



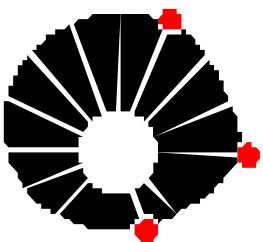
# Imaging biomarkers in recessive ataxias

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# Disclosures

- I am principal investigator in a clinical trial for Friedreich's ataxia (sponsored by PTC)
- Research grants:

FAPESP

CNPq

FARA

# Objectives

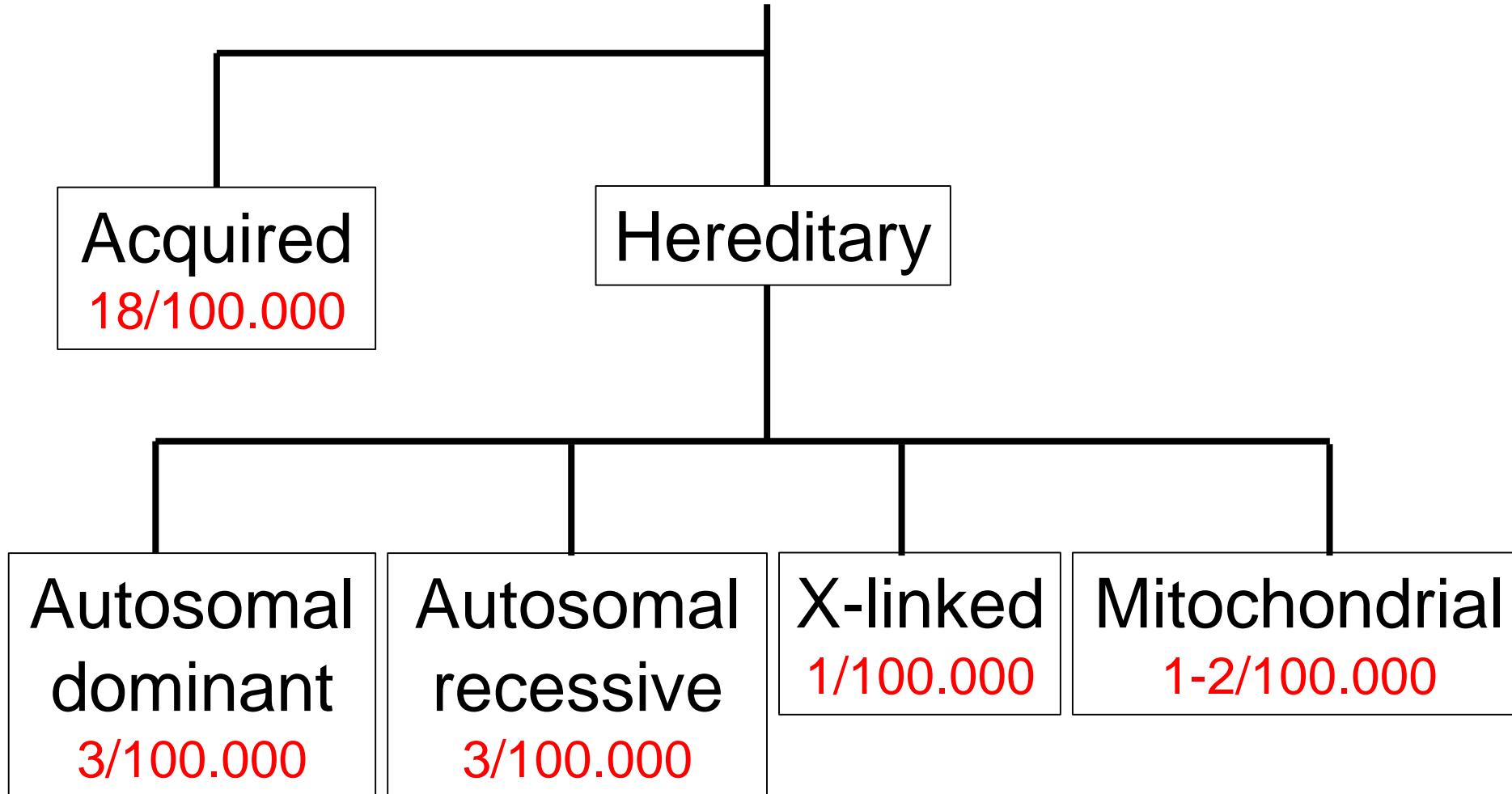
- To discuss imaging biomarkers in autosomal recessive ataxias:

Challenges

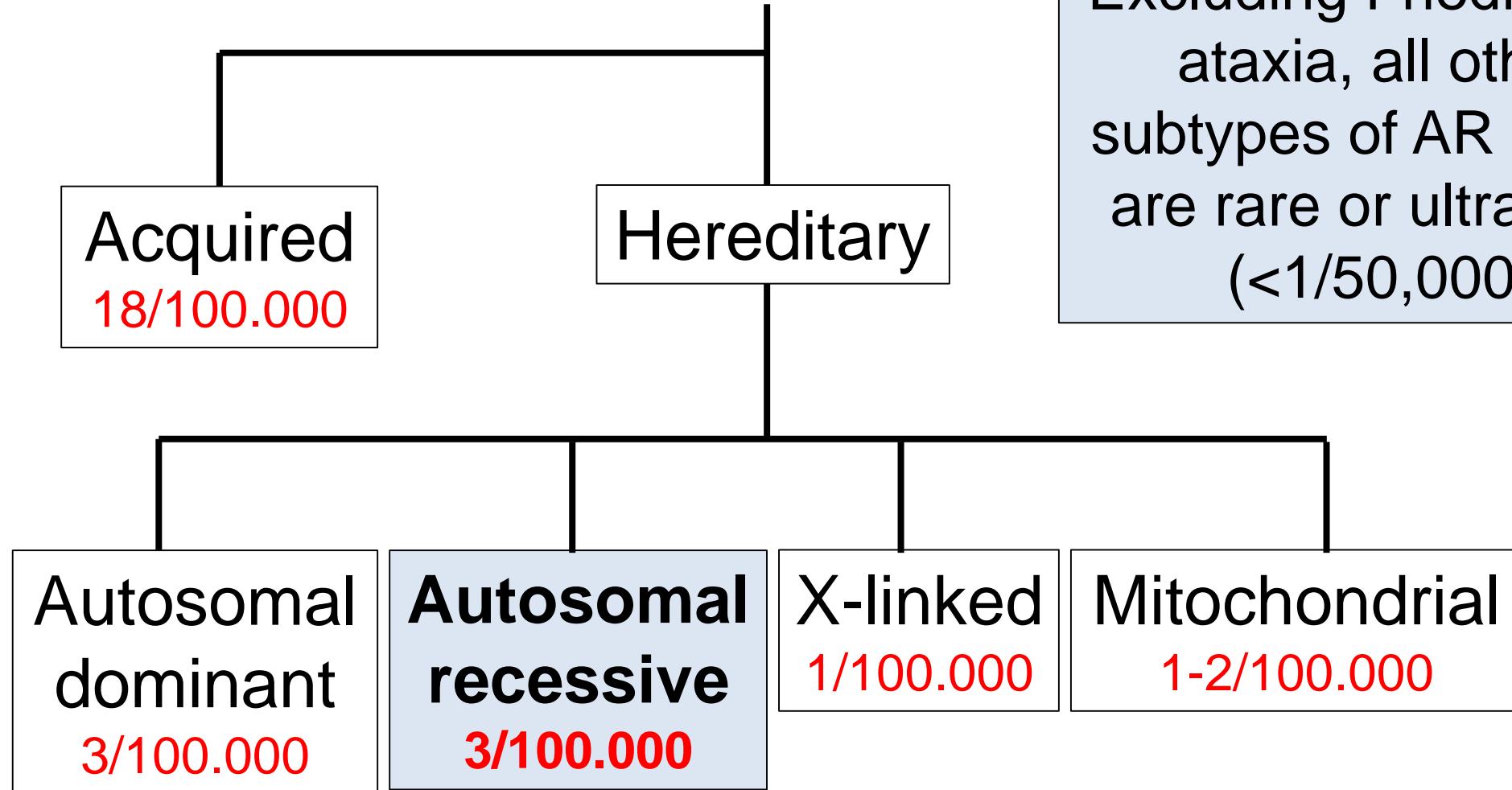
Current scenario (available data)

