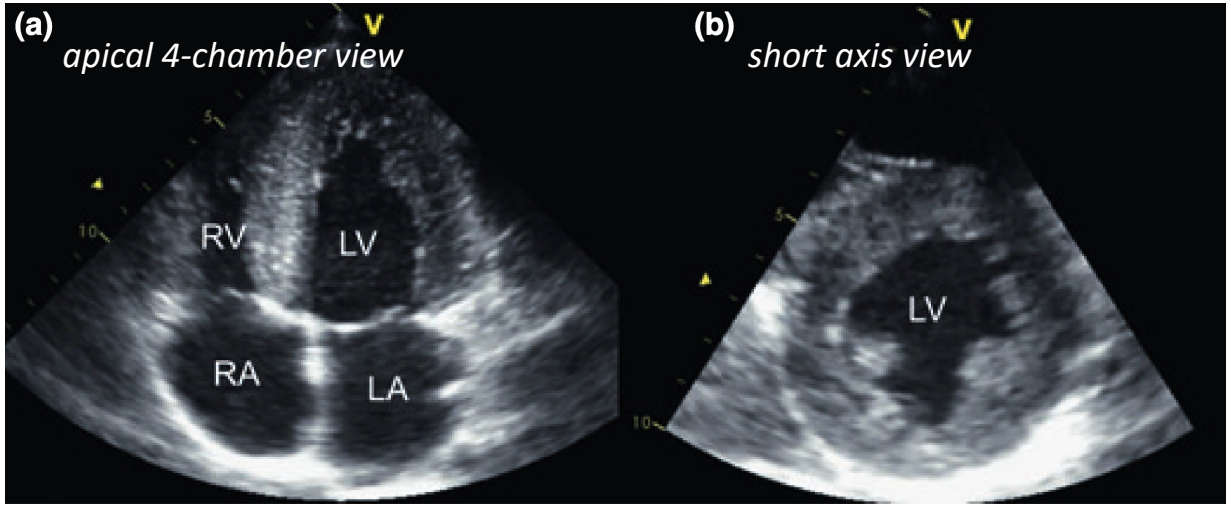
Pousset et al., *JAMA* 2015; Legrand et al.; *Archives of Cardiovasc Dis* 2022; Weidemann et al., *Int J Cardiol* 2015

Heart

Cardiomyopathy Measures: Echo

Diagnostics - Echocardiography

- 60% of patients with FA have septal hypertrophy on echocardiography



LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Weidemann et al.; *J Neurochem* 2013

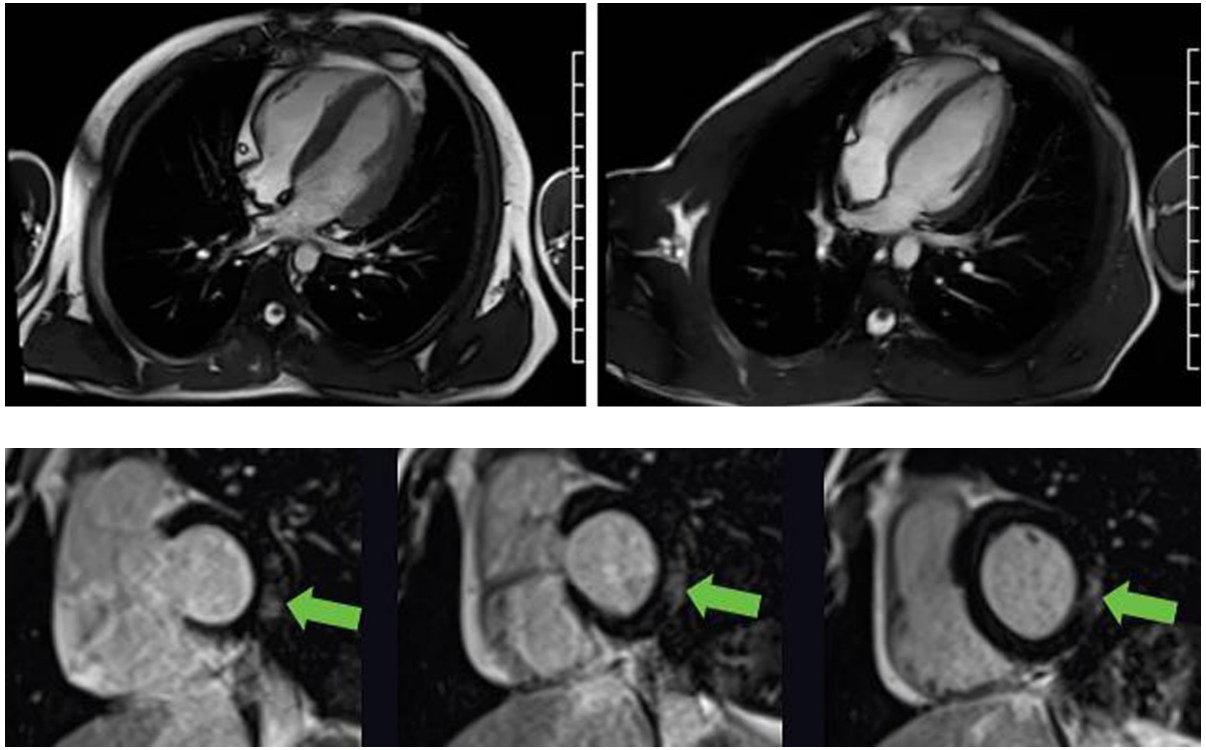
Legrand et al.; *Archives of Cardiovasc Dis* 2022; Weidemann et al., *Int J Cardiol* 2015

Heart

Cardiomyopathy Measures: cMRI

Diagnostics – Cardio MRI

- CMRI:
  - LV geometry, function, LV mass, fibrosis indices
- 50% of patients showed a CMRI-confirmed increase in LV mass or wall thickening
- half of patients with FA have lateral subepicardial or transmural late gadolinium enhancement (LGE), indicative of dense replacement fibrosis
- no significant changes over 1 year[2]



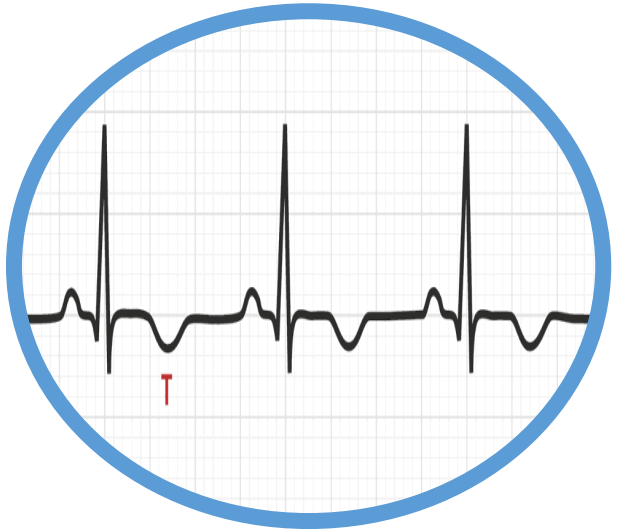
Legrand et al.; *Archives of Cardiovasc Dis* 2022

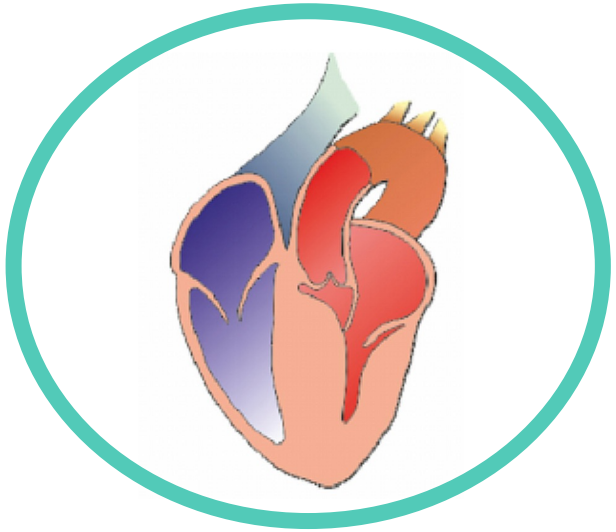
Pousset et al., *JAMA* 2015; [2]Legrand et al.; *Archives of Cardiovasc Dis* 2022; Weidemann et al., *Int J Cardiol* 2015

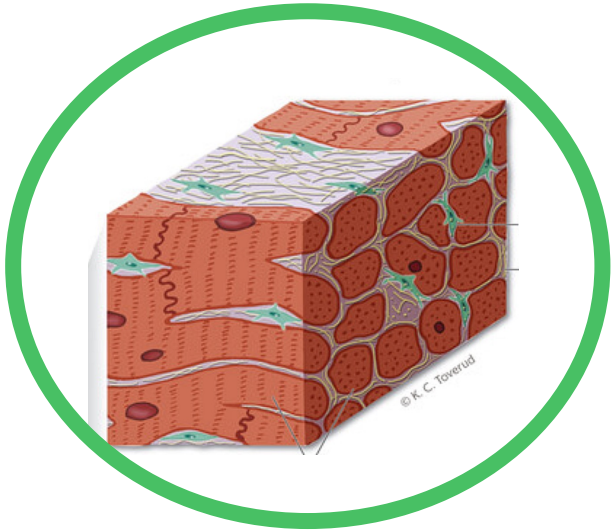
Heart

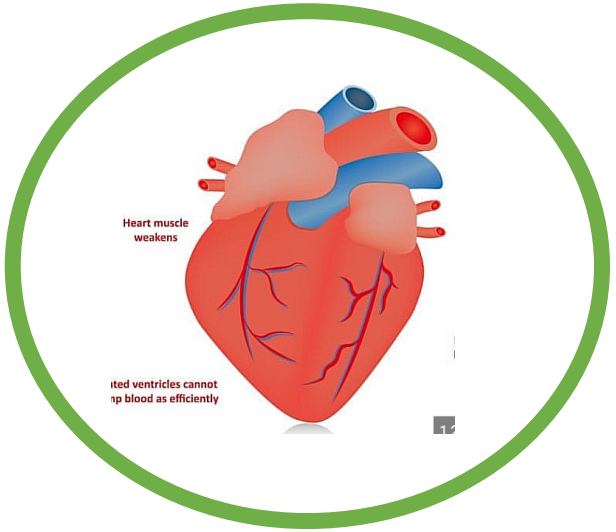
Cardiomyopathy

Electrical anomalies → Cardiac hypertrophy → Dense fibrosis → Cardiac dysfunction









Legrand et al.; *Archives of Cardiovasc Dis* 2022; Esepland et al.; 2018 (PMID 30344312); Weidemann et al., *Int J Cardiol* 2015; [8]Clinical Management Guidelines for Friedreich Ataxie (https://www.curefa.org/research/clinical-care-guidelines)

Heart

Recommendations

Monitor cardiac function

At diagnosis and then at least annually

- Electrocardiogramm (ECG)
- Echocardiogram

Cardiac symptoms and/or abnormal results

- Cardiology consultation

Note: Advanced imaging techniques in echocardiogry and/or cardiac magnetic resonsance imaging (e.g. strain and late gadolinium enhancement) are still to be more explored to validate the potential for identifying at-risk individuals with Friedreich ataxia

