



ESMI Cohort update

Jennifer Faber

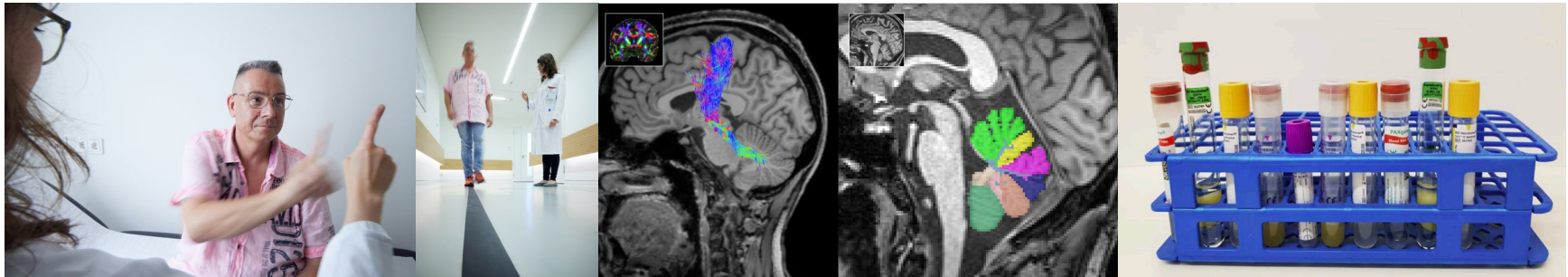
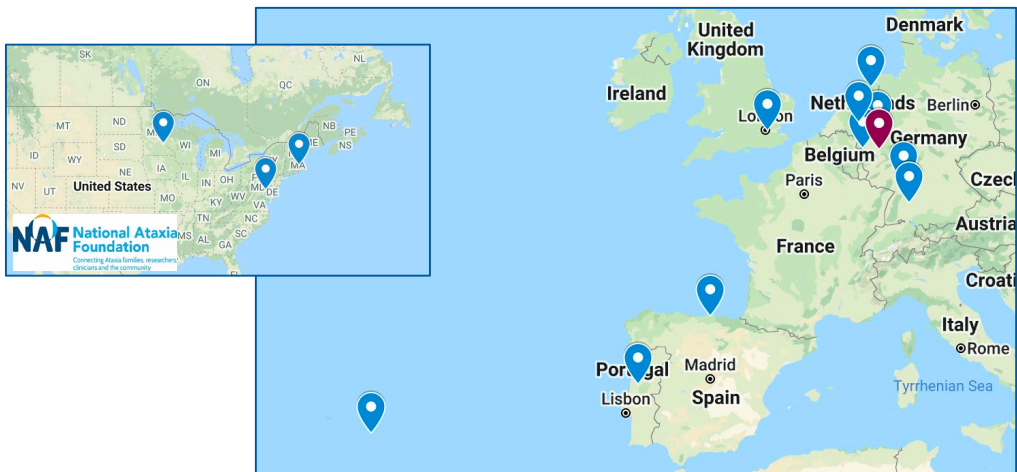
German Center for Neurodegenerative Diseases (DZNE), Bonn
Department of Neurology, University Hospital Bonn

Outline

- ESMI cohort & recruitment
- Biomarker identification
- Disease modeling

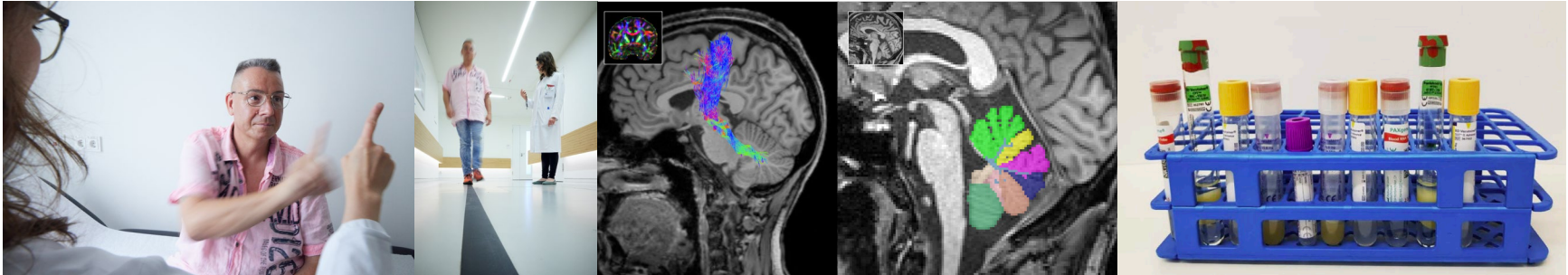
ESMI: European Spinocerebellar Ataxia Type 3/Machado-Joseph-Disease Initiative

Coordinator: Thomas Klockgether, DZNE Bonn



ESMI cohort

Visit	Baseline					Follow-up 1				Follow-up 2			
	Clinical	Biosampling		MRI	US sites (clin.+ MRI)	Clinical	Biosampling		MRI	Clinical	Biosampling		MRI
		Blood	CSF				Blood	CSF			Blood	CSF	
Healthy control	125	103	0	36	9	76	57	0	25	34	29	0	17
SCA3	338	300	38	111	6	265	244	7	71	185	151	2	35
	pre-ataxic: 68 ataxic: 265 untested at risk: 5					pre-ataxic: 48 ataxic: 217 untested at risk: 0				pre-ataxic: 37 ataxic: 148 untested at risk: 0			
				Visit		Follow-up 3				> Follow-up 3			
						Clinical	Biosampling		MRI	Clinical	Biosampling		MRI
							Blood	CSF			Blood	CSF	
				Healthy control		13	11	0	8	3	3	0	2
SCA3		83	78	0	18	50	45	0	8	pre-ataxic: 6 ataxic: 44 untested at risk: 0			
		pre-ataxic: 14 ataxic: 69 untested at risk: 0											