Unmet needs and future directions

# Ataxias



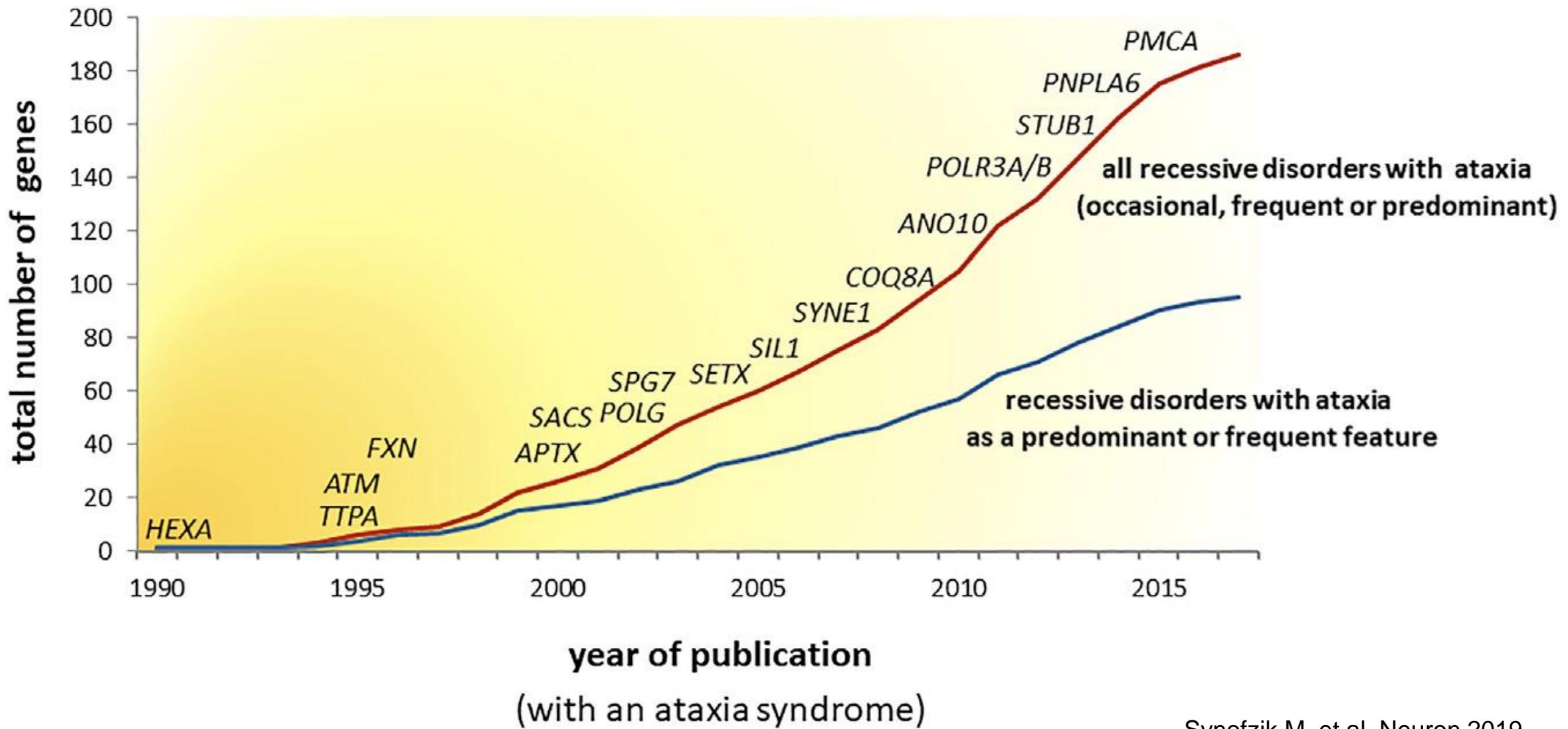
# Ataxias



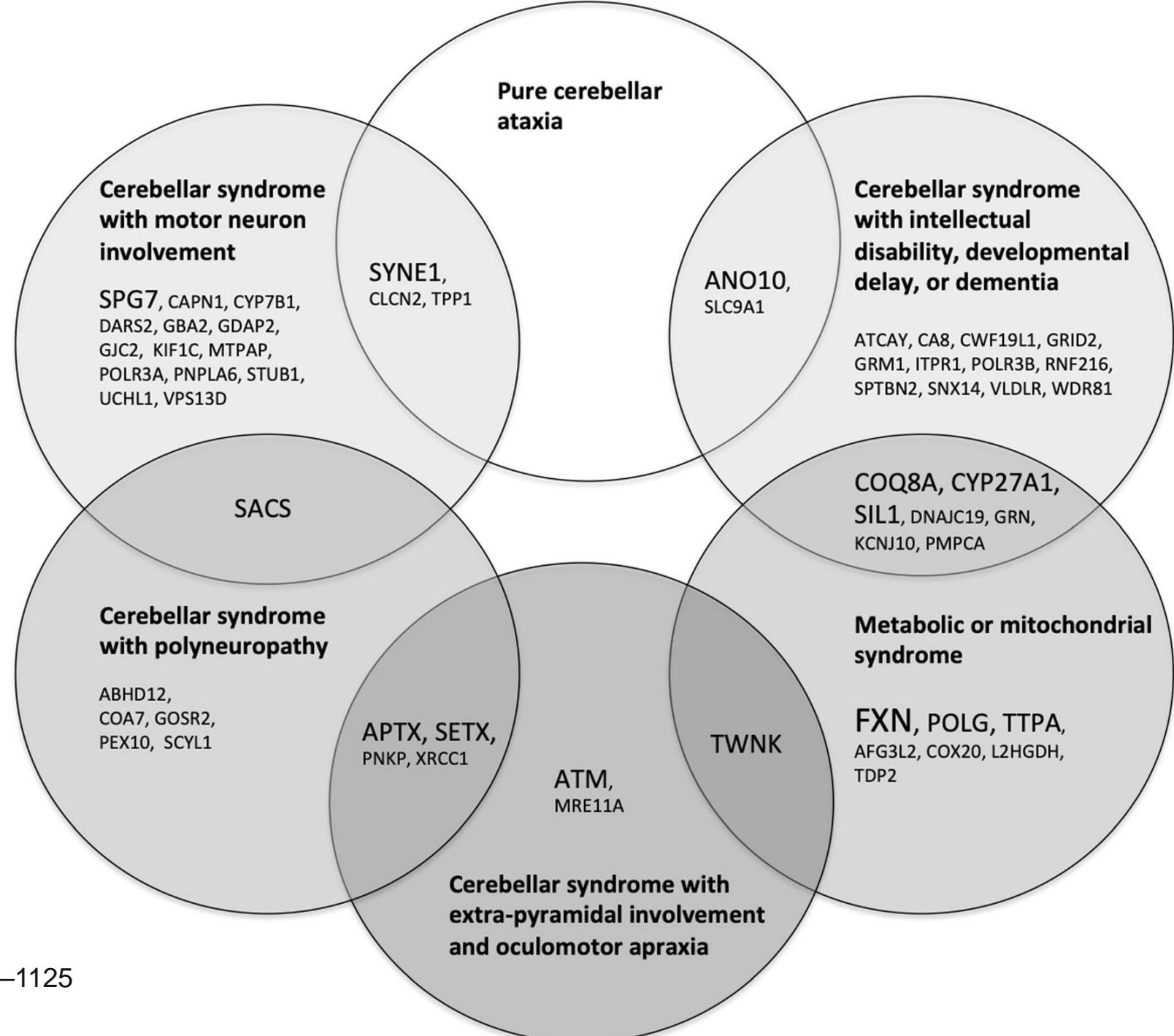
11% of all ataxias

Salman MS. Cerebellum 2018;17:4-11.