Cardiology consultation

Management for arrhythmias

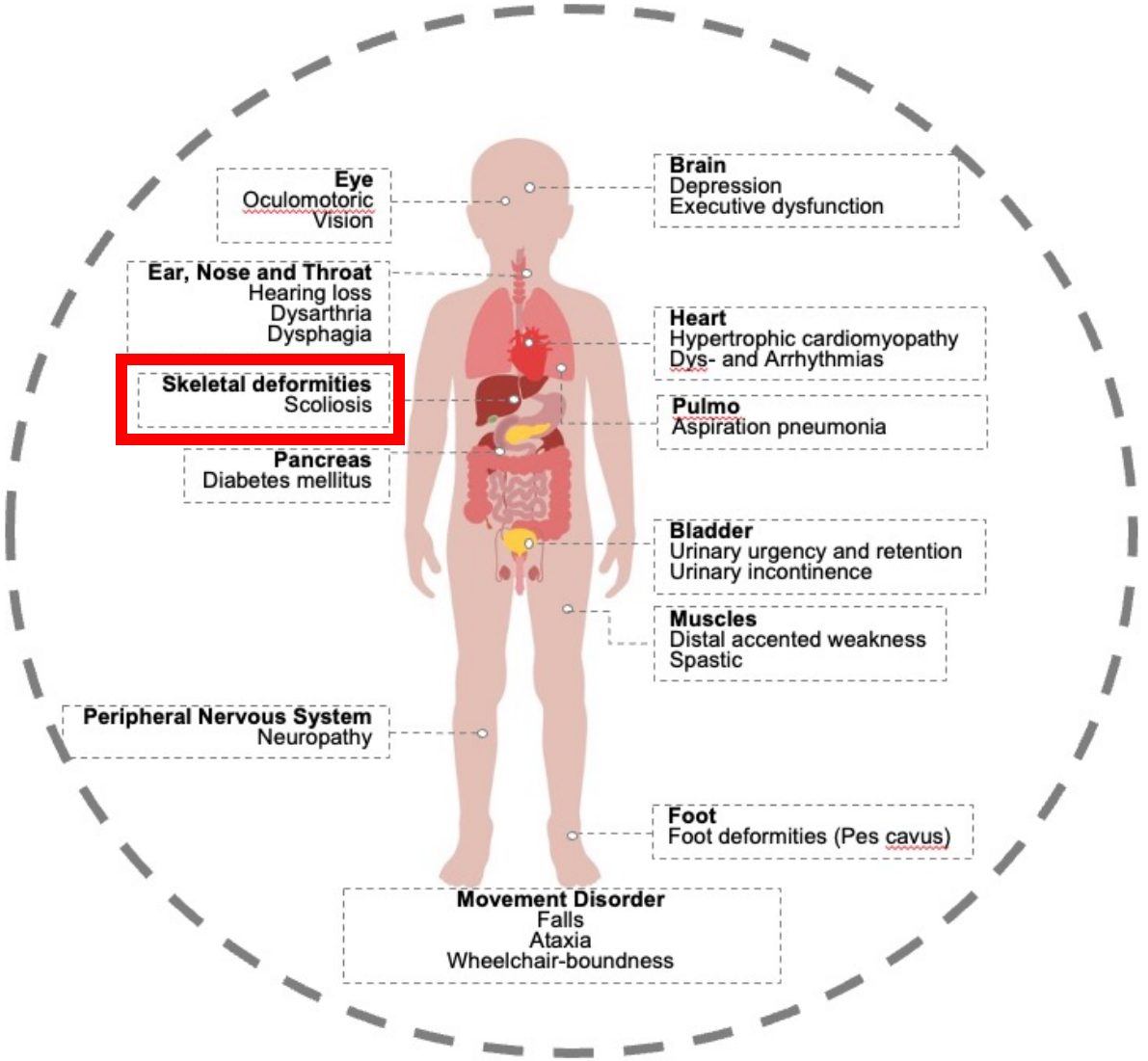
- Atrial tachyarrhythmias
- Ventricular arrhythmias

Management for heart failure

- Pharmacologic treatment
- Device therapy
- Fluid and operative management

Corben et al., *Orphanet J Rare Dis 2022;* Clinical Management Guidelines for Friedreich Ataxie (https://www.curefa.org/research/clinical-care-guidelines)

Multisystem complex disease

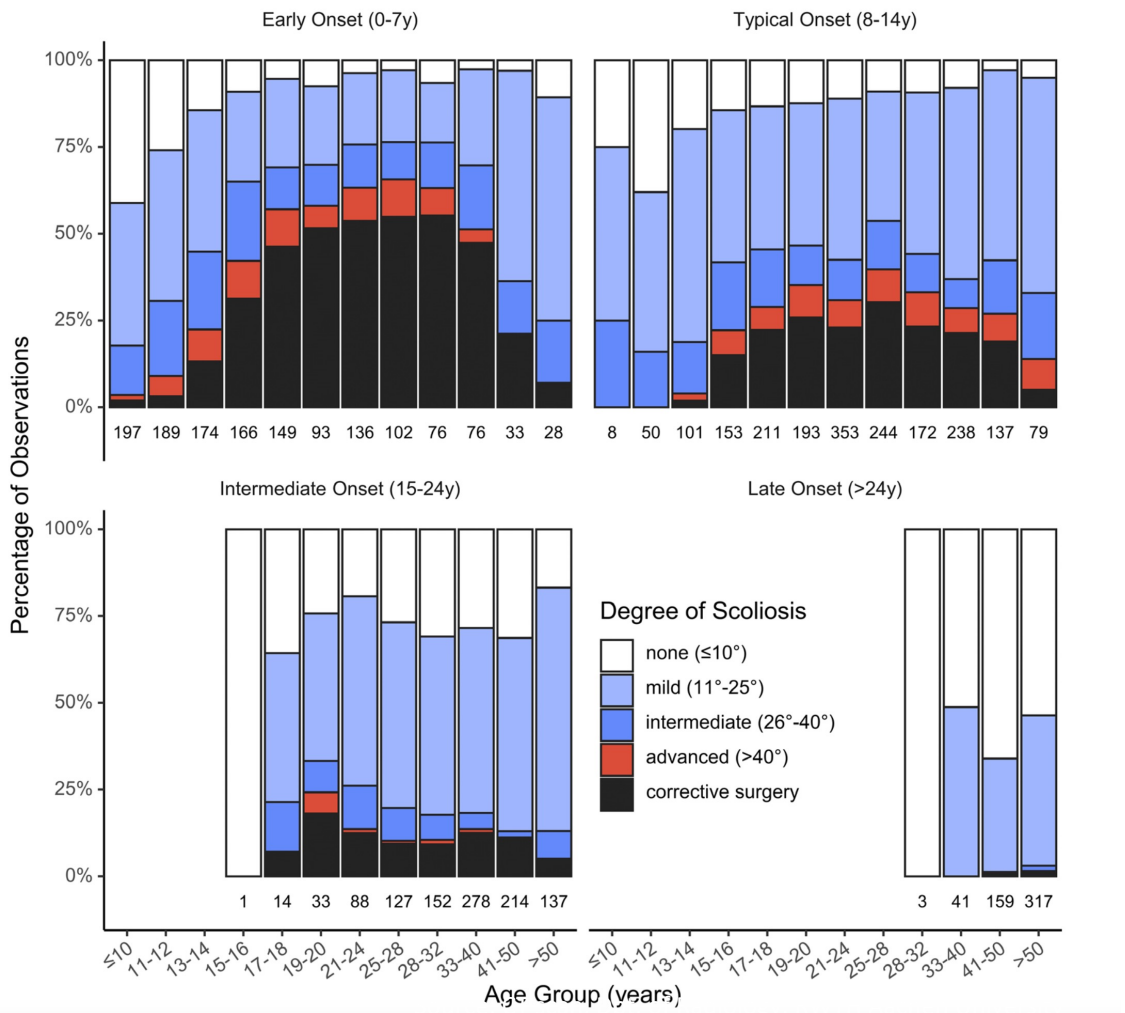


Musculoskeletal System

Scoliosis

Epidemiology

- In 650 FA patients of the EFACTS registry[1]
  - Second most frequent non-ataxia symptom (73.7%) [1]
  - Second most common first symptom (23.1%)[1]
  - Scoliosis was predicted by earlier age at onset and higher SARA scores[1]
  - Surgery in 11.6% in EFACTS[1]
- In 1116 FA patients of the FACOMS study >90% of FA patients with age of onset prior to 15 years of age developed intermediate to severe scoliosis
  - Major progression during the growth phase and puberty with 50% of need surgery
- Prevalence in literature varies from 33%-100%[3-7]



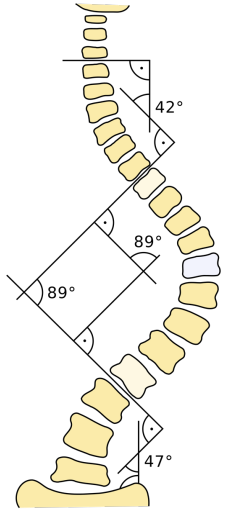
[1]Reetz et al., *Neurology* 2018; [2]Rummey, et al.; *Ann Clin Transl Neur* 2021; [3]Harding et al:, *Brain* 1981; [4]Durr et al.; *NEJM* 1996; [5]Schols et al., *Brain* 1997; [6]Delatycki et al. *Am J Med Genet 1999;* [7]McCabe et al; *J Neurol* 2000; Corben et al., *Orphanet J Rare Dis 2022;* [8]Clinical Management Guidelines for Friedreich Ataxie (https://www.curefa.org/research/clinical-care-guidelines)