(1) Biomarker identification & genetic modifiers:

NfL

Ataxin-3

Volumetry

Transcriptomics analysis

miRNA

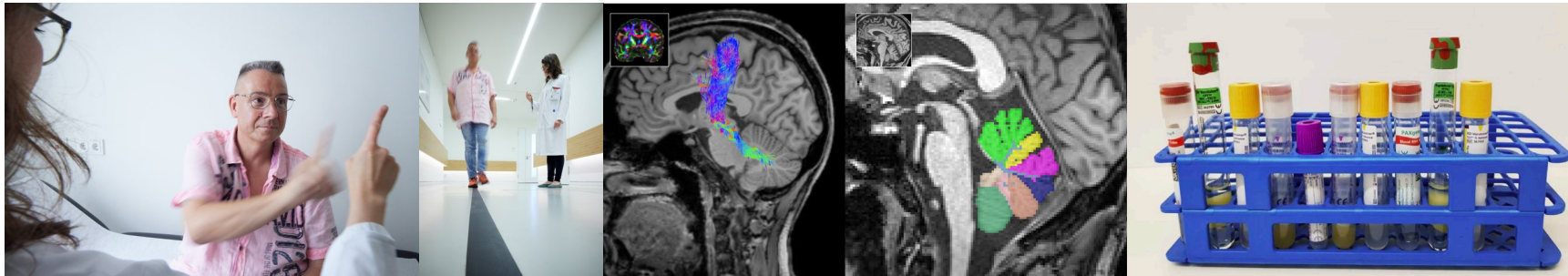
Tau/pTau

Sensor-free gait assessment

Polymorphisms

Diffusion imaging

...



(1) Biomarker identification & genetic modifiers:

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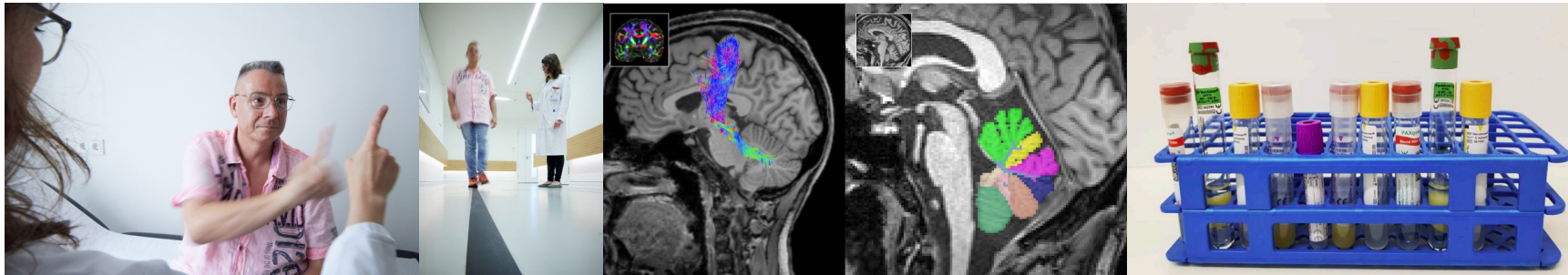
Sensor-free gait assessment

Polymorphisms

Diffusion imaging

...

(2) Data-driven disease model enriched with biomarker information



(1) Biomarker identification & genetic modifiers:

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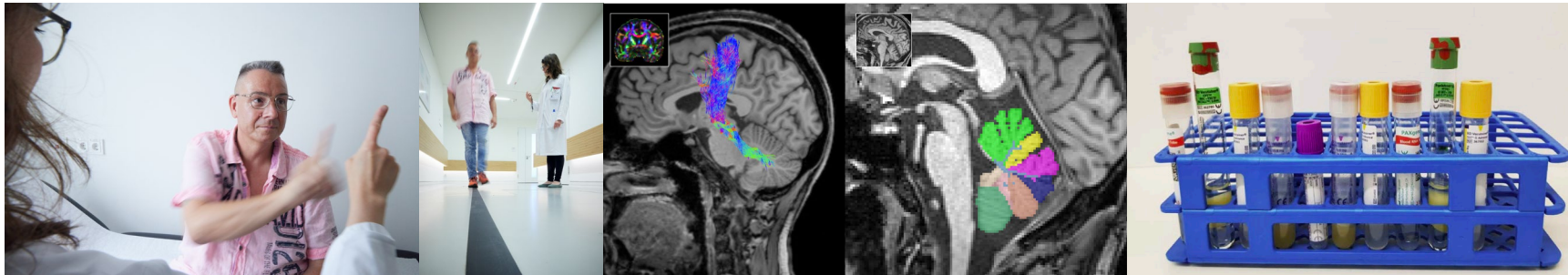
Sensor-free gait assessment