# AR ataxias: Genotypic heterogeneity

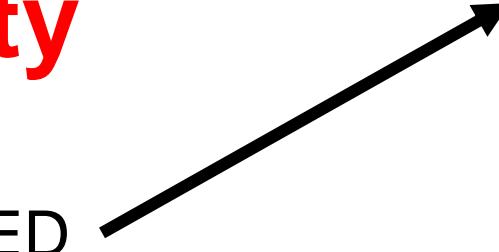


# AR ataxias: Phenotypic heterogeneity



# AR ataxias: Radiological heterogeneity

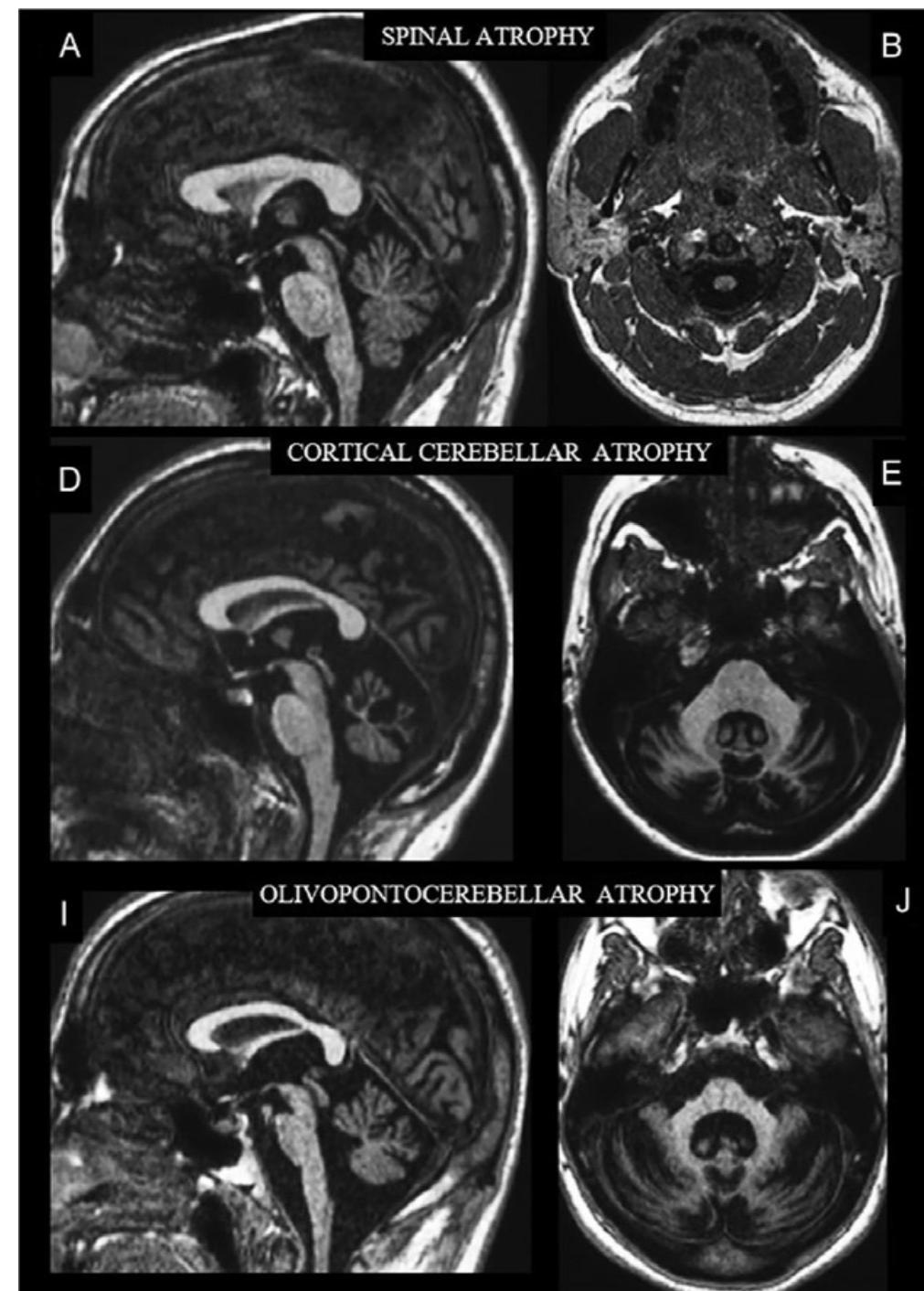
Friedreich's ataxia, AVED



Ataxia-telangiectasia



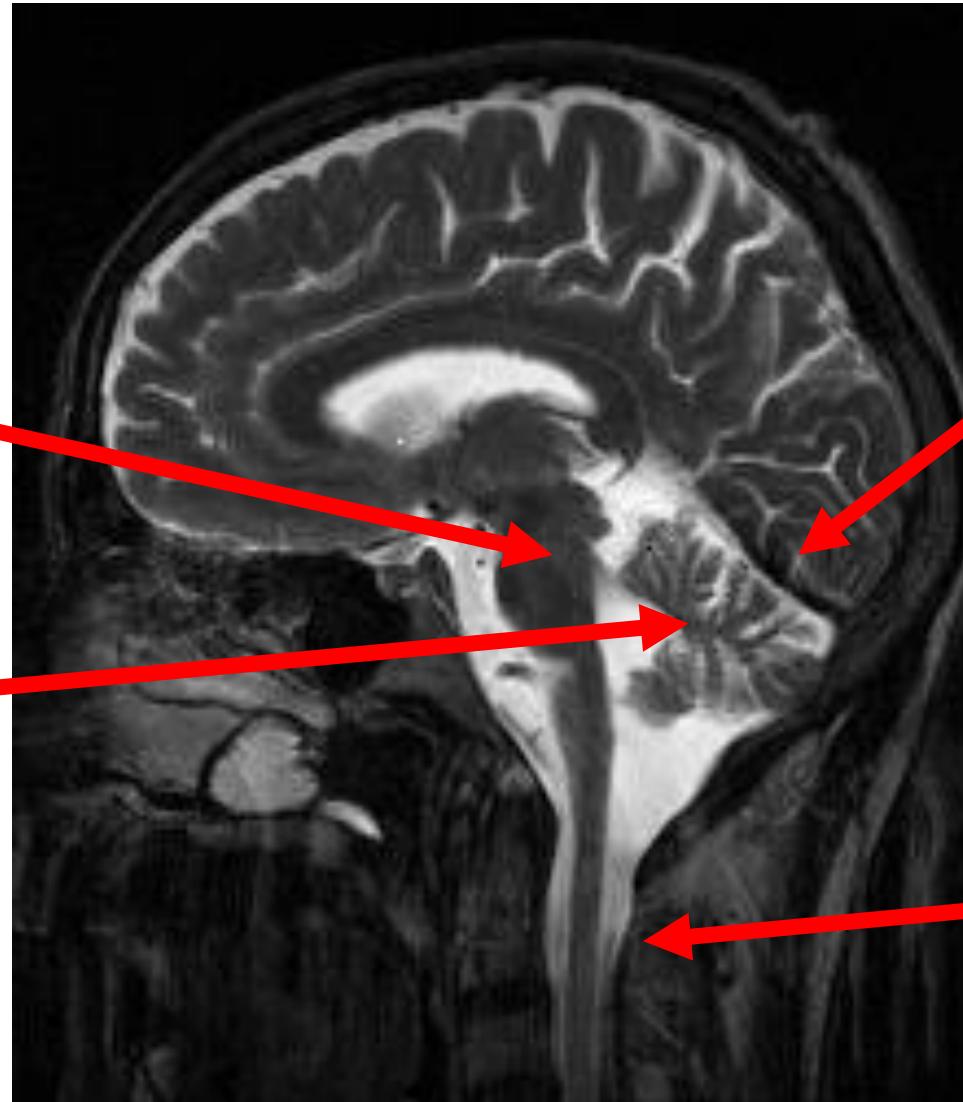
Congenital ataxias (PCH)