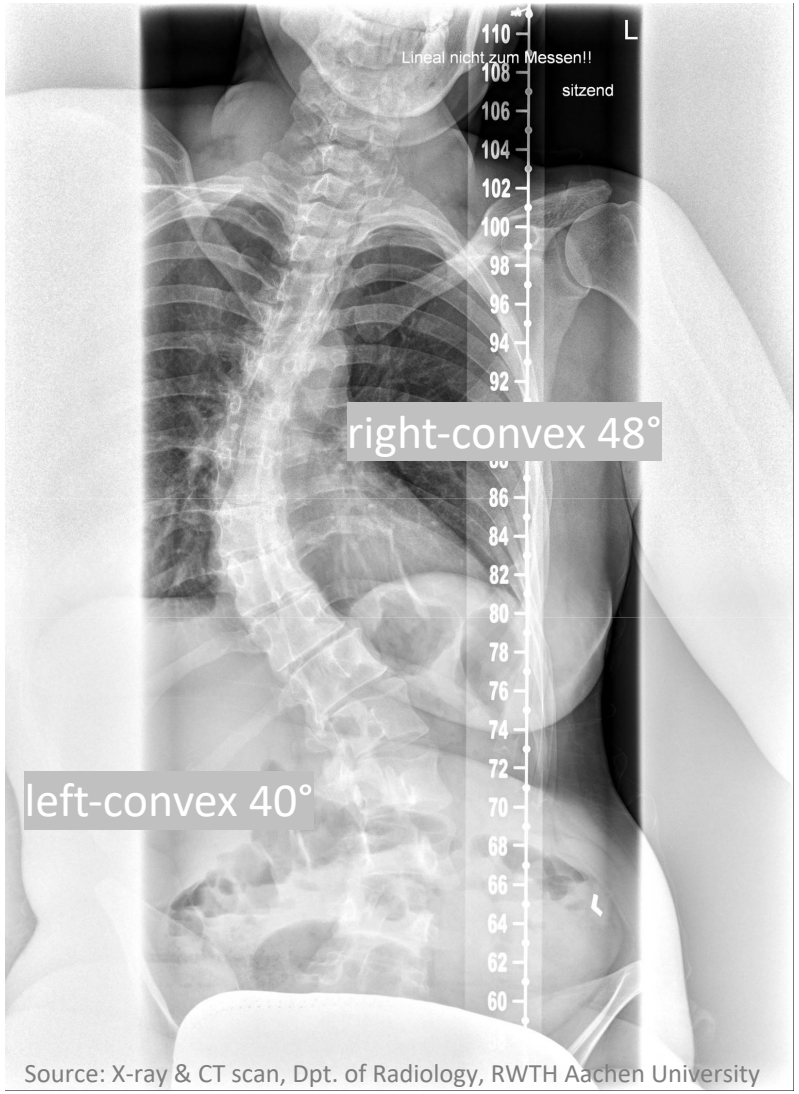
Musculoskeletal System

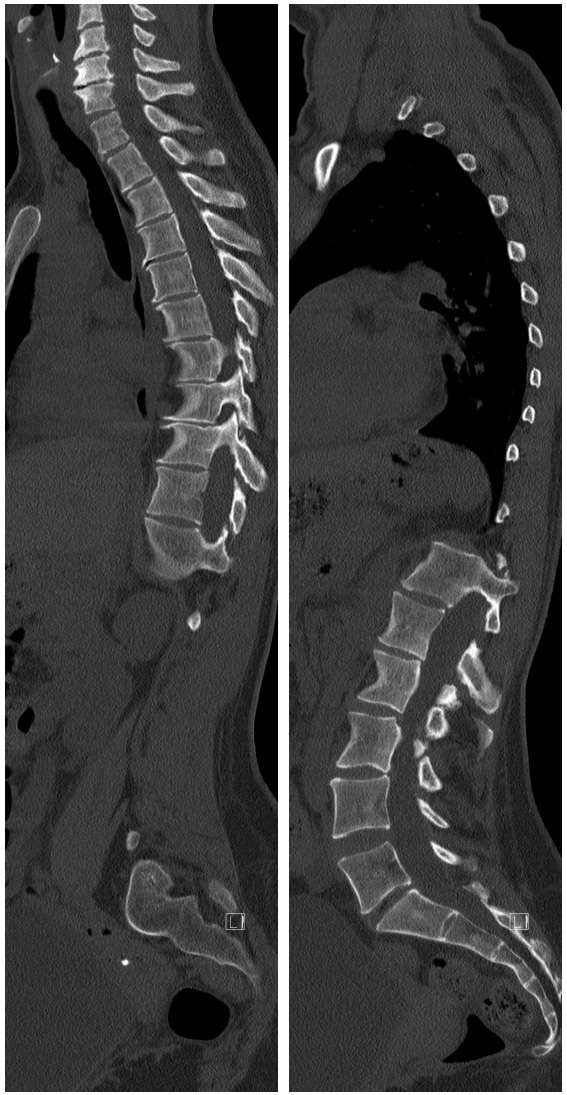
Scoliosis

Pathology & clinical presentation

- Etiology is still unclear
- Most rapid progression between the ages of 10 and 16
- High prevalence of double thoracic and/or lumbar curves
- ‘Cobb method’ is used in X-rays to determine the degree of curve







Source: X-ray & CT scan, Dpt. of Radiology, RWTH Aachen University

Corben et al., *Orphanet J Rare Dis 2022;* Clinical Management Guidelines for Friedreich Ataxie (https://www.curefa.org/research/clinical-care-guidelines)

Musculoskeletal System

Scoliosis

Treatment recommendations

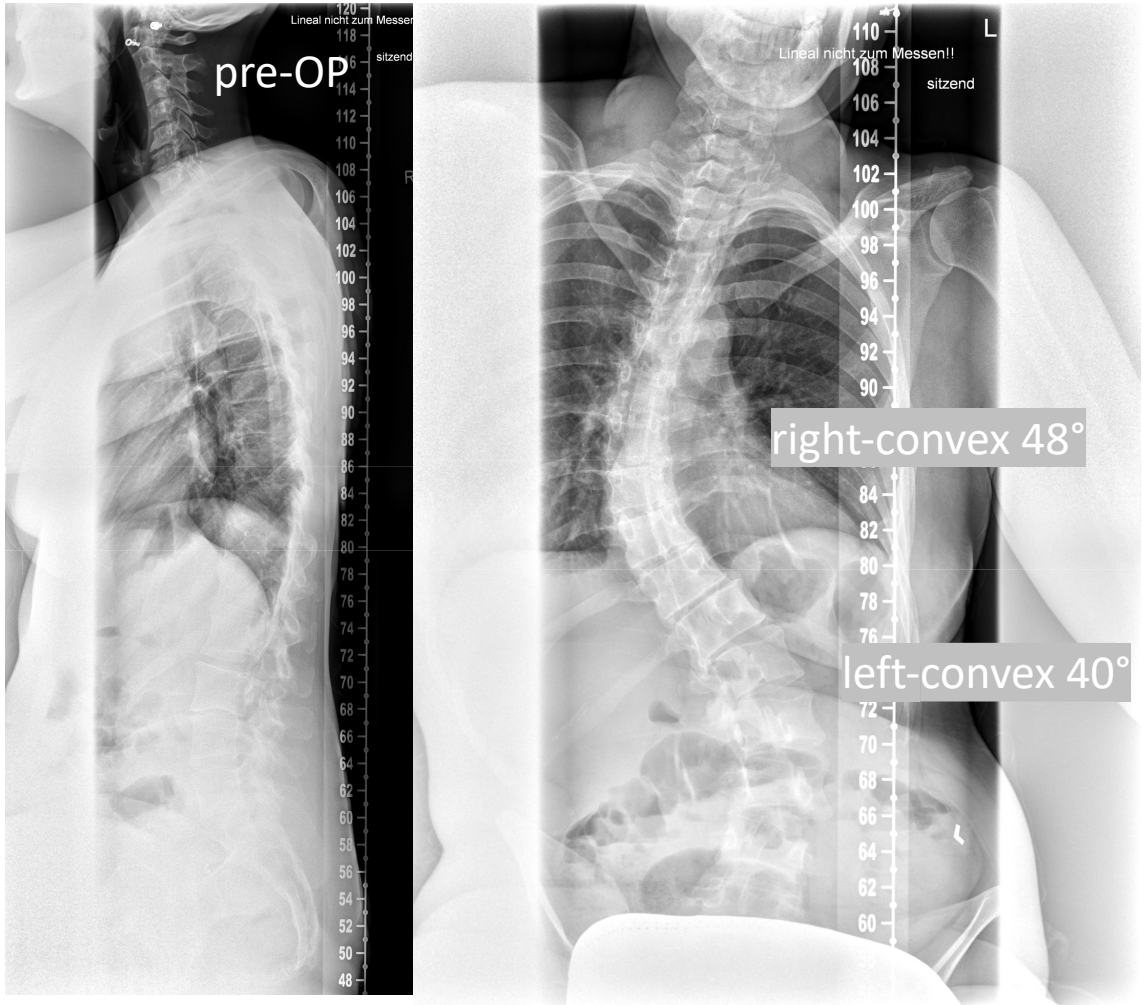
- **General recommendation**:
  - observation of children with a curve between 20° and 40°
  - > 40° evaluation of intervention
- ***Non-invasive***: bracing in ambulatory patients or customized seating
- ***Invasive***: surgery > 50-60°[2]
  - expert authors consider it is important to delay surgery for scoliosis in individuals with Friedreich ataxia for as long as possible by use of conservative management[3]
  - CAVE: when constriction of the internal organs and/or breathing problems occur surgery needs to be considered

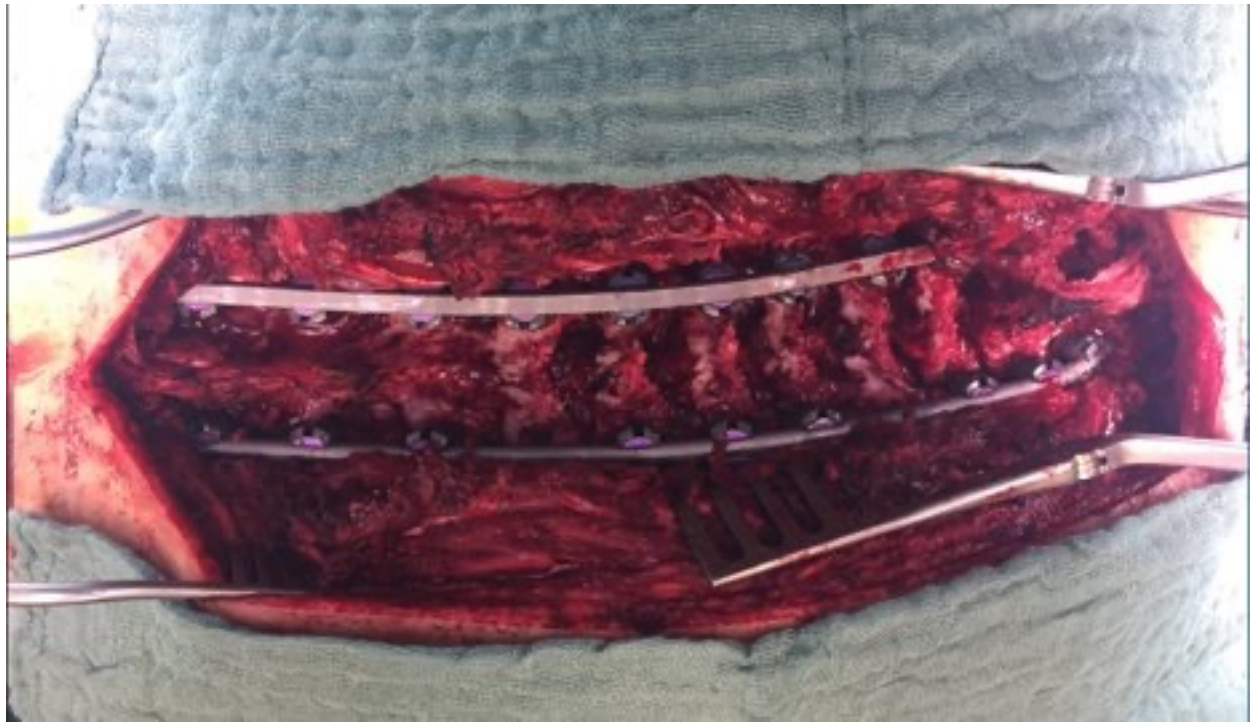
Source: German scoliosis network

[1]Reetz et al., *Neurology* 2018; [2]Rummey, et al.; *Ann Clin Transl Neur* 2021; [2]Milbrandt et al.; *J Ped Orthopaedics* 2008; Corben et al., *Orphanet J Rare Dis 2022;*
[3]Clinical Management Guidelines for Friedreich Ataxie (https://www.curefa.org/research/clinical-care-guidelines)