Polymorphisms

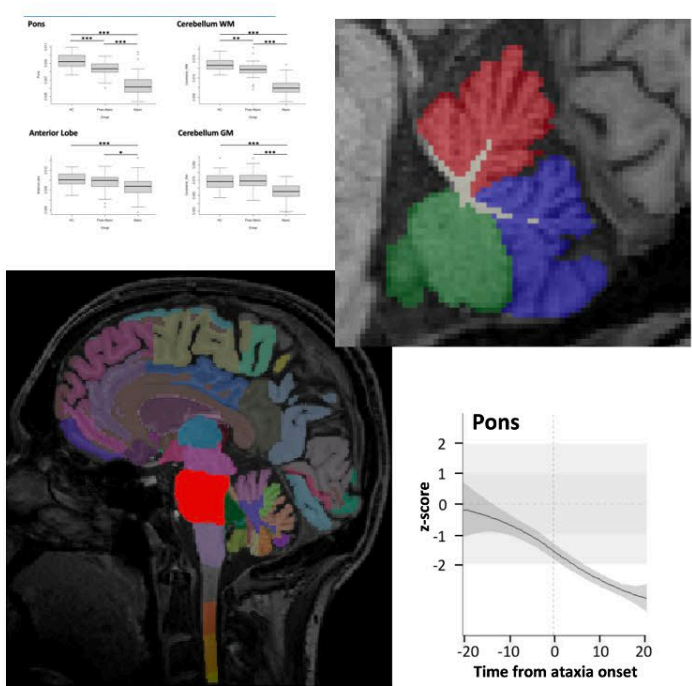
Diffusion imaging

...

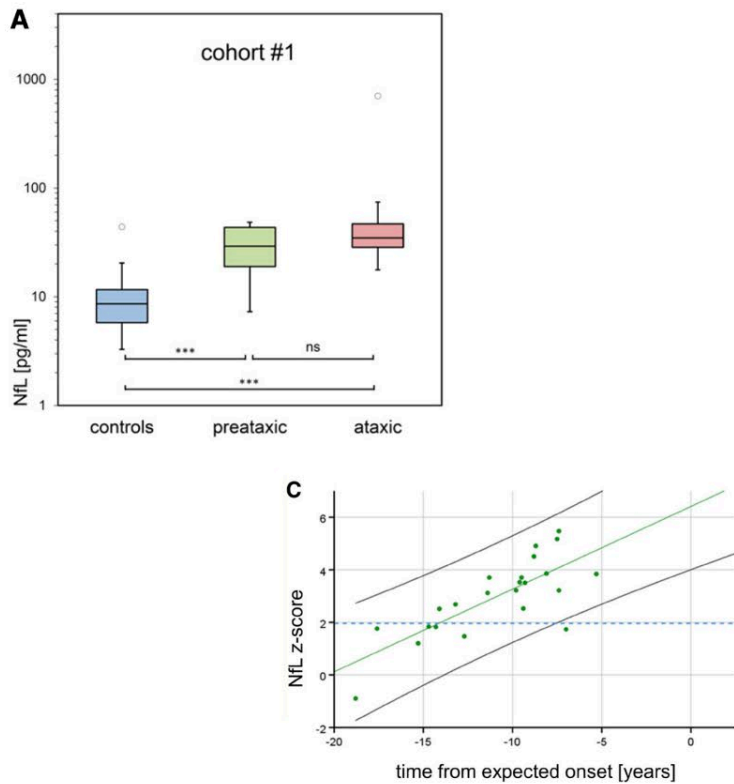
(2) Data-driven disease model enriched with biomarker information