# AR ataxias: Candidate imaging biomarkers

**DTI**  
(Cerebellum / brainstem)

**$^1\text{H}$ -MRS**  
(Cerebellum)

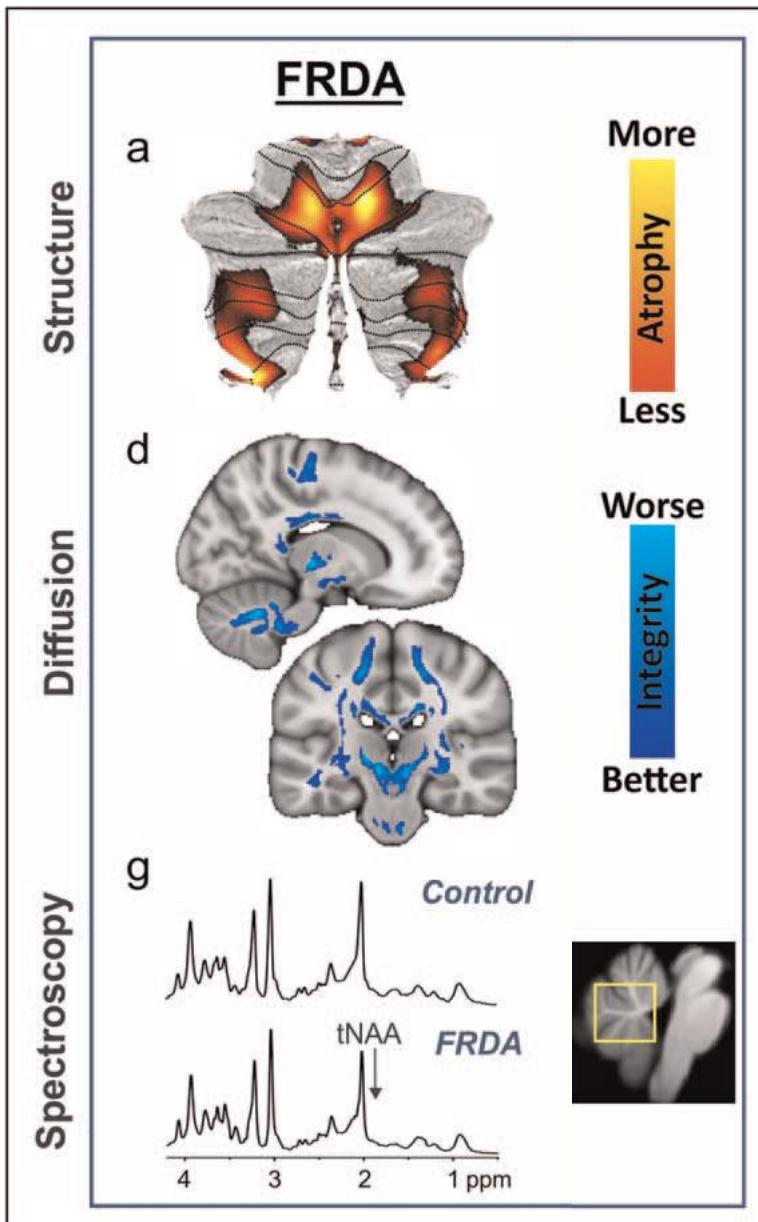


**Volumetry**  
(Cerebellum / brainstem)

**Morphometry**  
(Spinal cord)

# AR ataxias: Candidate imaging biomarkers

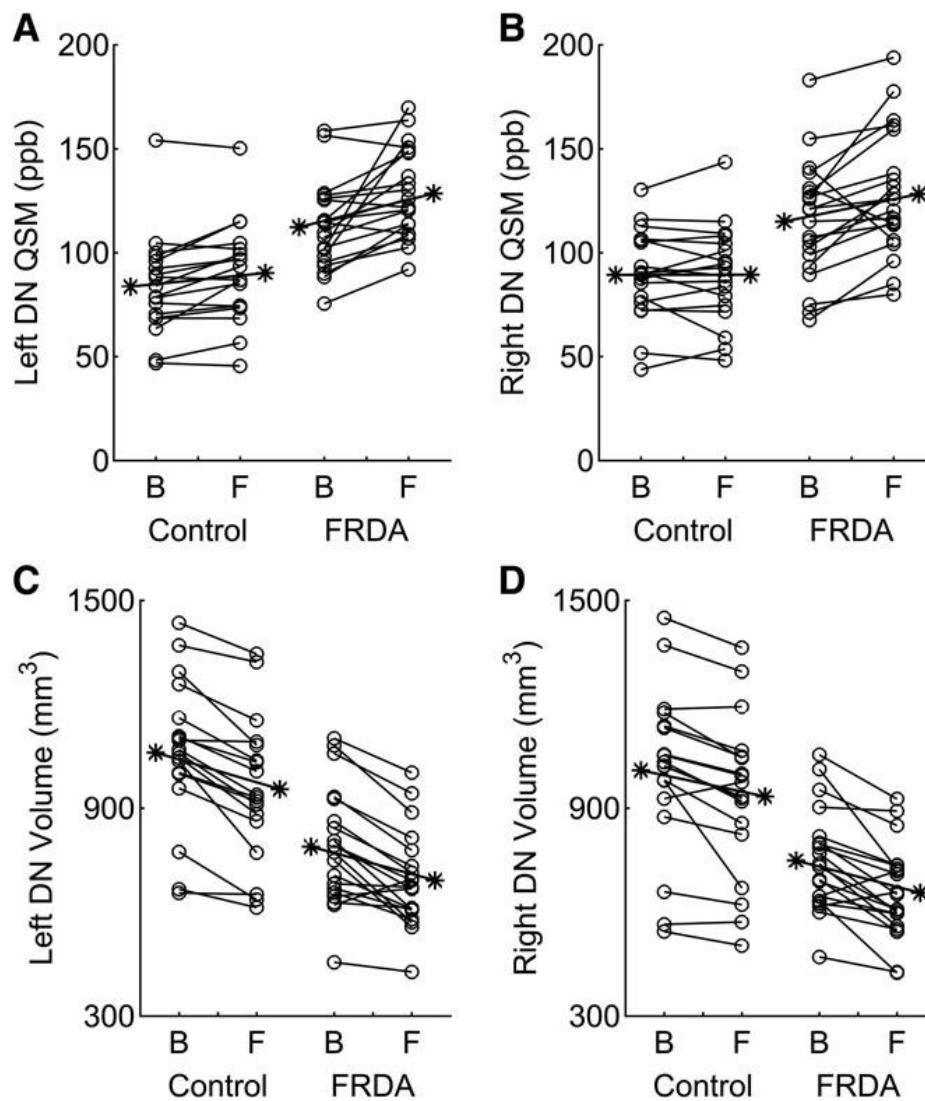
	Volumetry (Cerebellum/ brainstem)	DTI (Cerebellum/ brainstem)	<sup>1</sup> H-MRS (Cerebellum/ brainstem)	Morphometry (Spine)
Automated pipelines	+++	++	+/-	+/-
Availability	+++	++	+/-	+/-
Cross-sectional data	+++	++	+/-	+/-



# Quantitative Neuroimaging in AR ataxias

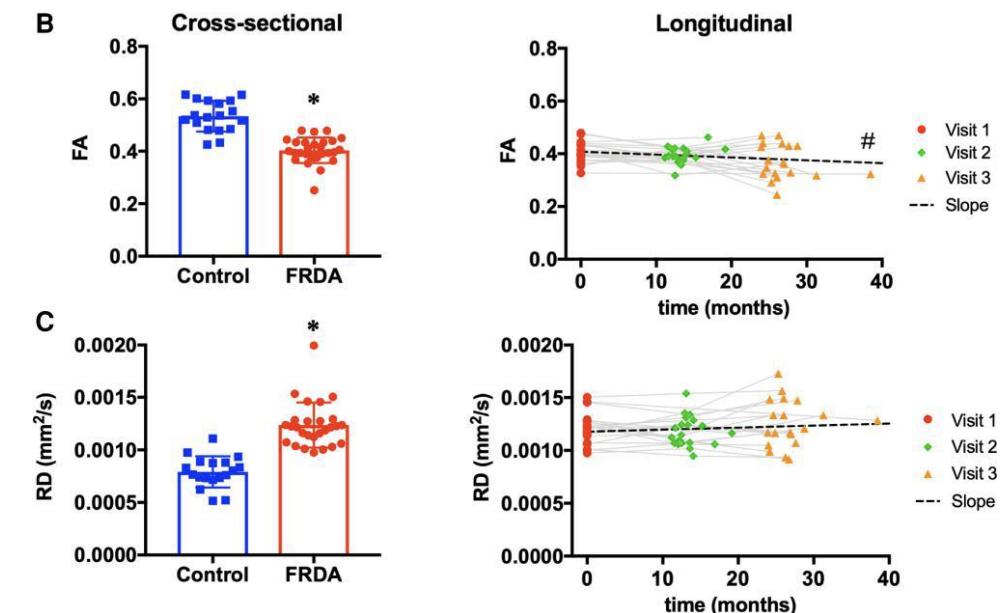
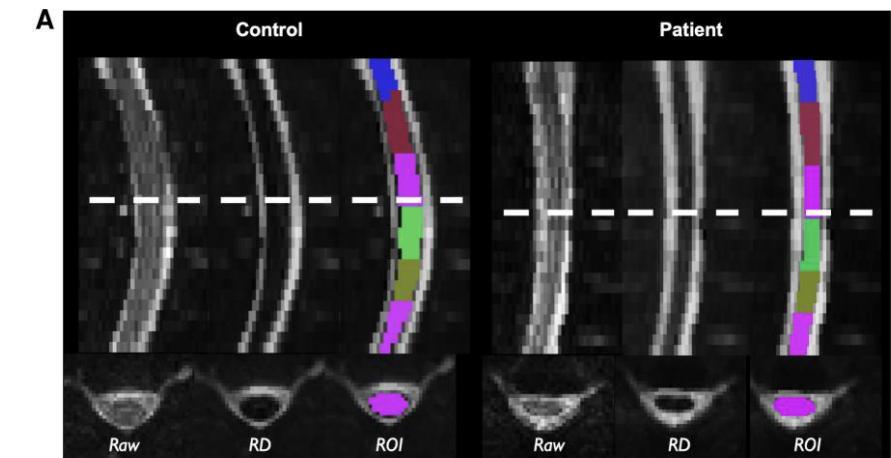
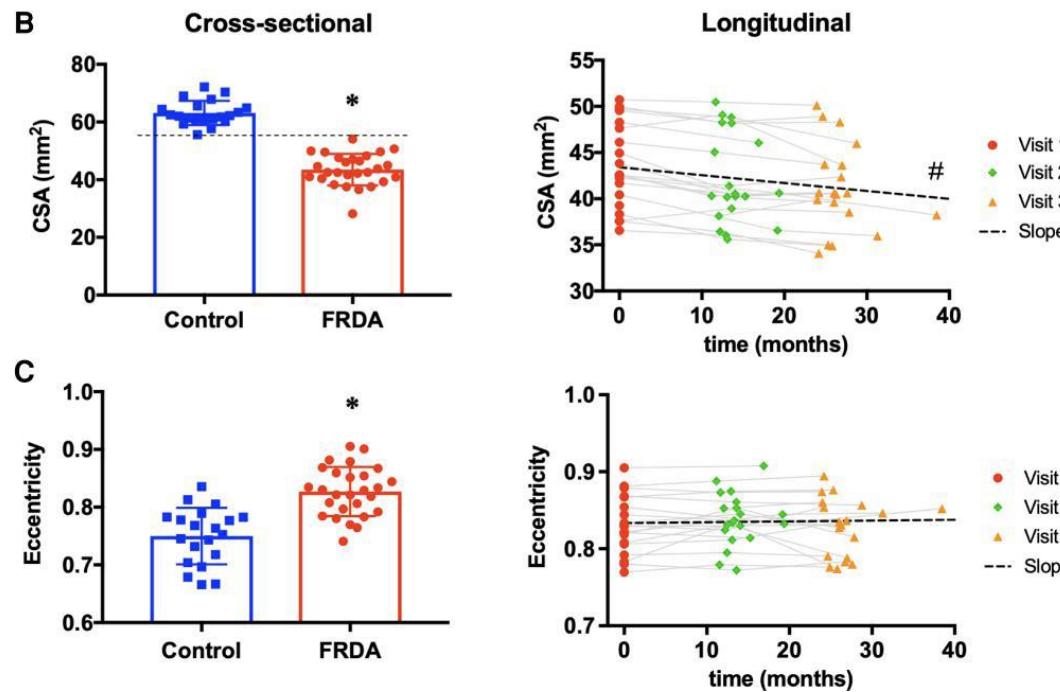
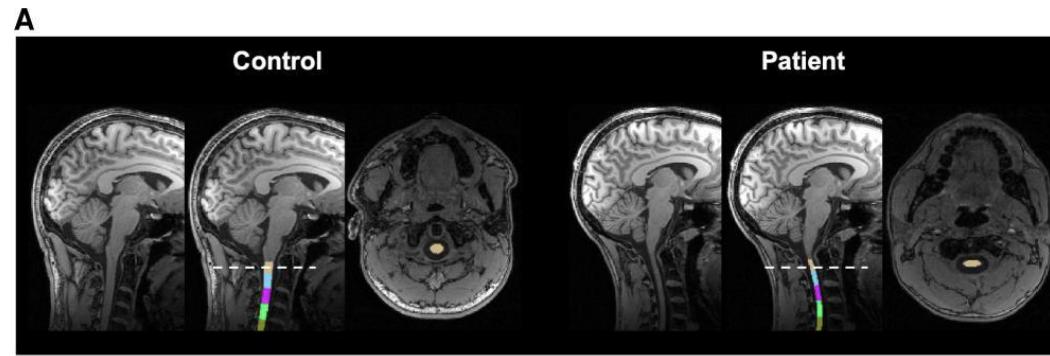
	Cross-sectional				Longitudinal
Ataxia (gene)	Volumetry (Cerebellum /brainstem)	DTI (Cerebellum /brainstem)	1H-MRS (Cerebellum /brainstem)	Morphometry (Spine)	Any technique
<i>FRDA</i>					
<i>ATM</i>					
<i>SPG7</i>					
<i>RFC1</i>					
<i>COQ8A</i>					
<i>SYNE1</i>					
<i>TTPA</i>					
<i>SACS</i>					