Musculoskeletal System

Surgery – Case Report

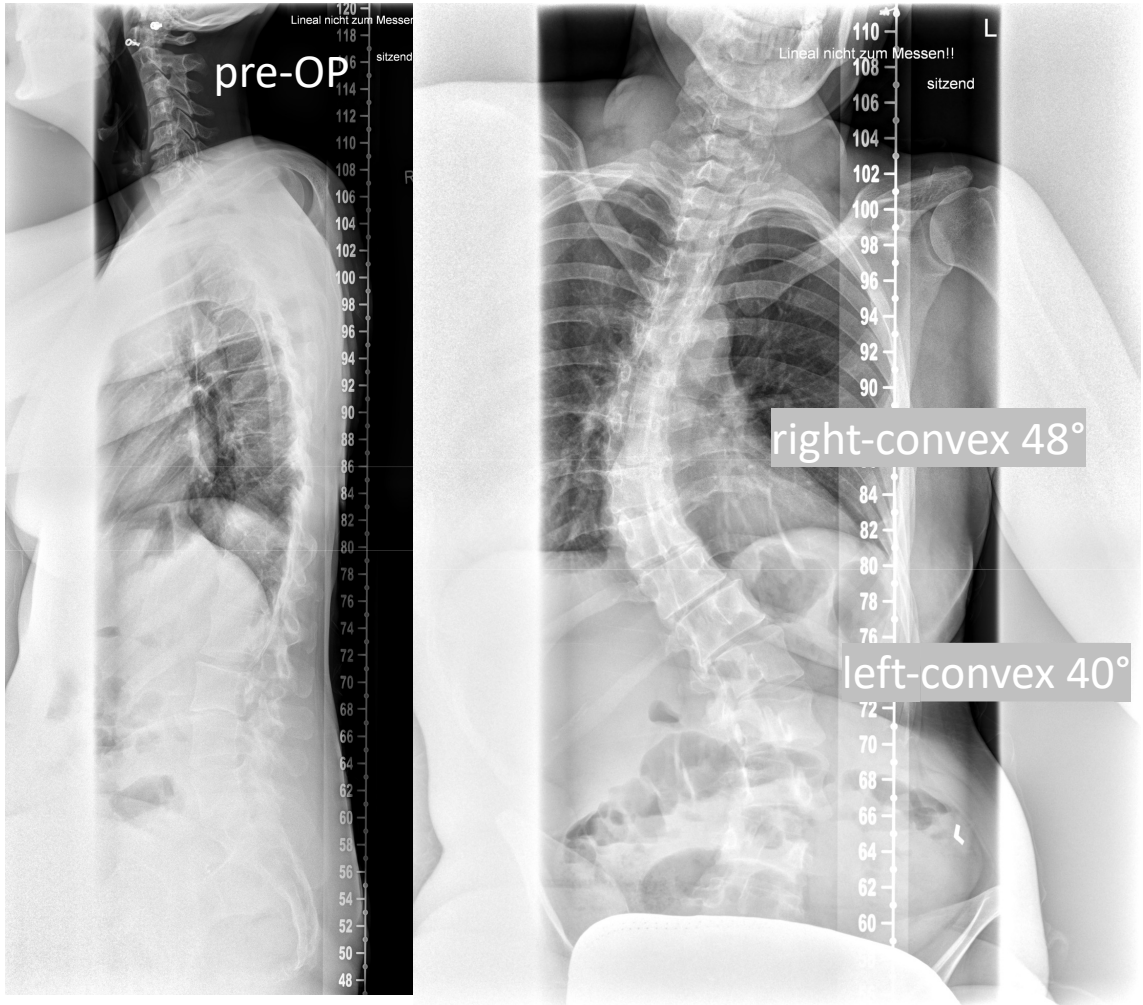


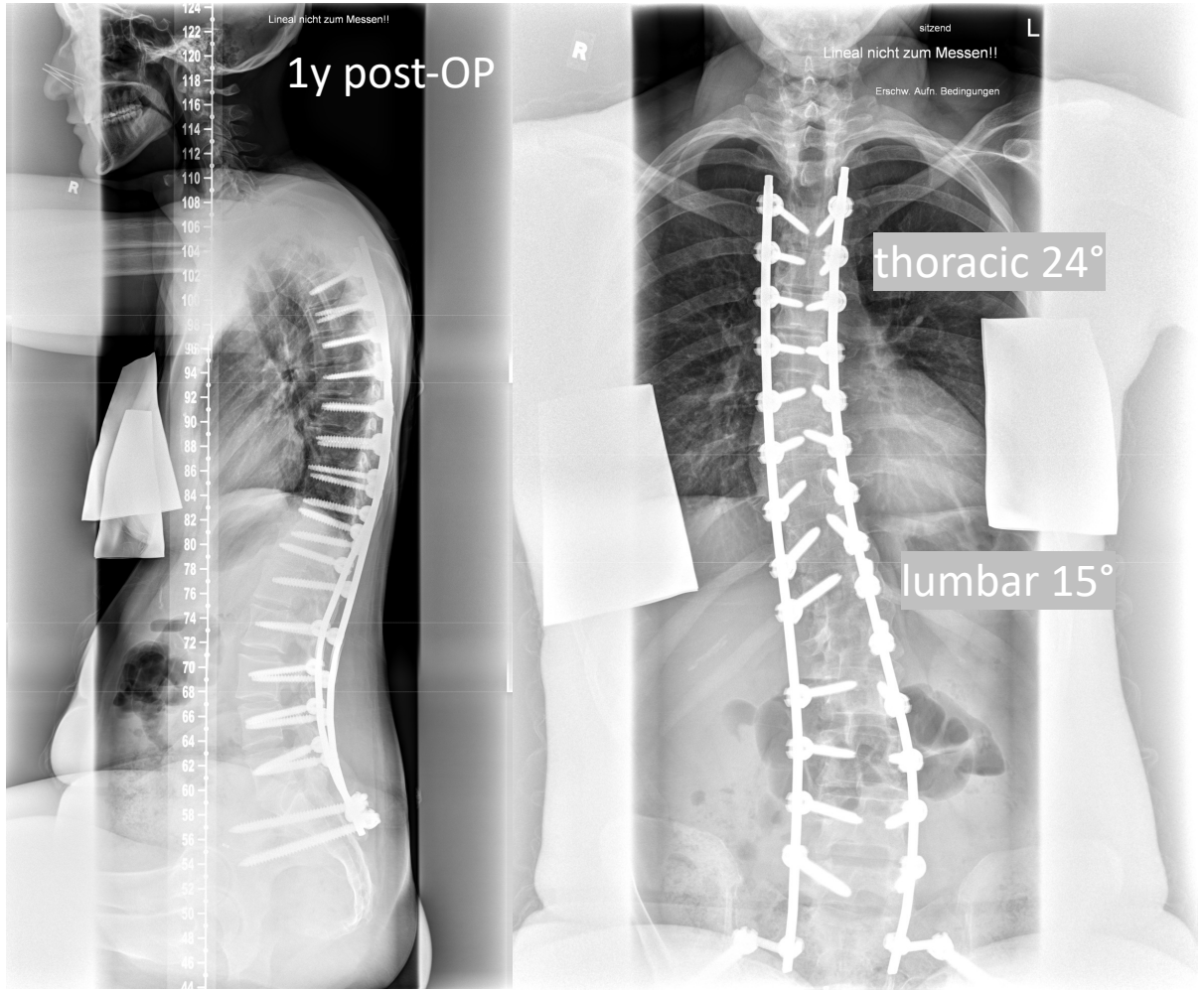


Source provided courtesy of Prof. Pishnamaz; Dpt. of Orthopaedics, Trauma and Reconstructive Surgery, RWTH Aachen University