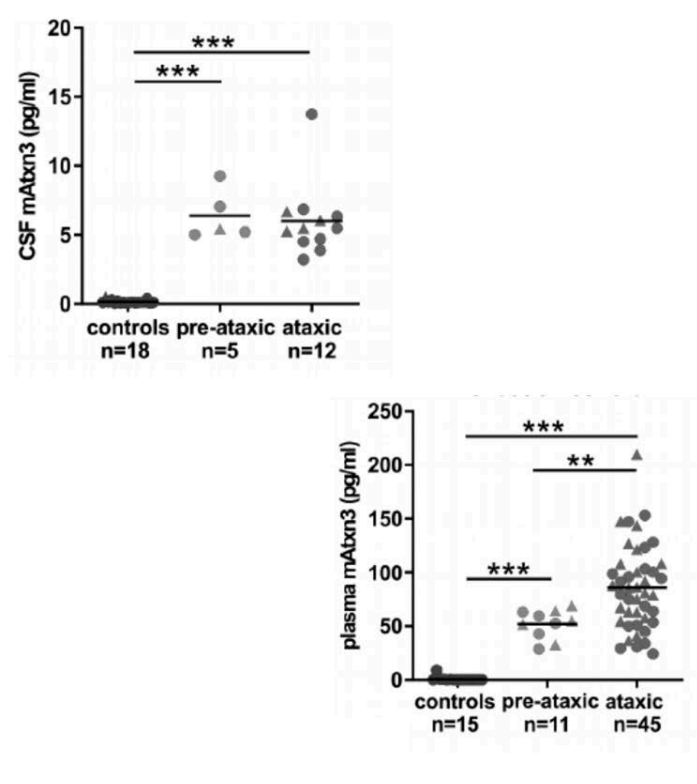
Disease Modeling



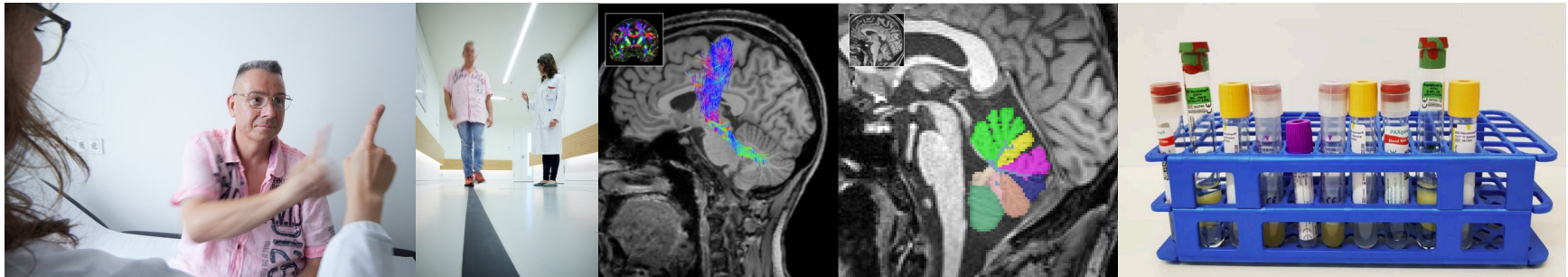
Volumetry: Pons, cerebellar WM
Anterior lobe, cerebellar GM



NfL



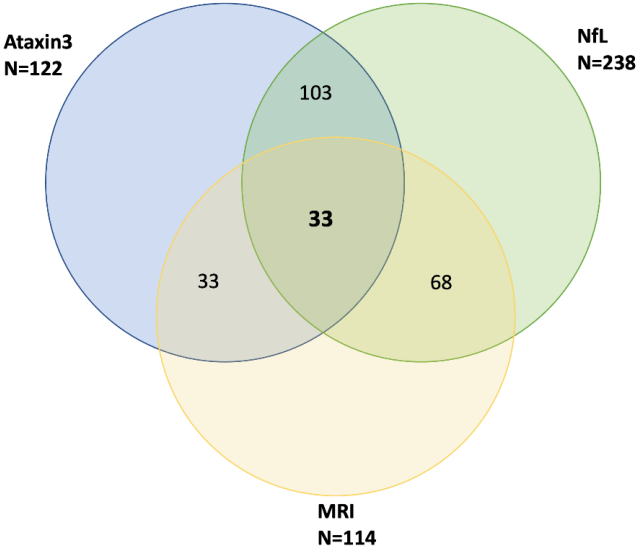
Ataxin-3



Biomarker Analyses

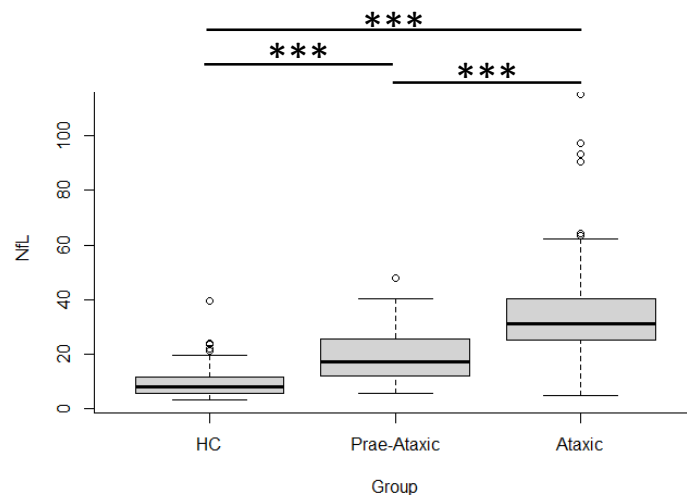
	HC (N=108)	Prae-Ataxic (N=57)	Ataxic (N=235)
age_at_visit			
Mean (SD)	46.1 (14.0)	35.5 (8.96)	51.3 (11.3)
Median [Min, Max]	43.9 [21.2, 82.1]	35.4 [20.9, 63.4]	51.6 [21.7, 78.7]
IQR [Q1, Q3]	24.2 [34.3, 58.5]	10.8 [29.0, 39.8]	14.9 [44.6, 59.5]
aoo			
Mean (SD)	NA	43.2 (9.09)	39.9 (10.5)
Median [Min, Max]	NA	41.8 [27.0, 62.4]	40.0 [14.0, 69.0]
IQR [Q1, Q3]	NA	14.6 [35.0, 49.6]	15.0 [33.0, 48.0]
Missing	108 (100%)	0 (0%)	0 (0%)
disease_duration			
Mean (SD)	NA	-7.68 (8.00)	11.3 (7.76)
Median [Min, Max]	NA	-7.73 [-26.8, 10.6]	10.4 [-23.9, 39.5]
IQR [Q1, Q3]	NA	6.87 [-12.0, -5.14]	9.39 [5.75, 15.1]
Missing	108 (100%)	0 (0%)	0 (0%)
CAGlonger			
Mean (SD)	NA	68.2 (3.69)	68.8 (4.16)
Median [Min, Max]	NA	68.0 [60.0, 77.0]	69.0 [55.0, 80.0]
IQR [Q1, Q3]	NA	5.00 [66.0, 71.0]	4.00 [67.0, 71.0]
Missing	108 (100%)	0 (0%)	6 (2.6%)
CAGshorter			
Mean (SD)	NA	21.4 (4.48)	22.0 (6.22)
Median [Min, Max]	NA	23.0 [14.0, 30.0]	23.0 [14.0, 64.0]
IQR [Q1, Q3]	NA	3.00 [20.0, 23.0]	7.00 [19.0, 26.0]
Missing	108 (100%)	7 (12.3%)	17 (7.2%)
sara			
Mean (SD)	0.304 (0.602)	1.07 (0.942)	14.2 (8.04)
Median [Min, Max]	0 [0, 4.00]	1.00 [0, 2.50]	11.5 [3.00, 40.0]
IQR [Q1, Q3]	0.500 [0, 0.500]	2.00 [0, 2.00]	11.0 [8.50, 19.5]
Missing	1 (0.9%)	0 (0%)	4 (1.7%)