# Imaging biomarkers in FRDA: Dentate nuclei



		Cohen's d		P
QSM (ppb)	Baseline	L	1.3	<10 <sup>-3</sup>
		R	1.0	0.002
Follow-up		L	1.7	<10 <sup>-5</sup>
		R	1.4	<10 <sup>-4</sup>
Longitudinal (year <sup>-1</sup> )		L	0.7	0.02
		R	0.91	0.005
Volume (mm³)	Baseline	L	1.4	<10 <sup>-4</sup>
		R	1.3	<10 <sup>-3</sup>
Follow-up		L	1.5	<10 <sup>-4</sup>
		R	1.5	<10 <sup>-4</sup>
Longitudinal (year <sup>-1</sup> )		L	0.15	0.32
		R	0.38	0.13

# Imaging biomarkers in FRDA: Spinal cord



# Imaging biomarkers in FRDA: Spinal cord

	<b>Modality</b>	<b>CTRL mean (sd)</b>	<b>FRDA mean (sd)</b>	<b>Cohen's d</b>	<b>Difference (%)</b>	<b>Raw P</b>	<b>Corrected P</b>	
<b>CSA (mm<sup>2</sup>) (C2–C3)</b>	Morphometry	63.2 (4.2)	43.7 (5.5)	-3.9	-31%	$2 \times 10^{-17}$	$8 \times 10^{-17}$	***
<b>Eccentricity (C2–C3)</b>	Morphometry	0.75 (0.05)	0.83 (0.04)	1.7	10%	$5 \times 10^{-7}$	$5 \times 10^{-7}$	***
<b>CSA WM (mm<sup>2</sup>) (C2–C3)</b>	Morphometry	50.6 (3.8)	33.2 (5.1)	-4.2	-34%	$4 \times 10^{-17}$	$10^{-16}$	***
<b>CSA GM (mm<sup>2</sup>) (C2–C3)</b>	Morphometry	12.4 (0.5)	10.6 (0.7)	-3.0	-15%	$2 \times 10^{-13}$	$4 \times 10^{-13}$	***
<b>FA (C3–C6)</b>	Diffusion	0.53 (0.06)	0.40 (0.05)	-2.5	-24%	$3 \times 10^{-10}$	$10^{-9}$	***
<b>MD (C3–C6) (10<sup>-3</sup> mm<sup>2</sup>/s)</b>	Diffusion	1.17 (0.18)	1.58 (0.20)	2.1	35%	$7 \times 10^{-9}$	$10^{-8}$	***
<b>RD (C3–C6) (10<sup>-3</sup> mm<sup>2</sup>/s)</b>	Diffusion	0.79 (0.15)	1.24 (0.21)	2.3	56%	$6 \times 10^{-10}$	$2 \times 10^{-9}$	***
<b>AD (C3–C6) (10<sup>-3</sup> mm<sup>2</sup>/s)</b>	Diffusion	1.93 (0.28)	2.26 (0.19)	1.4	17%	$4 \times 10^{-5}$	$4 \times 10^{-5}$	***
<b>tNAA/mIns (C4–C5)</b>	Spectroscopy	1.16 (0.23)	0.56 (0.12)	-3.4	-52%	$4 \times 10^{-14}$	$2 \times 10^{-13}$	***
<b>tNAA (C4–C5) (mM)</b>	Spectroscopy	8.6 (1.6)	5.5 (1.0)	-2.4	-36%	$10^{-9}$	$6 \times 10^{-9}$	***
<b>mIns (C4–C5) (mM)</b>	Spectroscopy	7.6 (1.4)	10.4 (1.8)	1.7	37%	$8 \times 10^{-7}$	$2 \times 10^{-6}$	***
<b>tCr (C4–C5) (mM)</b>	Spectroscopy	4.9 (1.0)	5.1 (1.4)	0.2	5%	0.49	0.98	ns
<b>tCho (C4–C5) (mM)</b>	Spectroscopy	2.4 (0.5)	2.3 (0.6)	-0.2	-5%	0.53	0.98	ns