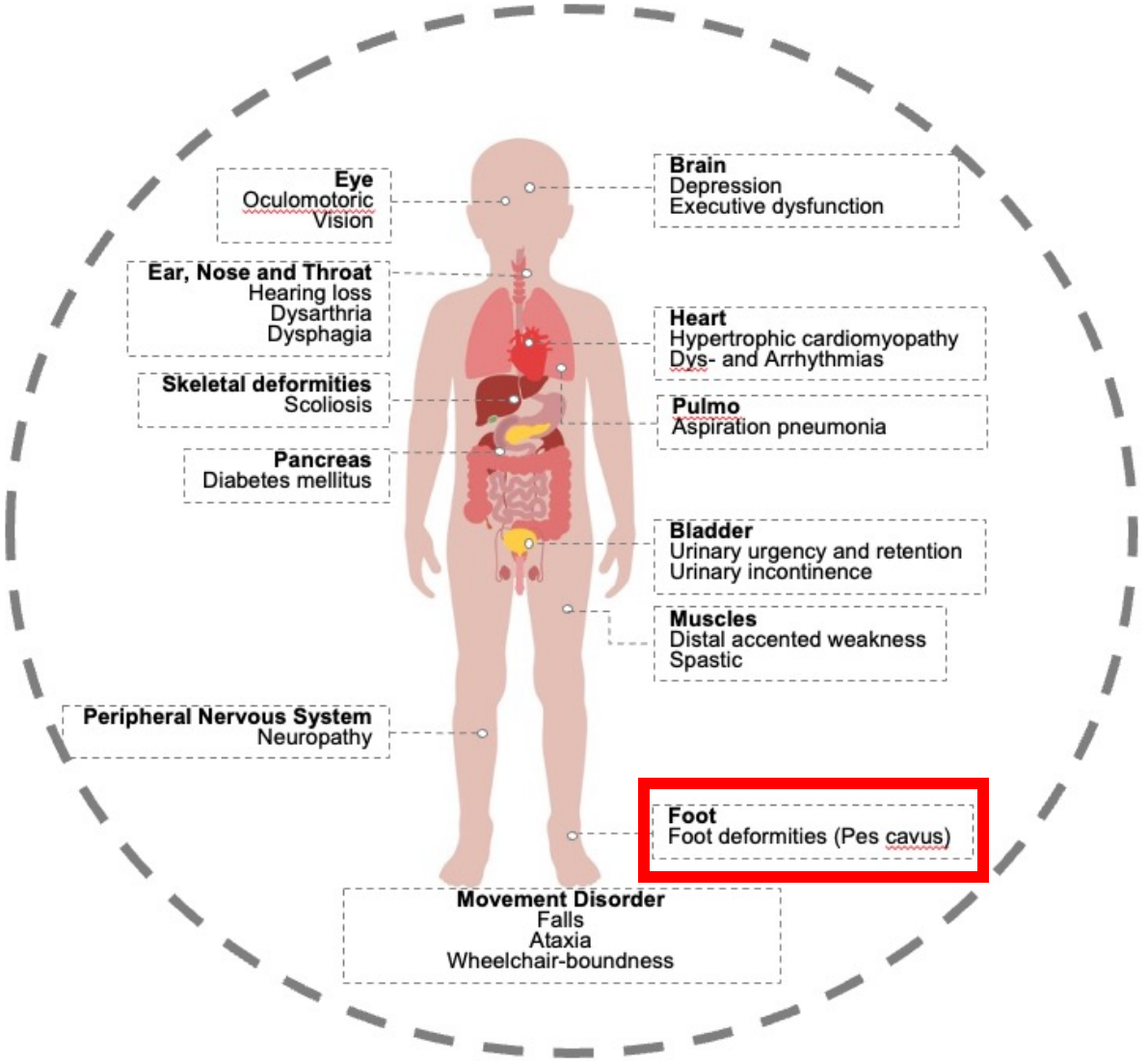
Musculoskeletal System

S-shaped thoraco-lumbar scoliosis



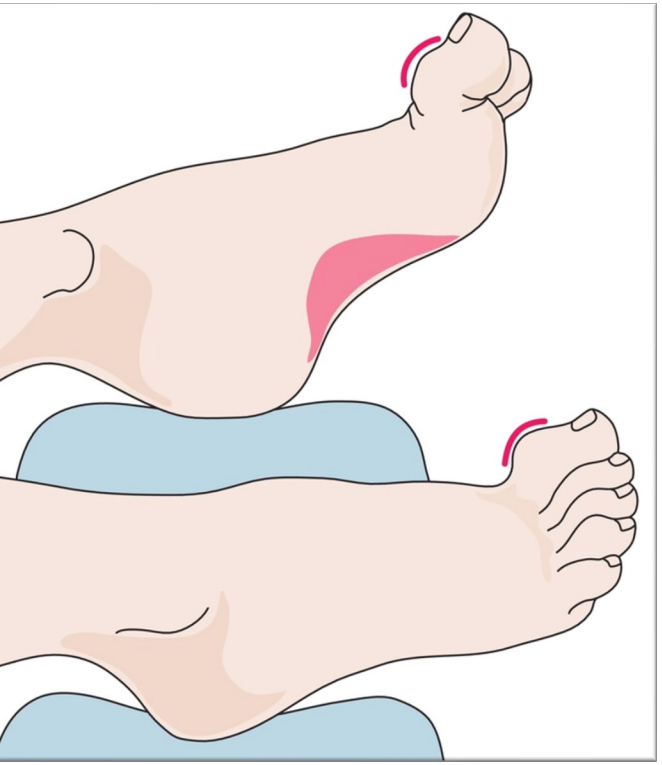


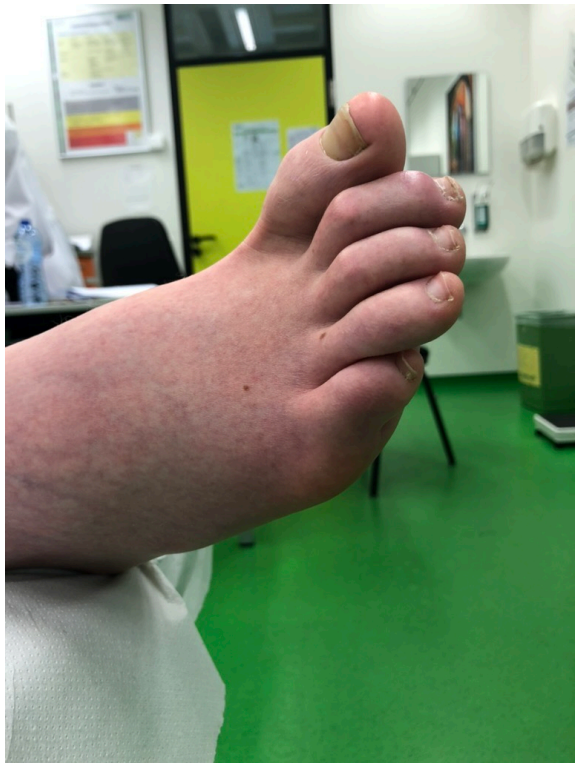
Multisystem complex disease

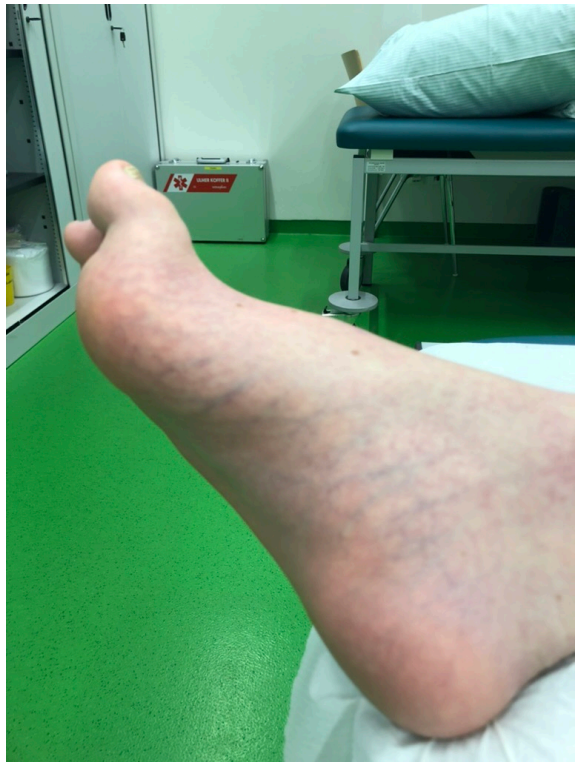


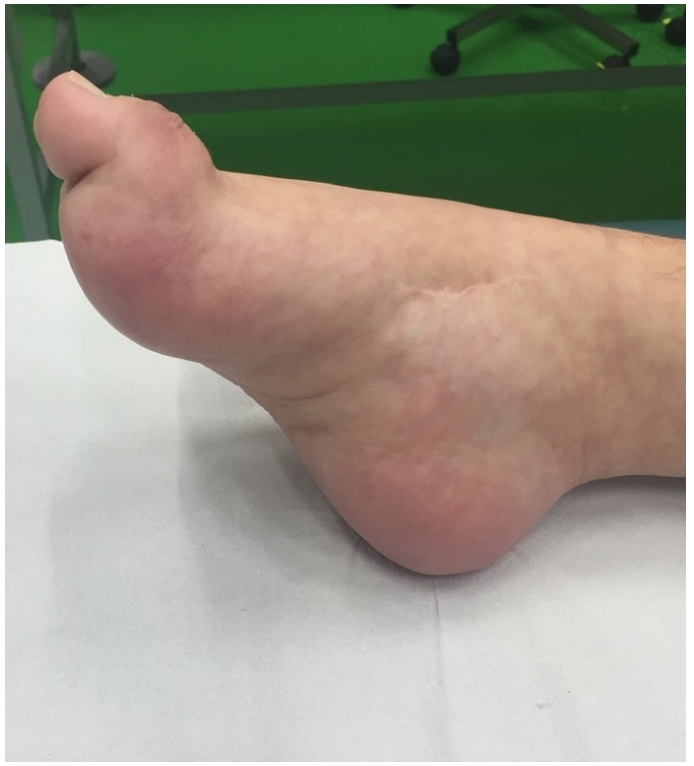
Musculoskeletal System

Feet deformities – clinical picture





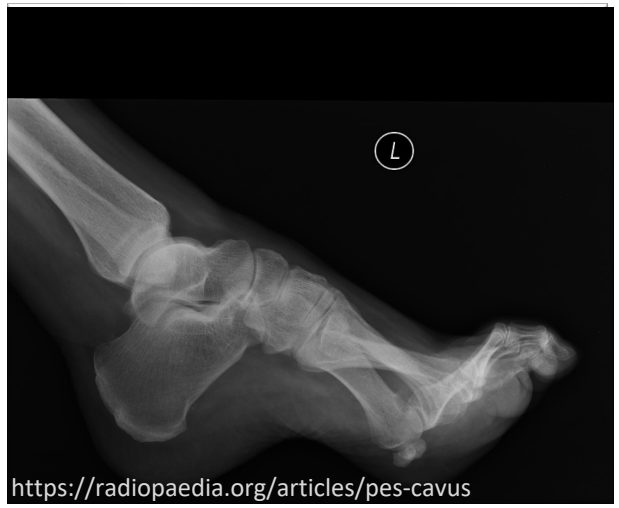




Right: pictures from FA patients at the Ataxia Outpatient Clinic, Department of Neurology, RWTH Aachen University Hospital

Musculoskeletal System

Feet deformities – background & treatment



Epidemiology

- 58% in 650 FA patients of the EFACTS registry[1]
  - 47 (7.2% had undergone surgery) [1]
  - Predictors: age at onset, SARA score; GAA repeat length on the shorter FXN allele (GAA1) and disease duration[1]
- Previous literature estimates 55%-90%[2-7]

Clinicial presentation

- pes cavus
- equinovarus deformities
- Often bilateral
  - Mechanical disadvantage
  - difficulties in locomotion, transfer and standing[8-10]

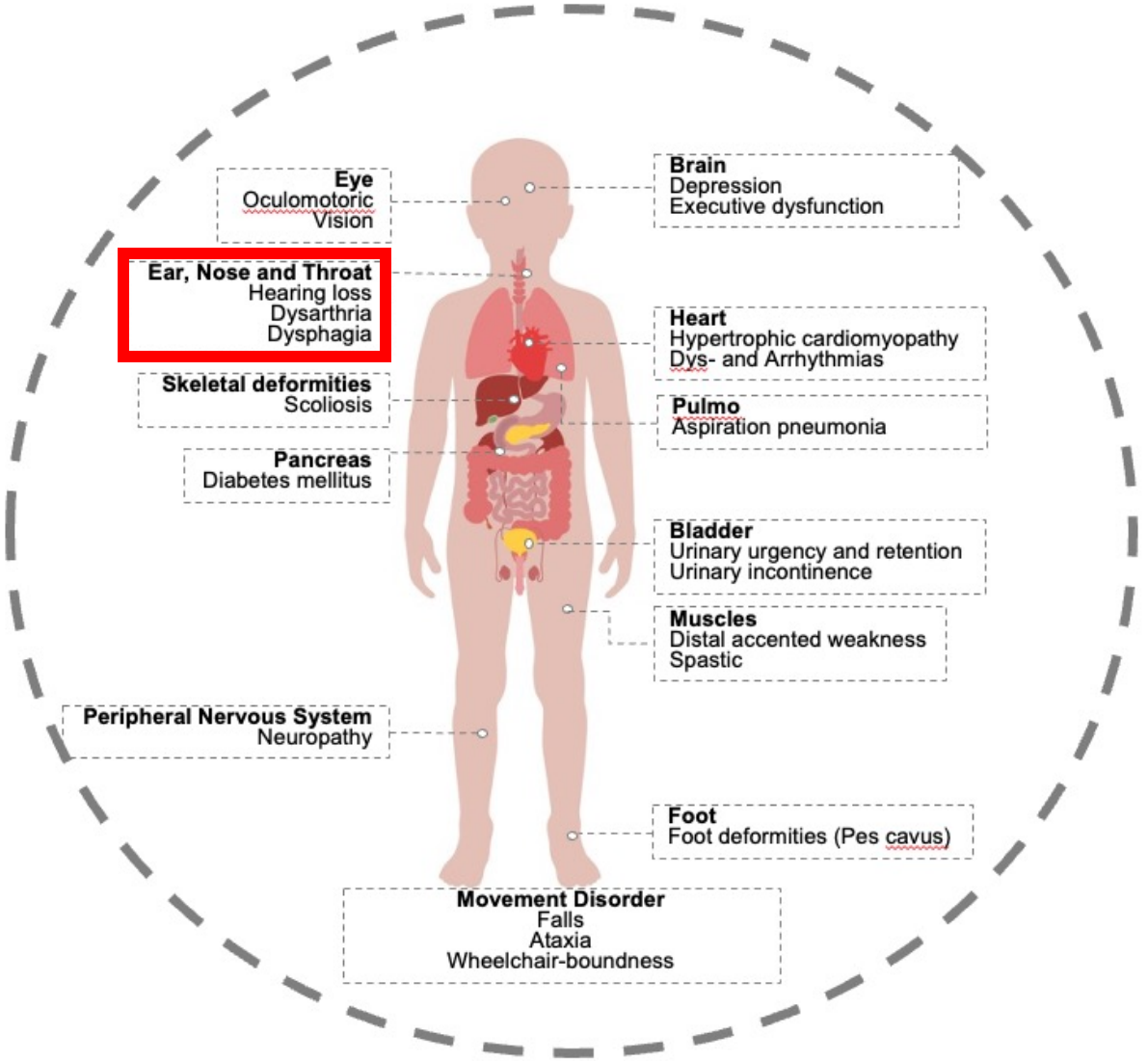
Treatment[12]

- Surgery
  - little evidence
- Orthotics (including ankle-foot orthotics, ankle braces and in-shoe orthotics)
- Physiotherapy
  - no data

Neuropathy: regular foot hygiene! !

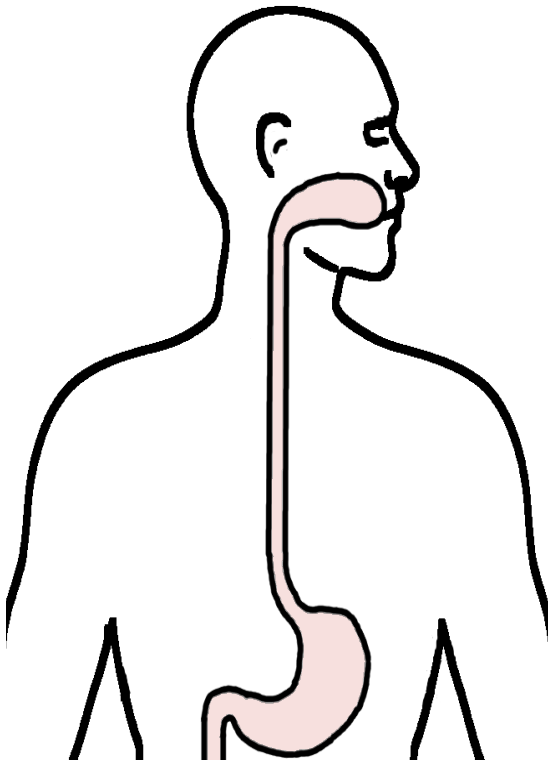
[1]Reetz et al., *Neurology* 2018; [2]Harding et al:, *Brain* 1981; [3]Filla et al.; *J Neurol* 1990; [4]Durr et al.; *NEJM* 1996; [5]Schols et al., *Brain* 1997; [6]Delatycki et al. *Am J Med Genet 1999;* [7]McCabe et al; *J Neurol* 2000; [8]Delatycki et al. *Clin Orthop Relat Res* 2005; [9]Keenan et al., *Foot Ankle Clin* 2011; [10]Maring et al; *Phys Ther.* 2007; [12] Corben et al., *Orphanet J Rare Dis 2022;* Clinical Manag. Guidelines for Friedreich Ataxie (https://www.curefa.org/research/clinical-care-guidelines)