Availability of imaging and fluid biomarker
(Mutation carrier only)

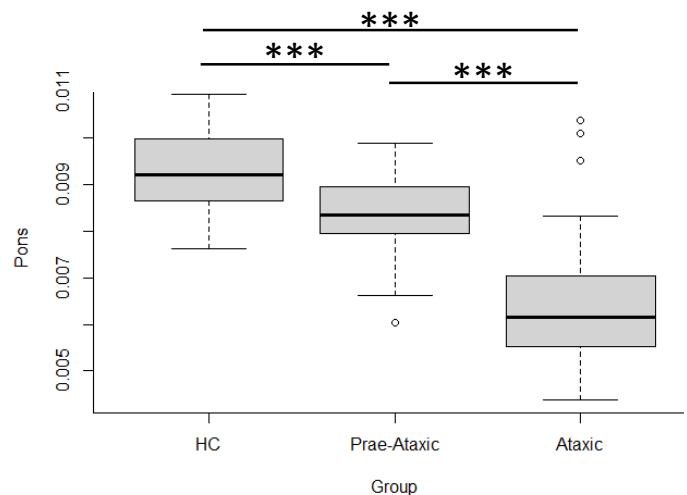


Disease Modeling

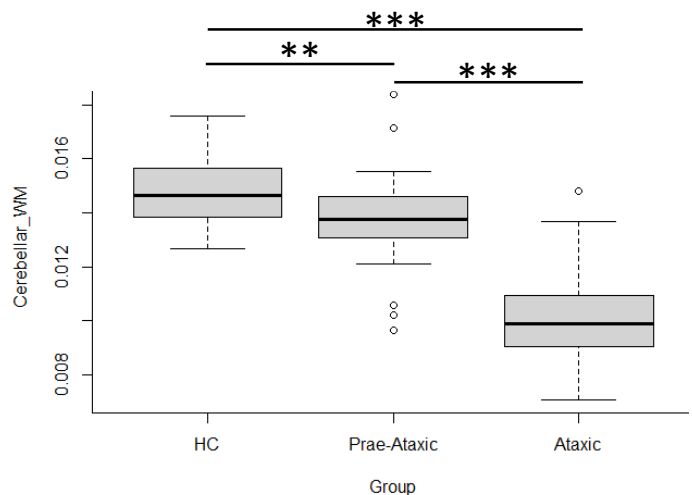
NfL



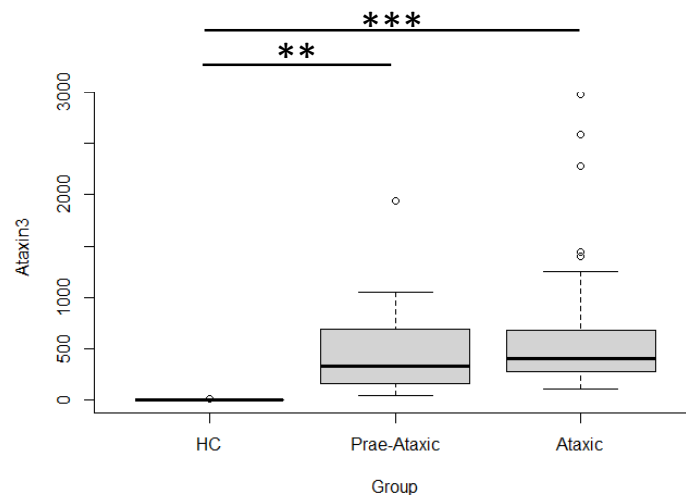
Pons



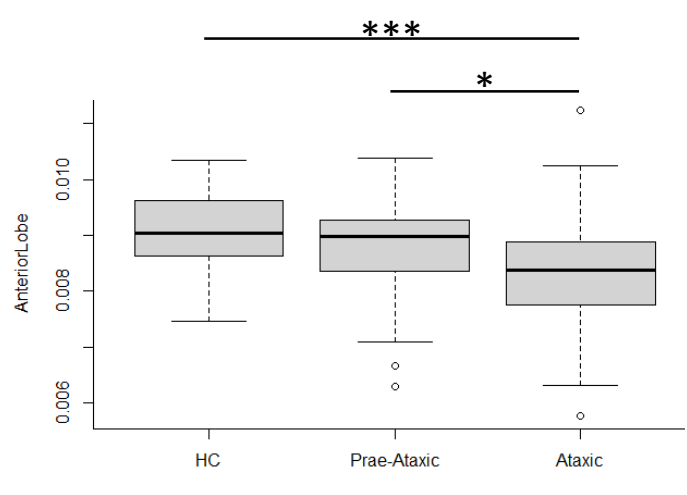
Cerebellum WM



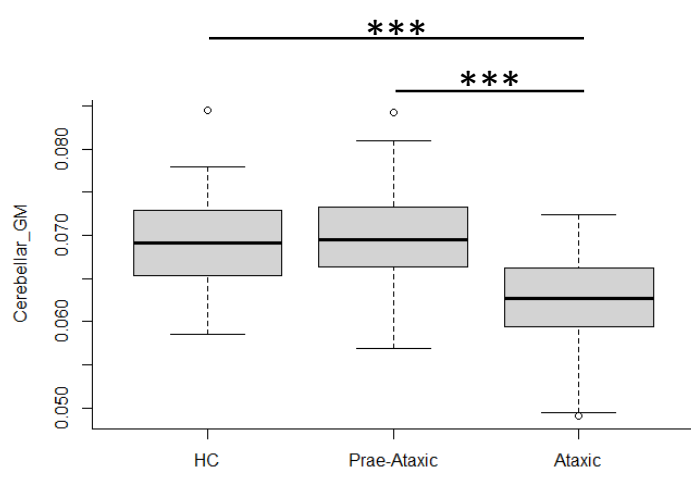
Ataxin3



Anterior Lobe



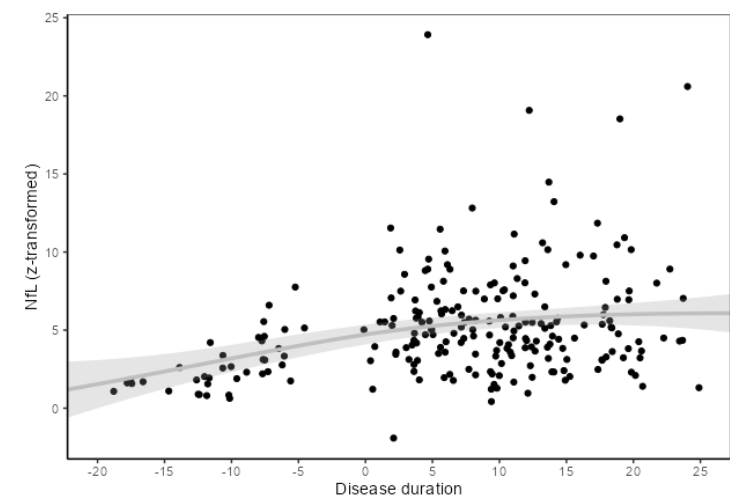