# Imaging biomarkers in Ataxia-telangiectasia

## Cerebellar volumetry

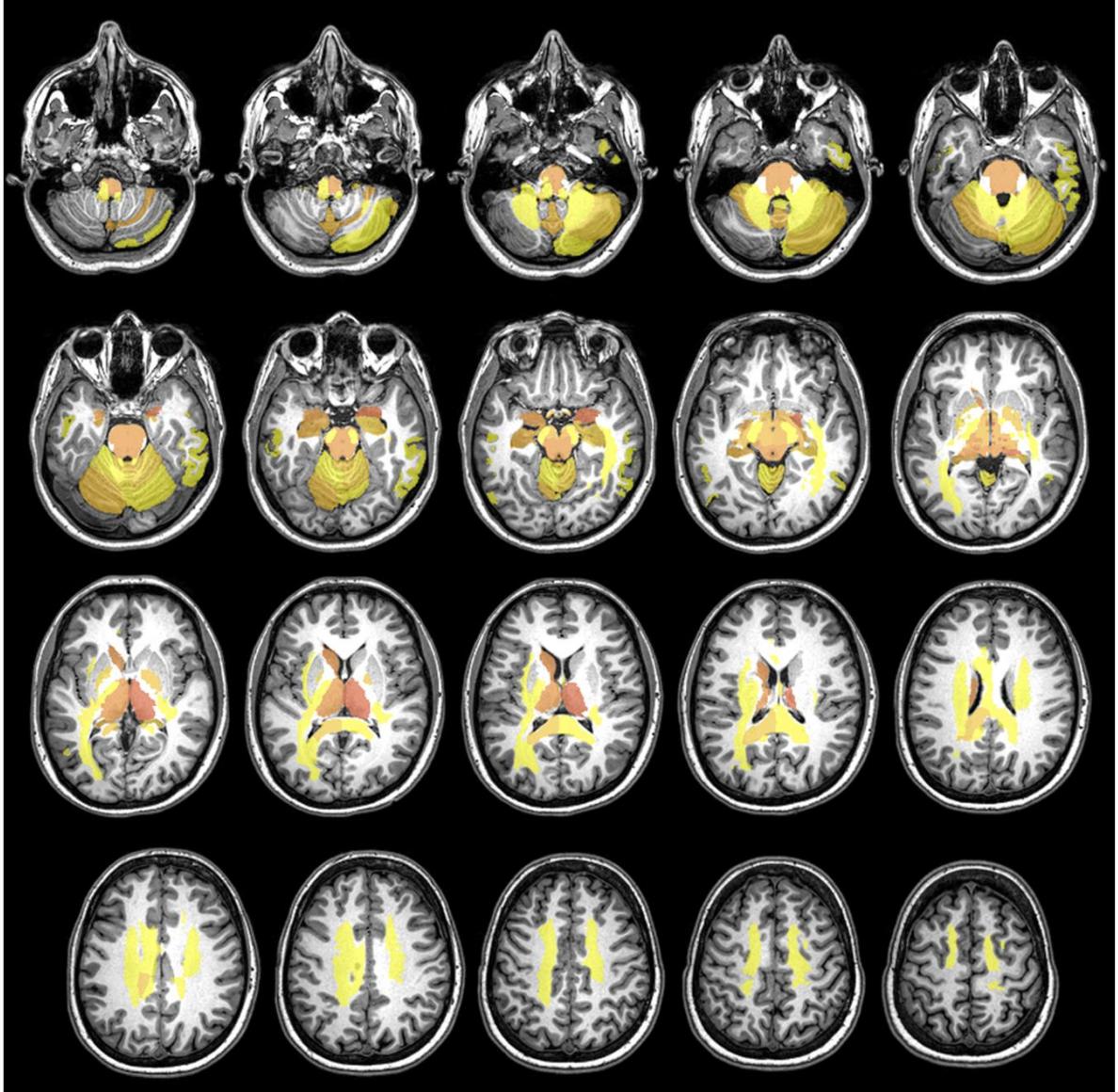
	A-T group		Healthy controls		Independent samples T-Test (two tailed)	
	Mean	S.D.	Mean	S.D.	t	P
Fractional total cerebellar volume	5.3%	0.9%	8.7%	0.5%	-15.80	$2.8 \times 10^{-19}$
Fractional cerebellar hemisphere grey matter volume	3.5%	0.6%	6.0%	0.4%	-15.71	$3.4 \times 10^{-19}$
Fractional cerebellar hemisphere white matter volume	1.5%	0.3%	2.1%	0.3%	-7.07	$1.2 \times 10^{-8}$
Fractional vermis lobule I-V volume	0.15%	0.03%	0.28%	0.03%	-13.73	$4.0 \times 10^{-17}$
Fractional vermis lobule VI-VII volume	0.06%	0.01%	0.11%	0.02%	-9.06	$2.0 \times 10^{-11}$
Fractional vermis lobule VIII-X volume	0.10%	0.03%	0.18%	0.02%	-11.43	$1.8 \times 10^{-14}$
Fractional 4th ventricular volume	0.19%	0.04%	0.13%	0.04%	5.23	$5 \times 10^{-6}$

## Cerebellar Spectroscopy

	A-T group		Healthy controls		Mann-Whitney U
	Median	Range	Median	Range	P
tNAA/tCr	0.99	0.91–1.39	1.11	1.02–1.17	0.002
tCho/tCr	0.30	0.19–0.34	0.27	0.24–0.29	0.007
Ins/tCr	0.65	0.55–0.83	0.62	0.56–0.68	0.118
Glx/tCr	0.48	0.43–0.66	0.54	0.49–0.65	0.037
GSH/tCr	0.11	0.07–0.17	0.12	0.11–0.13	0.118
tNAA/tCho	3.22	2.83–7.35	4.23	3.71–4.58	0.002

Dineen RA, et al. NeuroImage:  
Clinical 25 (2020) 102110

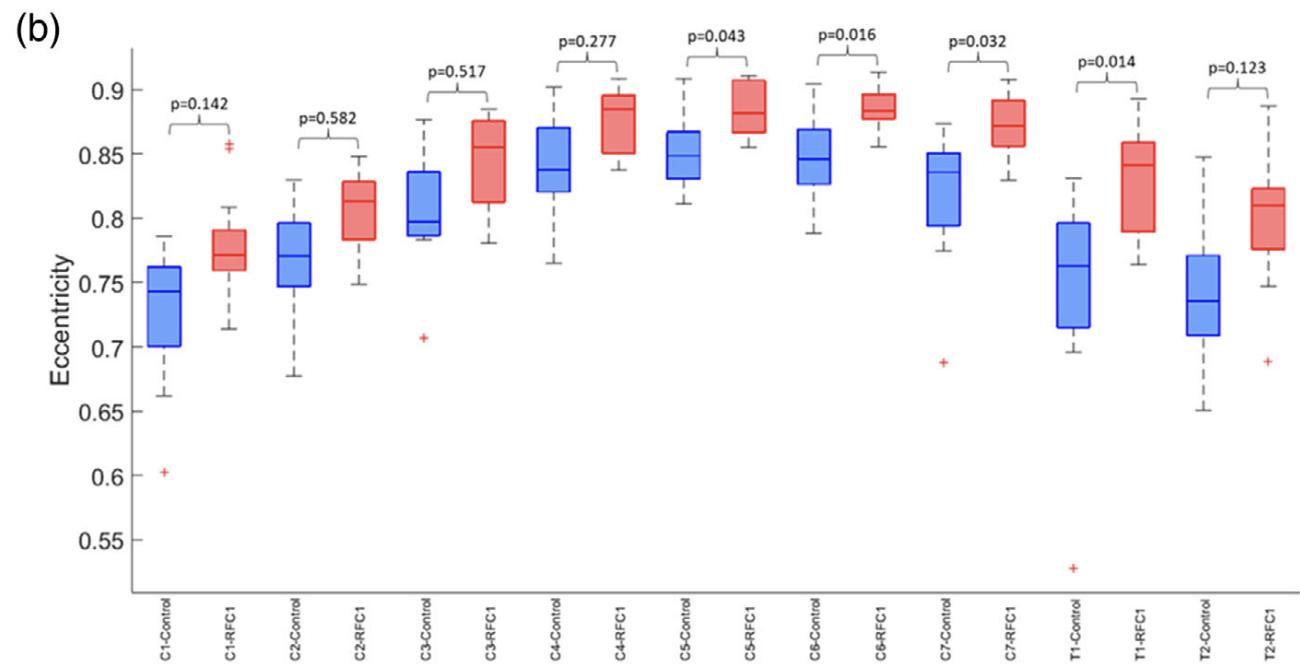
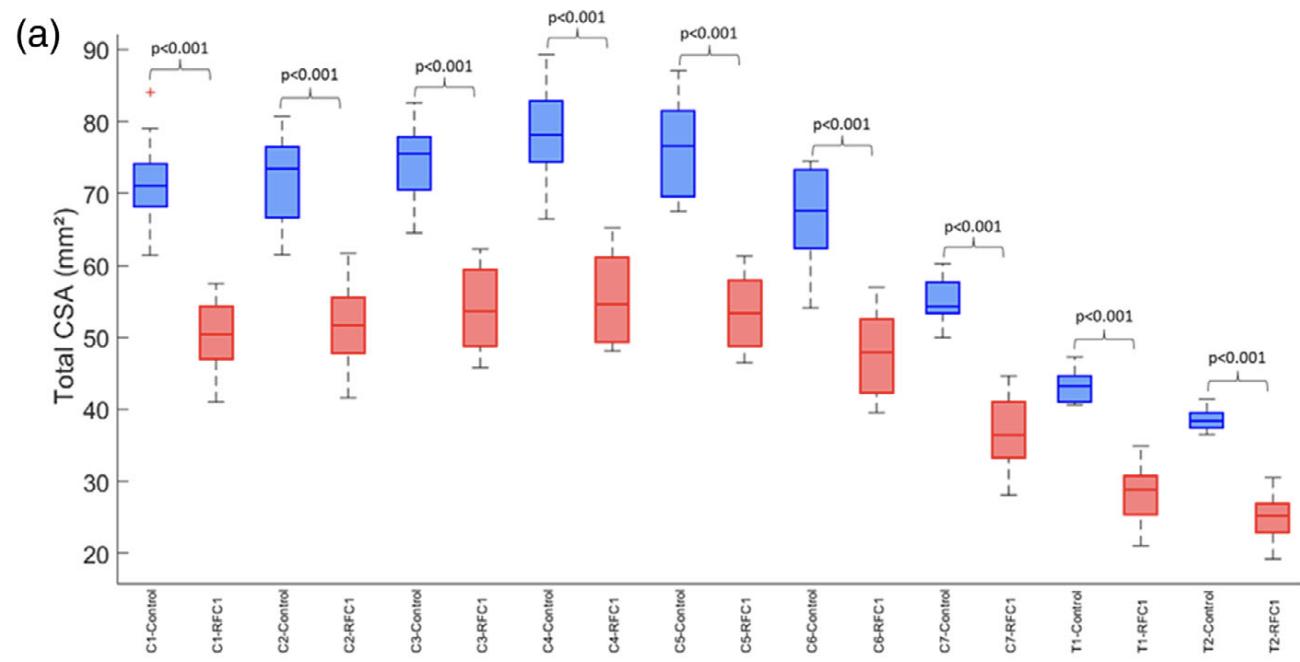
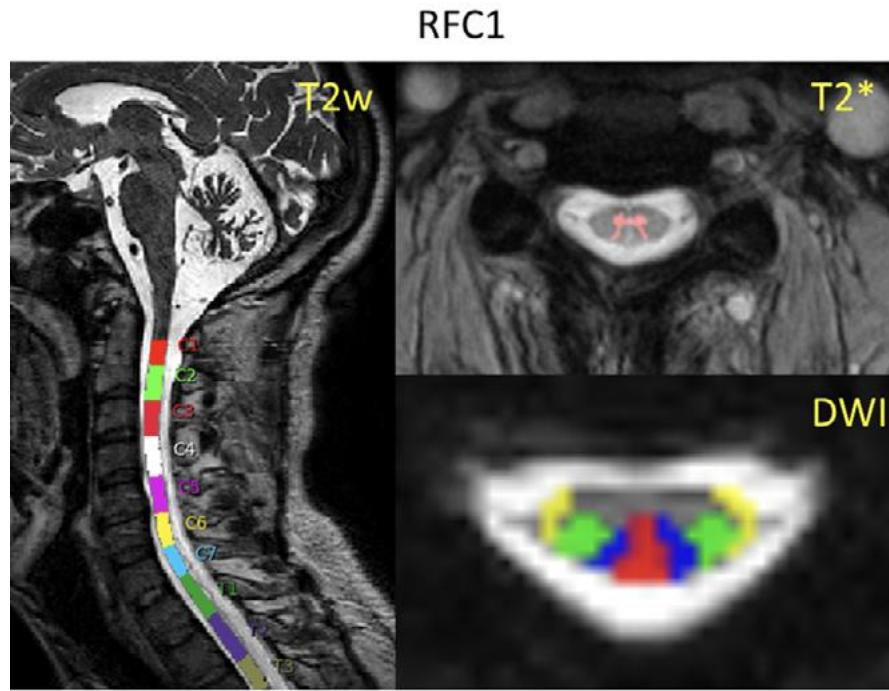
# Imaging biomarkers in RFC1-ataxia: Brain volumetry / diffusivity analyses