Multisystem complex disease



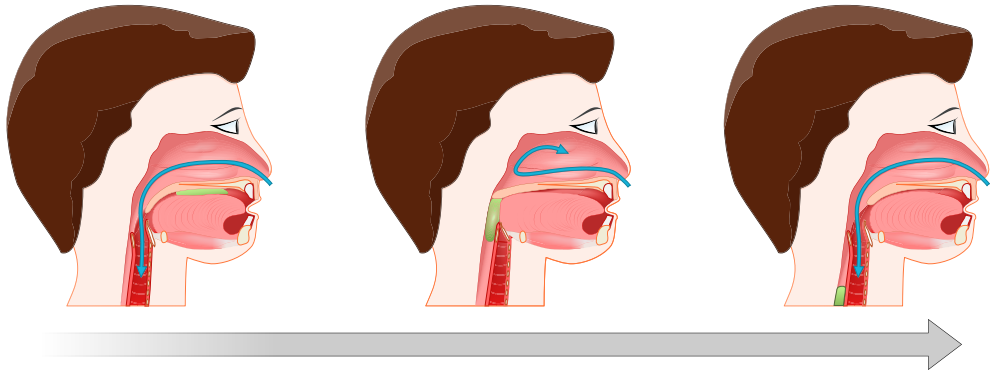
Dysphagia

Swallowing problem



Epidemiology

- In 650 FA patients of the EFACTS registry[1]
  - 68.7% reported dysphagia
  - dysphagia was more common in FA patients with typical onset that with late onset
- literature estimates up to 98%
- No relevant progression over 12 month
- Overall, less data



Symptoms of dysphagia

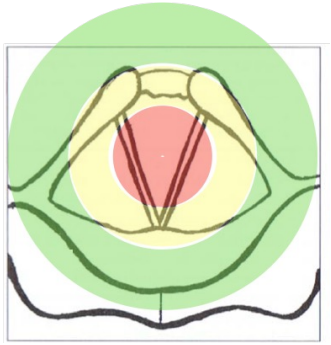
- Dribbling
- Difficulty chewing food
- Food pocketing in the mouth or sticking in the throat
- Coughing
- Choking during oral intake
- Nasal regurgitation
- Avoiding specific food or liquid consistencies
- Anxiety associated with oral intake
- Taking long time to complete meals
- Avoidance of social eating

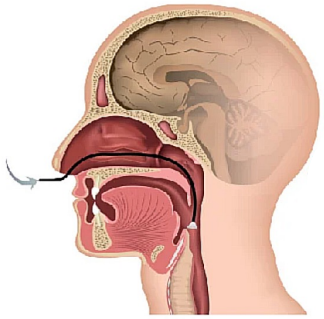
Reetz et al., *Neurology* 2018; Keage et al., Neuromuscular Disorders 2019; Keage et al., Dysphagia 2017; Vogel et al., J Neurol 2014; Corben et al., *Orphanet J Rare Dis 2022;* Clinical Management Guidelines for Friedreich Ataxie (https://www.curefa.org/research/clinical-care-guidelines); Management of the ataxias towards best clinical practice (https://www.ern-rnd.eu/wp-content/uploads/2023/07/Final-guideline-AtaxiaUK_english.pdf)

Dysphagia

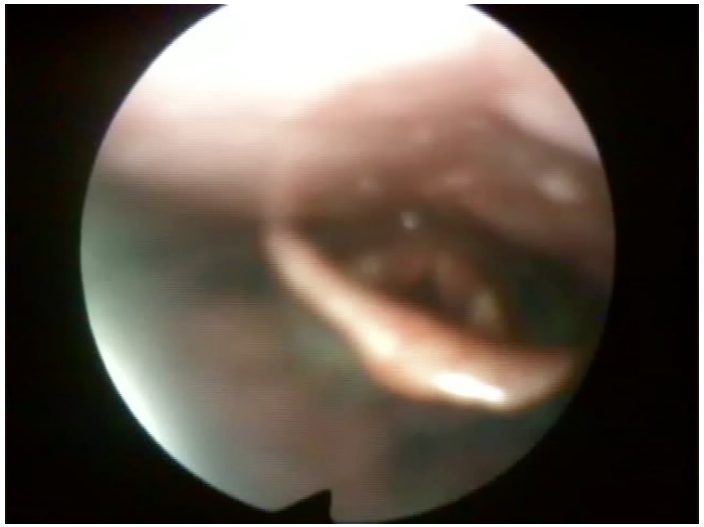
Case Report

– fiberoptic endoscopic evaluation of swallowing (FEES)





Jan 2023



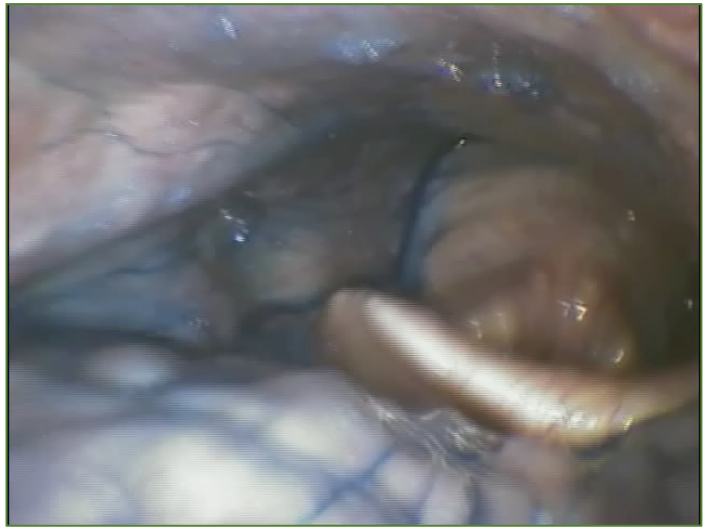
FEES: moderate oropharyngeal dysphagia with silent aspiration of fluid and sometimes high pharyngeal retention of solid food

Treatment

functional dysphagia therapy;

exspiratory muscle strength training

Jun 2023



FEES report: mild oropharyngeal dysphagia with slightly increased risk of aspiration of liquids

Dysphagia & Dysarthria

Treatment

Best Practice Statement

Dysphagia

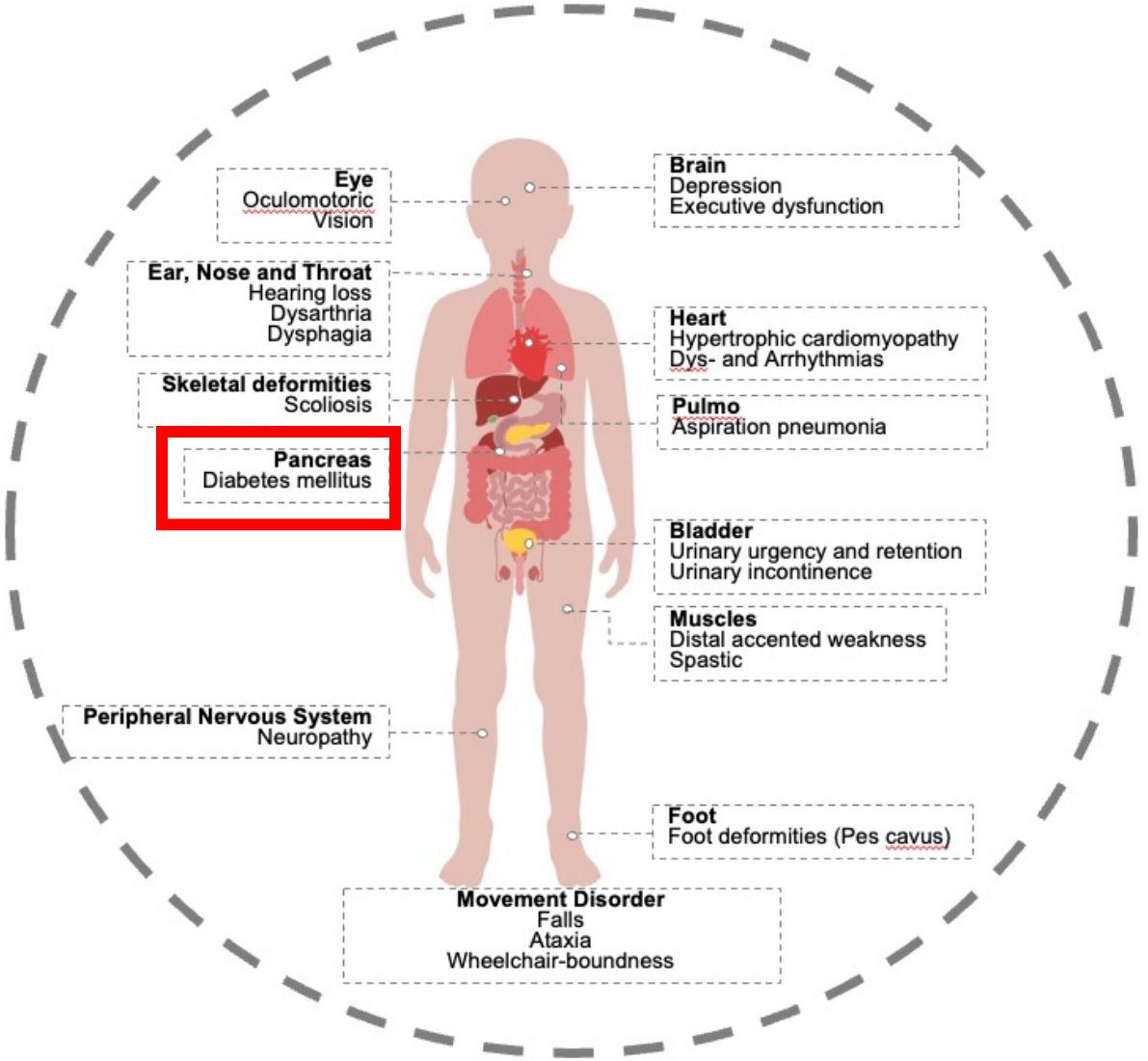
- Individuals with Friedreich ataxia who are experiencing difficulties in swallowing should be offered detailed expert counselling on dysphagia management strategies.

Dysarthria

- Targeted intensive behavioral therapy for improving speech in individuals with dysarthria is recommended.