Cerebellum GM



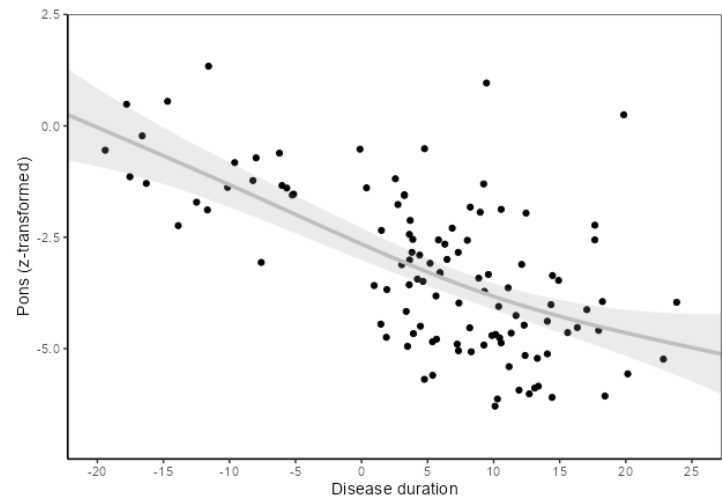
* p < 0.05; ** p < 0.01; *** p < 0.001

Disease Modeling – Disease duration

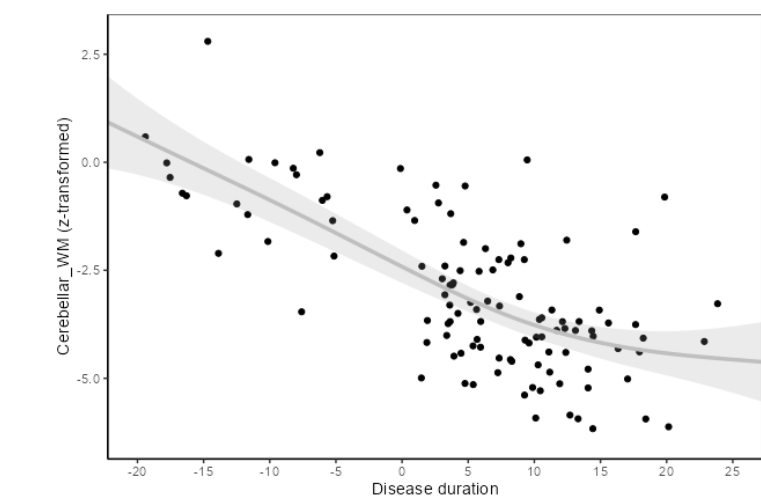
NfL



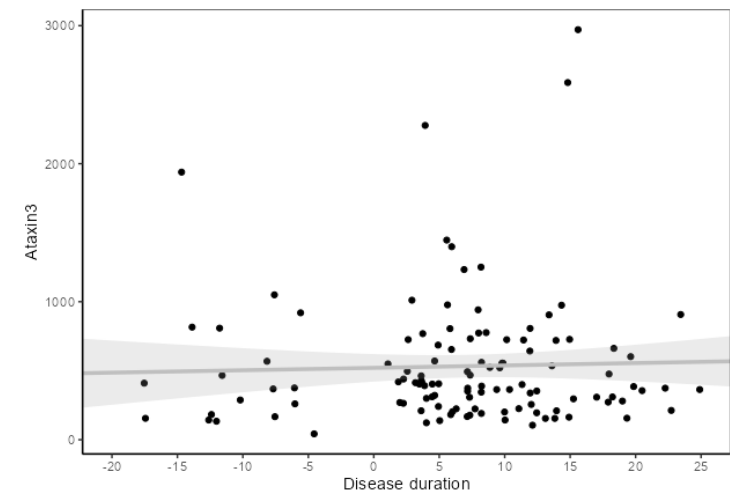
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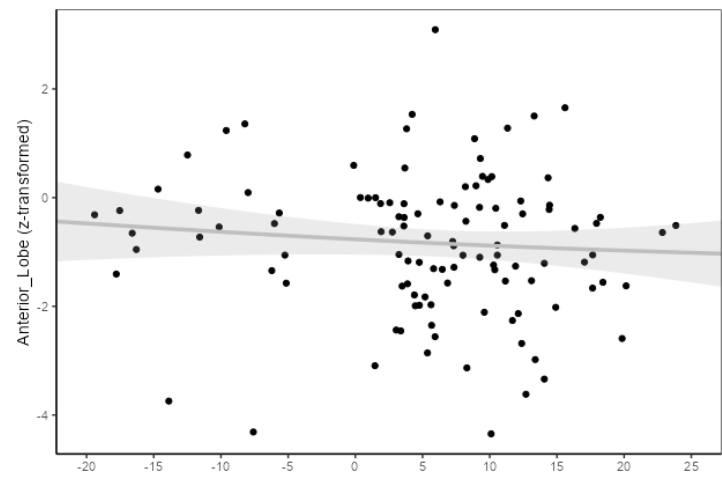
Cerebellum WM



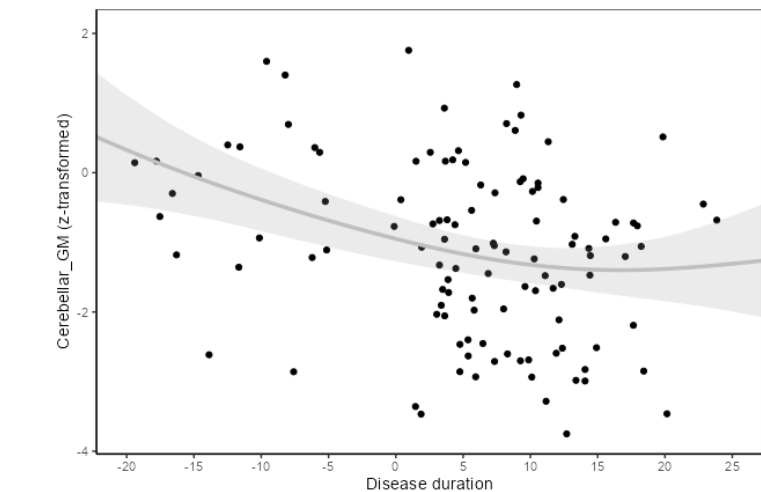