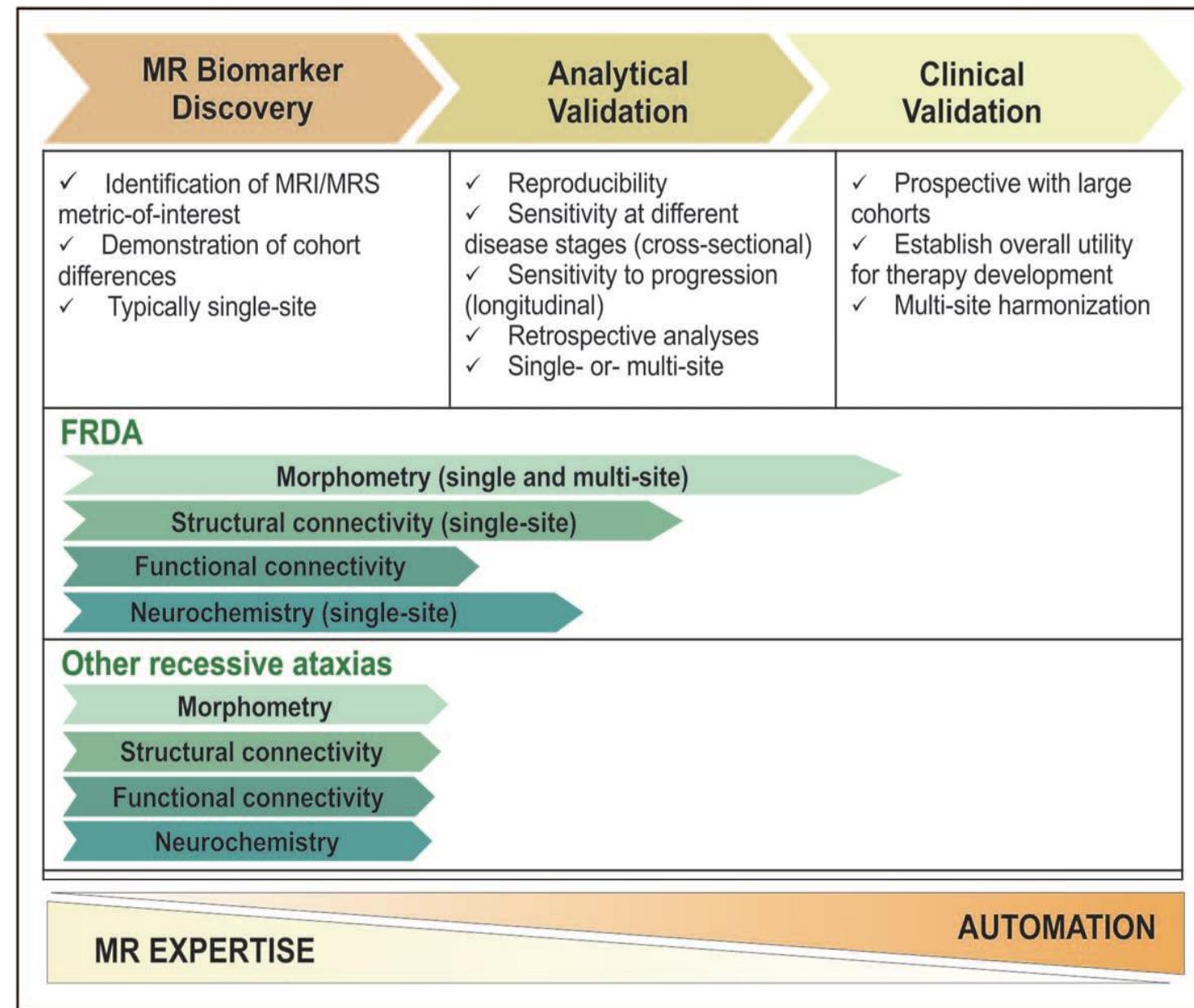
Effect Size



# Imaging biomarkers in RFC1-ataxia: Spinal cord



# Imaging biomarkers in AR ataxia: Current scenario



# Imaging biomarkers in AR ataxias: unmet needs

- For most AR ataxias: no candidate imaging biomarker

*Cross-sectional studies*

- For some AR ataxias (FRDA, RFC1): good candidate biomarkers, but still waiting for validation

*Longitudinal multicentric studies*

- Harmonization of protocols and analysis pipelines (across centers and MRI vendors)

# Imaging biomarkers in AR ataxias: Future directions

## Ongoing collaborative studies

Consortium (disease)	Centers
TRACK-FA ( <i>FRDA</i> )	Germany, USA, Canada, Brazil, Australia
PROSPAX ( <i>SPG7/ARSACS</i> )	Multiple EU sites
RFC1 NHS ( <i>RFC1</i> -ataxia)	Multiple EU sites