Corben et al., *Orphanet J Rare Dis 2022;* Clinical Management Guidelines for Friedreich Ataxie (https://www.curefa.org/research/clinical-care-guidelines)

Multisystem complex disease



Endocrine and metabolism

Diabetes

Diabetes

Epidemiology
- Prevalence varies between 5% and 40%

Symptoms
- hyperglycemia (polyuria, polydipsia, unexplained weight loss)

Recommendation
- annual screening for diabetes mellitus with HbA1c and fasting plasma glucose in children and adults with Friedreich ataxia

Nutritional Status

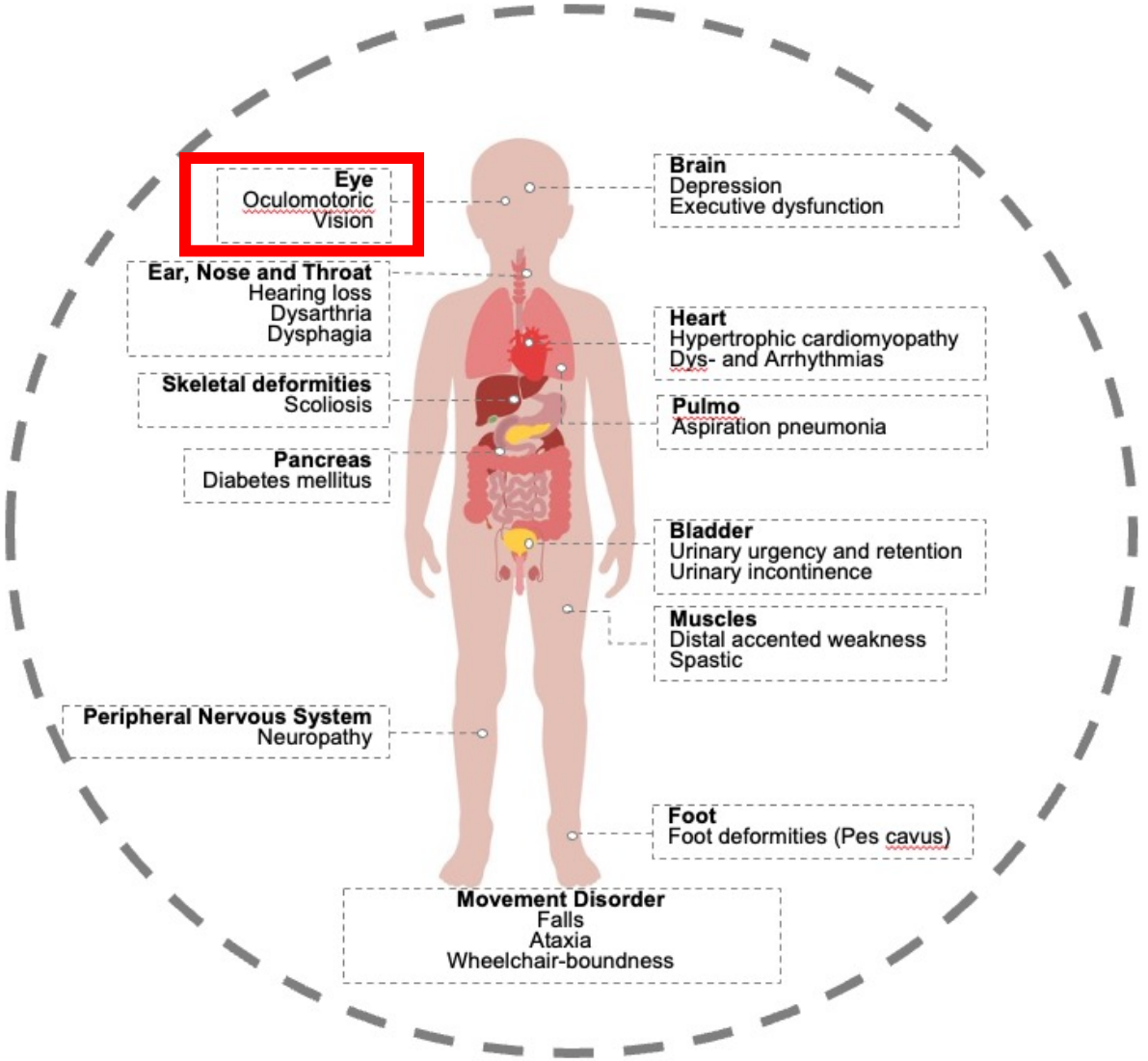
Epidemiology
- FACOMS: 17% of children were underweight and 33% of adults were overweight or obese

Measures
- Body mass index

Recommendation
- annual assessment of height, weight, and BMI

Reetz et al., *Neurology* 2018; Greeley et al., *J Neurol Sci* 2014; Hewer et al., *JNNP* 1968, McCormick et al., *ACTN* 2017; Patel et al.; *ACTN* 2016; Patel et al., Neurol Genet 2021; Corben et al., *Orphanet J Rare Dis 2022;* Clinical Management Guidelines for Friedreich Ataxie (https://www.curefa.org/research/clinical-care-guidelines)

Multisystem complex disease



Vision, Oculomotor & Auditory function

Vision & Oculomotor

Epidemiology

- EFACTS: abnormal eye movements (90.5%); accommodation and refraction disorders (36.8%); blindness and low vision 3.1%

Symptoms

- loss of peripheral vision, color vision, central vision
- optic atrophy, square wave jerks, and difficulty with fixation

Recommendation

- Evaluation by a low vision specialist when vision worsening

Auditory function

Epidemiology

- EFACTS: hearing loss 10.9%

Symptoms & dysfunction

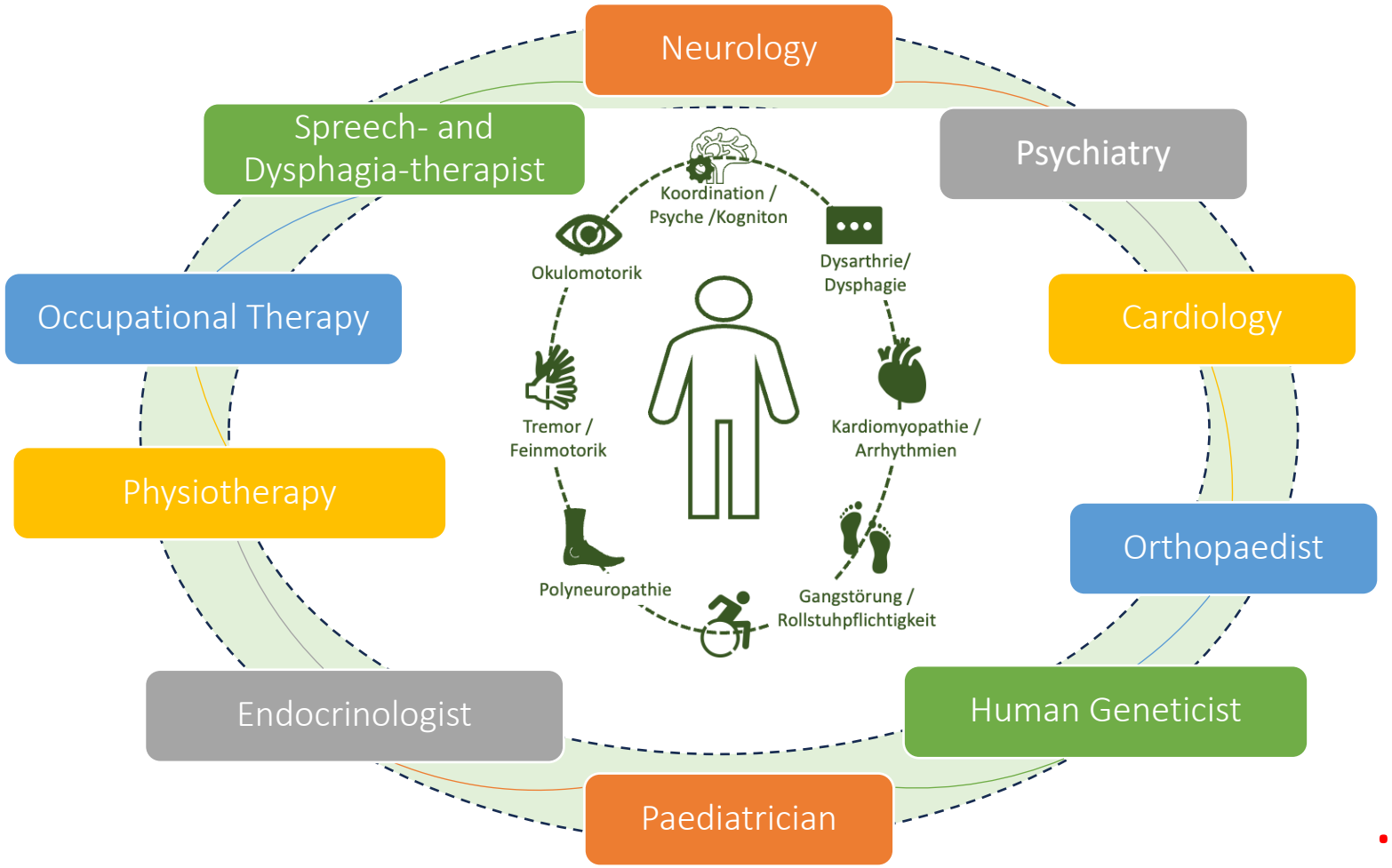
- auditory neuropathy and abnormal perception of complex signals including speech

Recommendation

- Evaluation on an annual basis or more regularly if a change in auditory performance or balance is noticed

Reetz et al., *Neurology* 2018; Corben et al., *Orphanet J Rare Dis 2022;* Clinical Management Guidelines for Friedreich Ataxie (https://www.curefa.org/research/clinical-care-guidelines)

Interdisciplinary approach



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)

Question 3

Which answers are correct? (Multiple choice)

a. Electrical abnormalities such as T-inversion or flattening are often found in the electrocardiogramm in patients with Friedreich ataxia.
b. Palpitations, dyspnoe or chest discomfort can be symptoms of cardiomyopathy.
c. Almost all patients with Friedreich ataxia have diabetes mellitus.
d. Some patients with Friedreich ataxia show typically triple scoliosis curves on X-rays.
e. Individuals with Friedreich ataxia who are experiencing difficulties in swallowing should be offered detailed expert counselling on dysphagia management strategies.

Recommended best practice based on clinical experience and expert opinion

Symptomatic treatments

- Muscle spasticity, spams & joint contractures
- Dystonia
- Scoliosis
- Pain
- Cardiac involvement
- Bladder problems
- Gastroenterological problems
- Swallowing & dysphagia
- Nutrition
- Hearing
- Vision
- Cognition & Depression

Health professional interventions

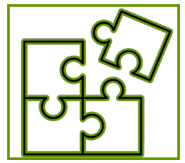
Physiotherapy

- recommended at an early stage in order to establish strategies to maintain function
  - exercise*, coordination, balance, strength

*in patients with cardiac complications, exercise program should be coordinated with the cardiologist

Speech and language therapy

- recommended for difficulties with communication and/or swallowing



Occupational therapy

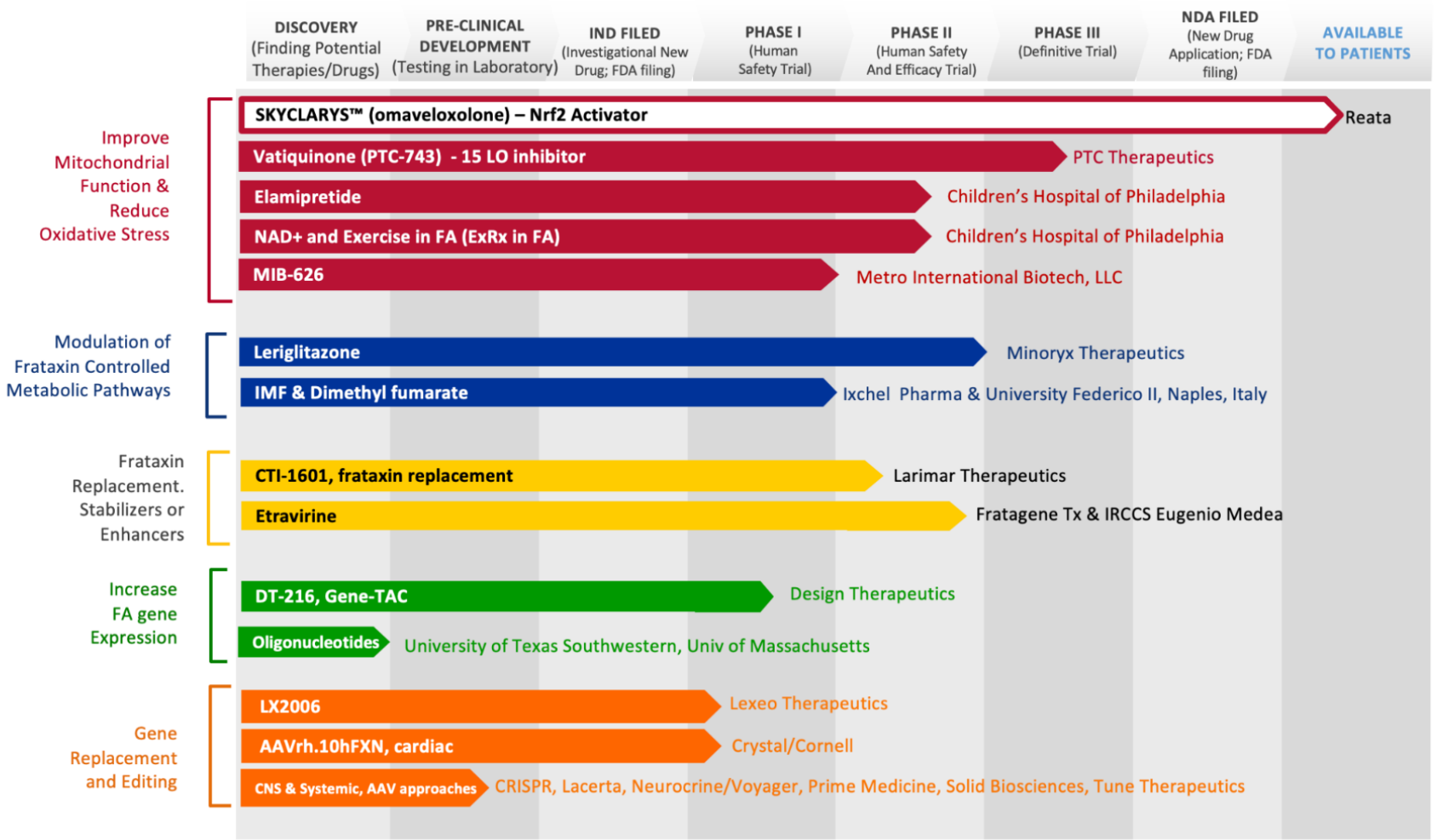
- recommended to maintain everyday activities