Ataxin3



Anterior Lobe



Cerebellum GM

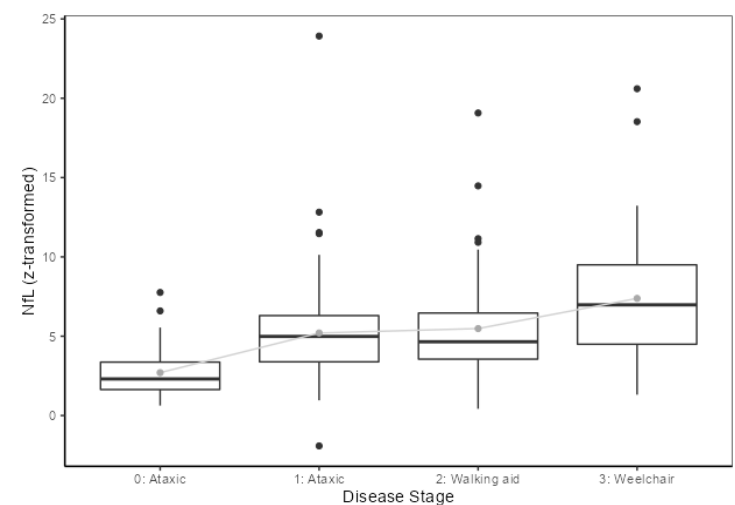


Disease duration

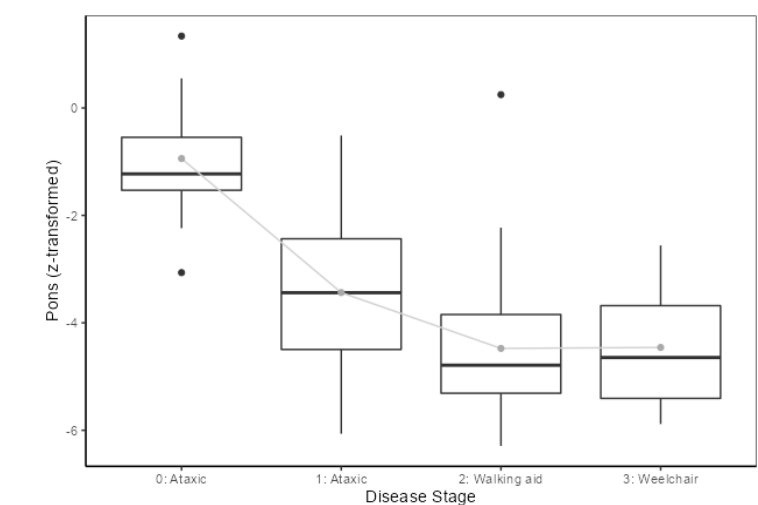
Disease duration: reported if applicable, if missing but symptomatic estimated based on number of CAG repeats length of the longer allele, if pre-symptomatic estimated based on number of CAG repeats of the longer allele and actual age