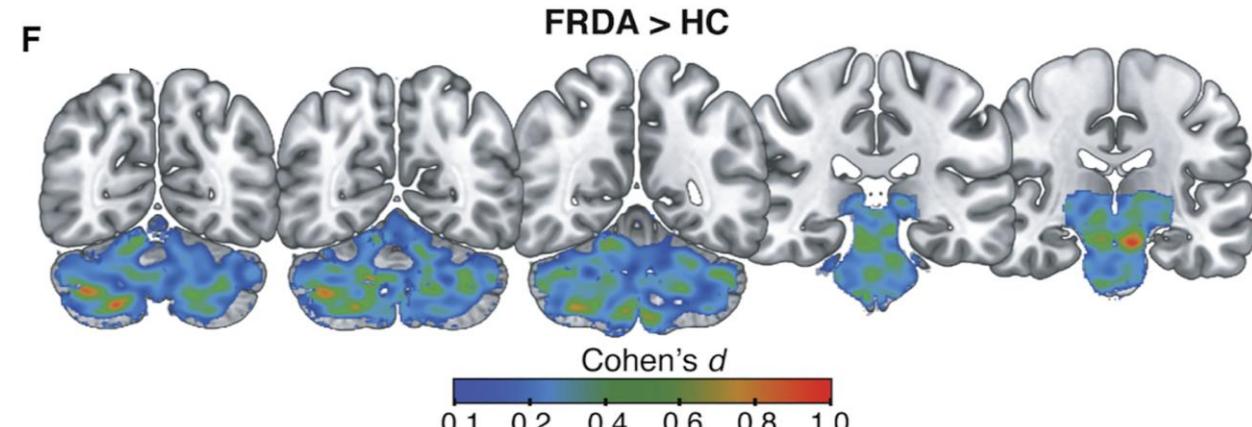
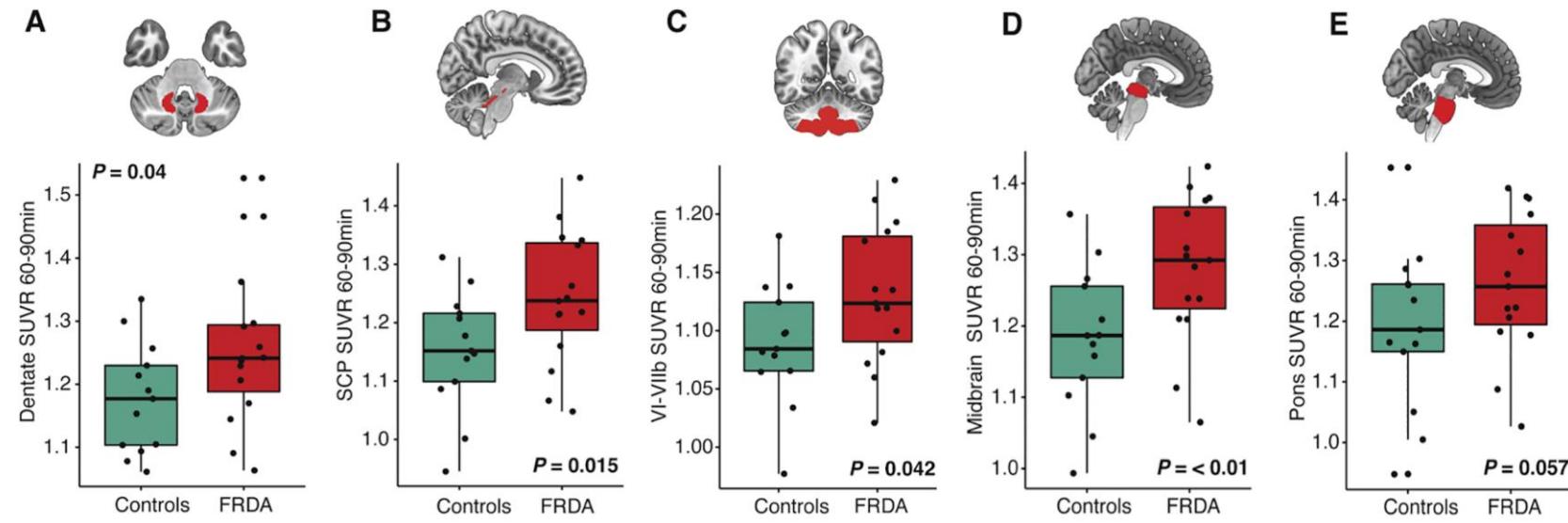
## Objectives

Identify and validate imaging markers across disease stages  
Harmonize MRI / MRS protocols across multiple sites

# Imaging biomarkers in AR ataxias: Future directions

Novel imaging biomarkers:

PET-MRI using the glial activation marker  $[^{18}\text{F}]\text{-FEMPA}$  in FRDA

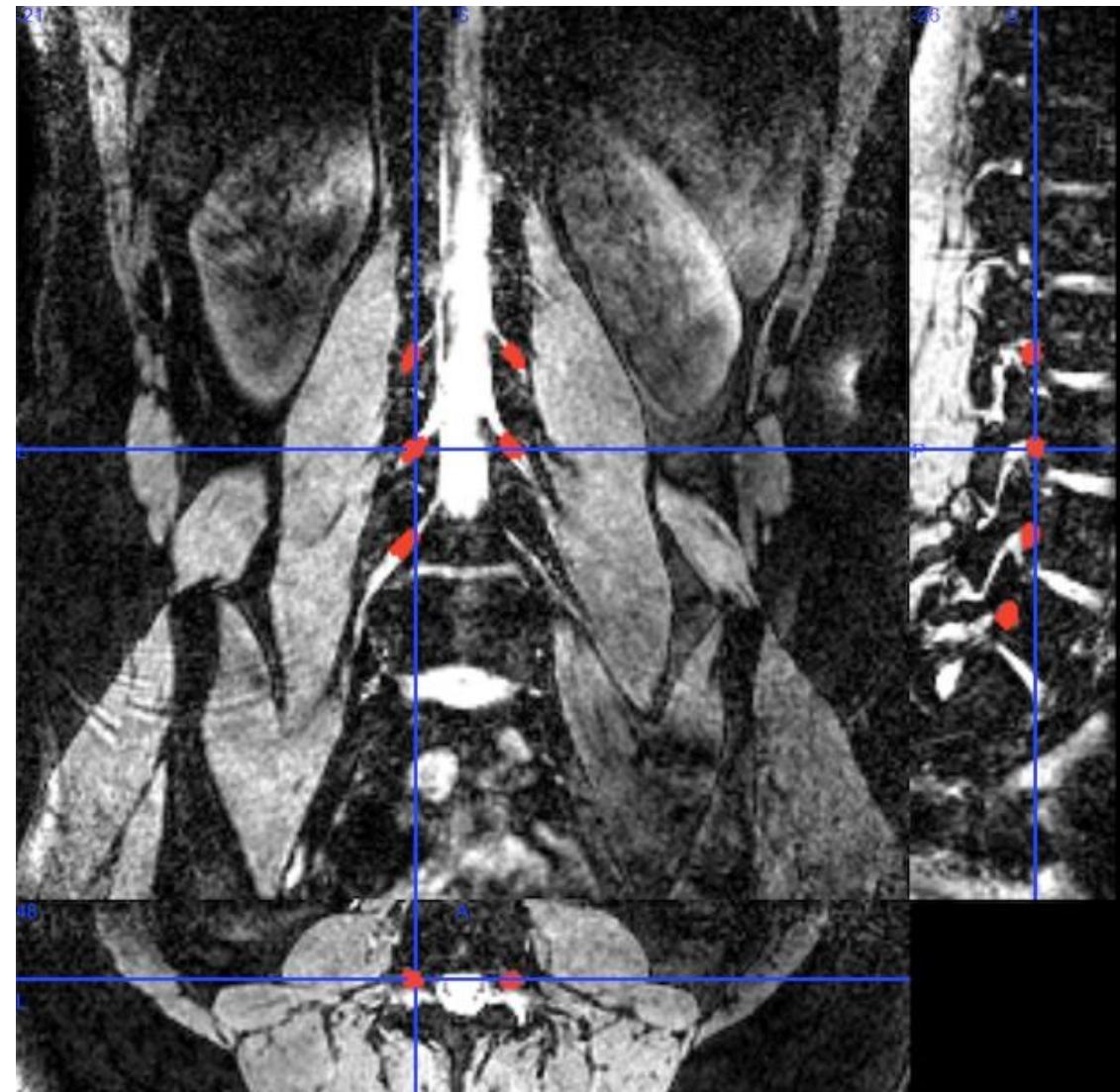


# Imaging biomarkers in AR ataxias: Future directions

## Novel imaging biomarkers:

DRG volumetry in FRDA using a high resolution T2 scan

Spine Level	Control Group (mm <sup>3</sup> ) (n=11)	FA Group (mm <sup>3</sup> ) (n=13)	p-value
L1	75.65 ± 35.74	60.63 ± 22.87	0.225
L2	134.48 ± 43.19	117.59 ± 40.83	0.336
L3	201.15 ± 51.41	157.77 ± 44.83	0.037
L4	216.52 ± 41.16	174.26 ± 53.41	0.047
L5	304.69 ± 72.16	227.38 ± 53.29	0.006



## Take-home messages

- Imaging studies in AR ataxias are challenging:
  - Rarity of specific subtypes
  - Genotypic, phenotypic and radiological heterogeneity
- Current scenario/unmet needs:
  - FRDA (longitudinal / multicenter studies)
  - RFC1, ATM, SPG7, COQ8A and SYNE1 (Cross-sectional/ single center studies)
- Future directions: Collaborative studies
  - Novel imaging candidates (disease-specific)

# Ataxia research group - UNICAMP

- Marcondes França
- Alberto Martinez
- Thiago Junqueira
- Melina Pazian
- Tauana Leoni
- Fabrício Diniz
- Carelis Gonzalez
- Joyce Macedo
- Fabricio Borba
- Renan França
- Mariana Rabelo
- Felipe Franco
- Juliana Guimarães

## Collaborators

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Prof Orlando Barsottini (Unifesp)  
Prof Wilson Marques (USP-RP)  
Prof Laura Jardim (UFRGS)

### USA

Prof Andréa Faria (Johns Hopkins)

### Australia

Prof Ian Harding (Monash University)

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