Assistive devices

Palliative Care

Management of the ataxias towards best clinical practice (https://www.ern-rnd.eu/wp-content/uploads/2023/07/Final-guideline-AtaxiaUK_english.pdf); Corben et al., *Orphanet J Rare Dis 2022;* Clinical Management Guidelines for Friedreich Ataxie (https://www.curefa.org/research/clinical-care-guidelines)

Treatment Pipeline



FARA Friedreich's Ataxia Research Alliance

https://www.curefa.org/images/research/FAtreatmentPipeline-June2023.png)

Omaveloxolone

FEBRUARY 28, 2023

SKYCLARYS™ (omaveloxolone) is an oral, once-daily medication indicated for the treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older in the U.S.

SKYCLARYS has received Orphan Drug, Fast Track, and Rare Pediatric Disease Designations from the FDA. Additionally, the company's Marketing Authorization Application for omaveloxolone is under review in Europe by the European Medicines Agency (EMA). The European Commission has granted Orphan Drug designation in Europe to omaveloxolone for the treatment of Friedreich's ataxia.

In Germany, a compassionate use programm has been approved by the Federal Institute for Drugs and Medical Devices (BfARM) in Germany.

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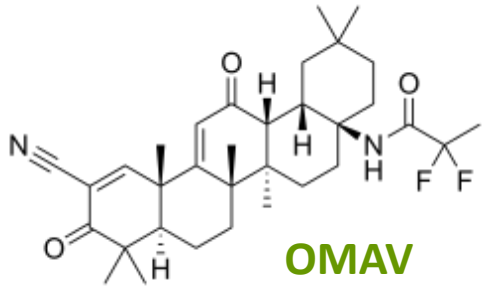
Omaveloxolone



OMAV

Increasing

Improve

Nrf2

mitochondrial function

reducing oxidative stress

preventing lipid peroxidation

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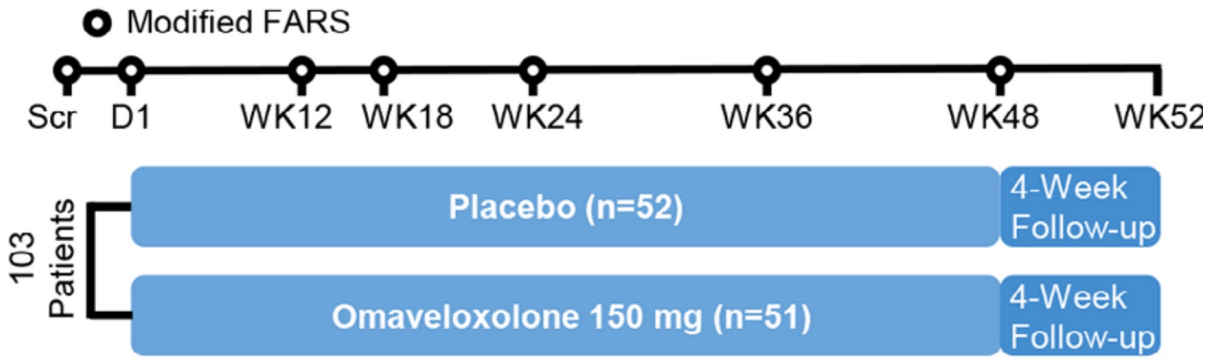
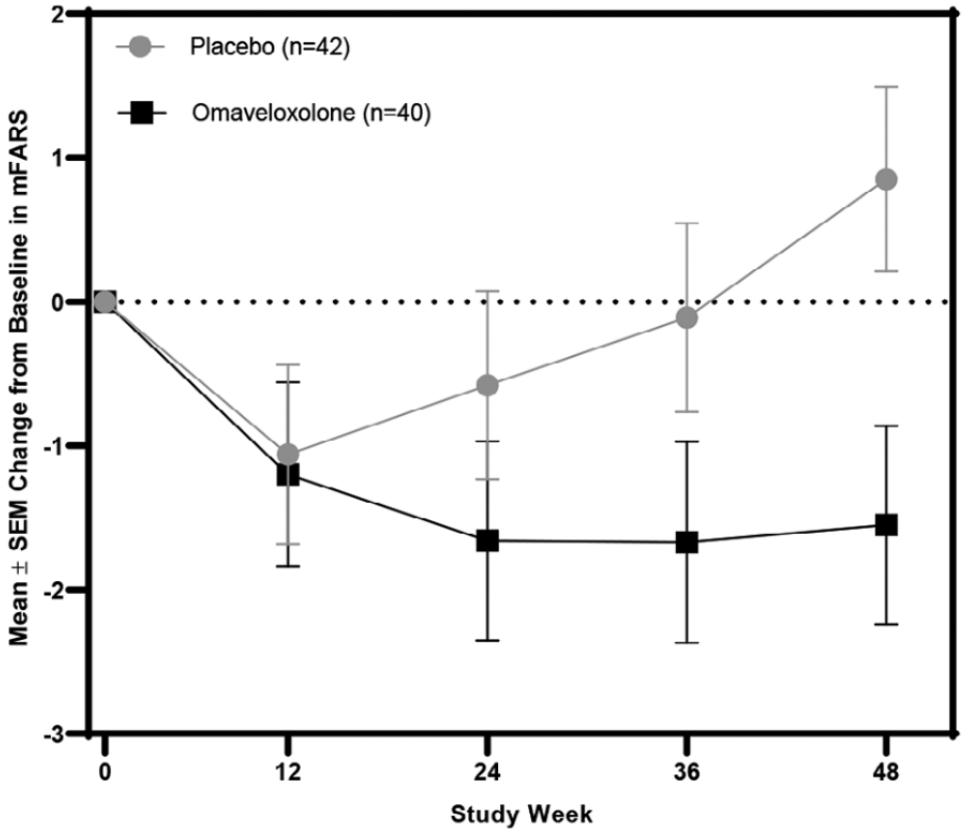
Omaveloxolone

48-week randomized, placebo-controlled, and double-blind study



Study schema for the MOXIe Part 2



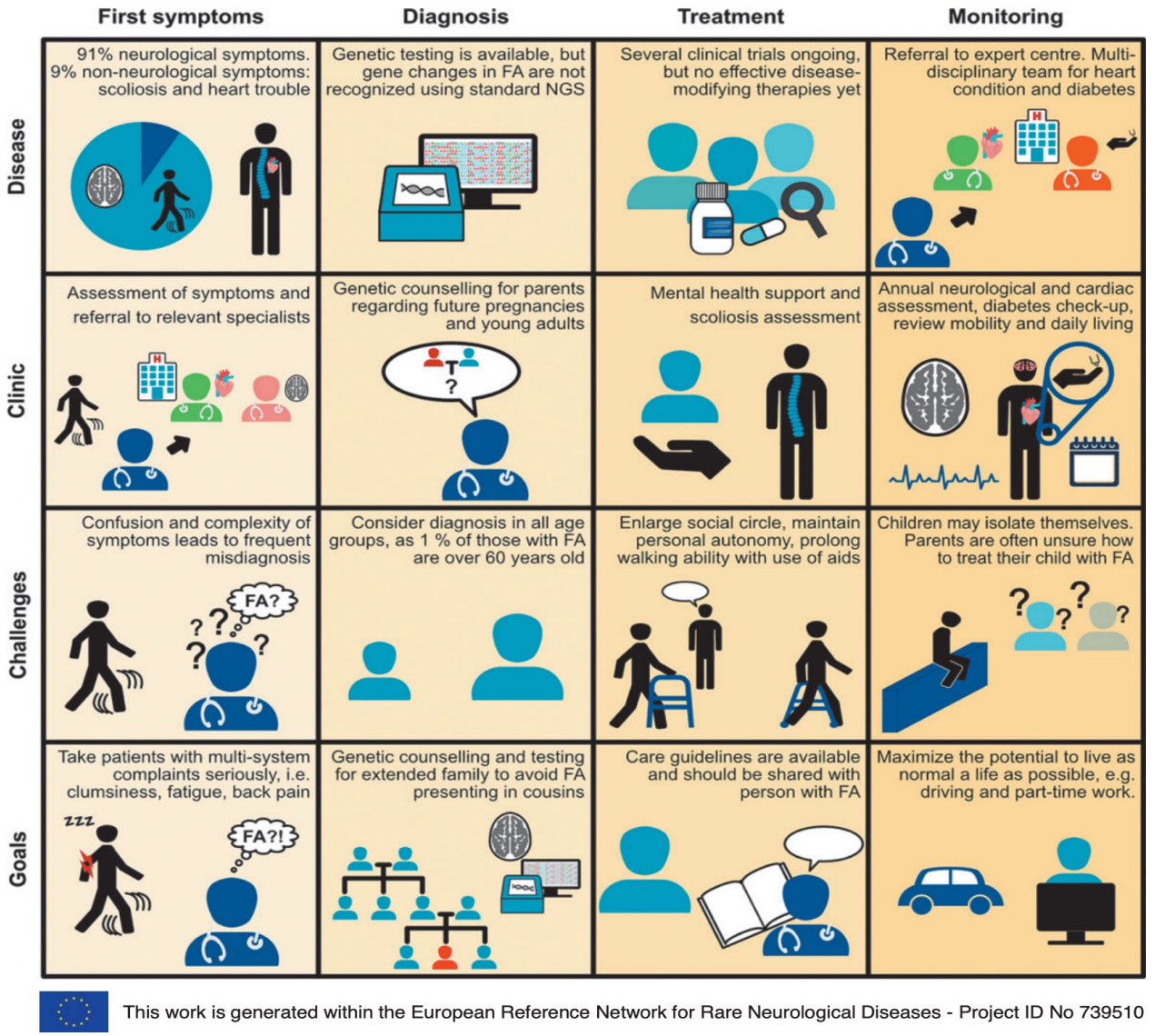
Mean changes from baseline in modified Friedrich's Ataxia Rating Scale (mFARS) score over time in the full analysis set (FAS) for patients randomized to omaveloxolone (n = 40) or placebo (n = 42).

Lynch et al., *Ann Neurol* 2021

More information

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

FARA Friedreich's Ataxia Research Alliance



https://www.ern-rnd.eu; https://www.curefa.org/

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)

Key conclusions

- Friedreich ataxia is a multisystem complex neurodegenerative disease.
- Neurological progression can be measured with clinical and functional rating scales.
- Non-neurological co-morbidities are of critical importance and need to be monitored as well on an annual basis and/or when symptoms occur, in particular screening and/or monitoring for cardiomyopathy, neuromuscular symptoms and diabetes mellitus.
- To learn more about rare diseases, we need natural history studies and research in order to enable better care and treatment for patients with Friedreich ataxia and their families.