Disease Modeling – Disease stages (normal – ataxic – walking aid – wheelchair)

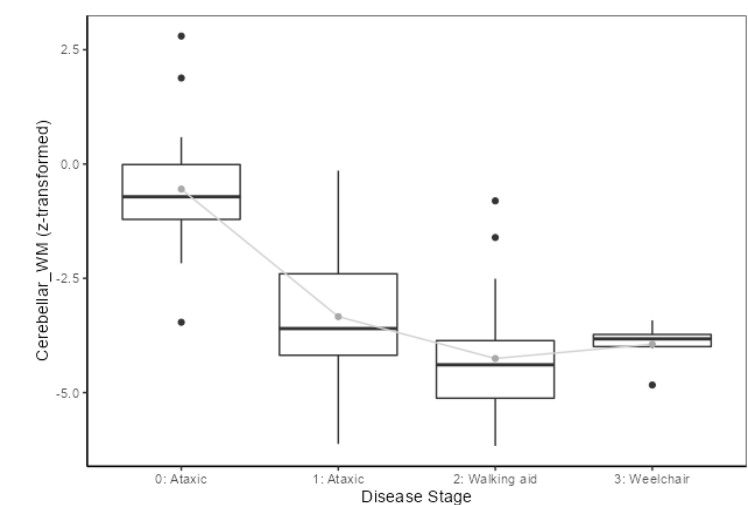
NfL



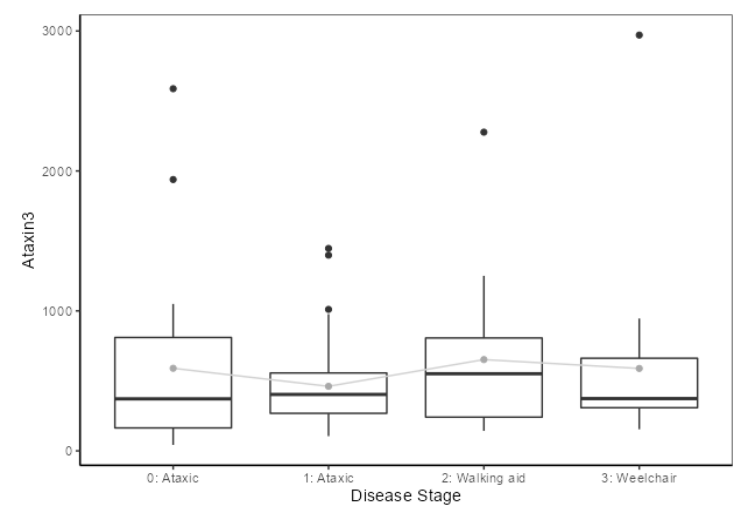
Pons



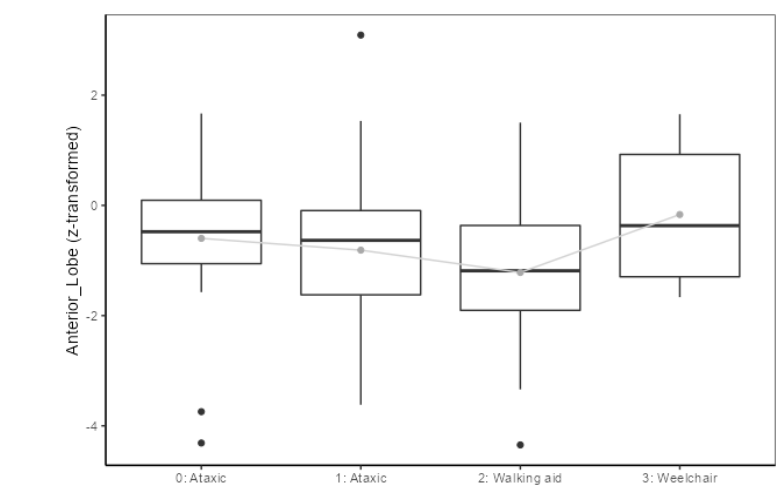
Cerebellum WM



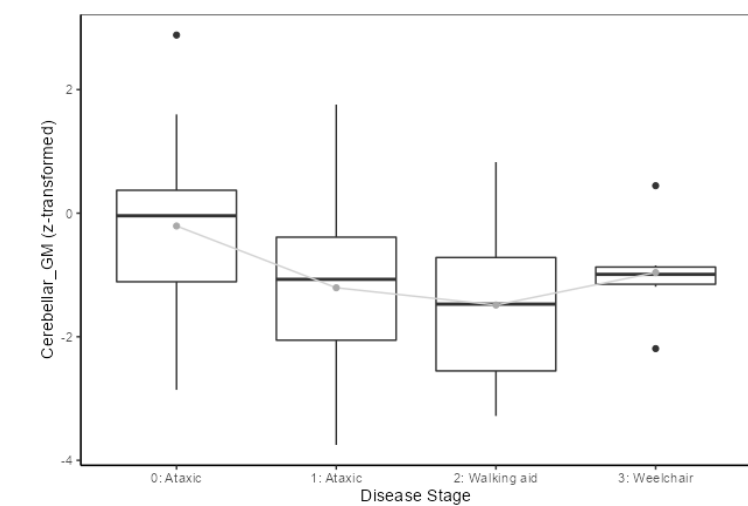
Ataxin3



Anterior Lobe

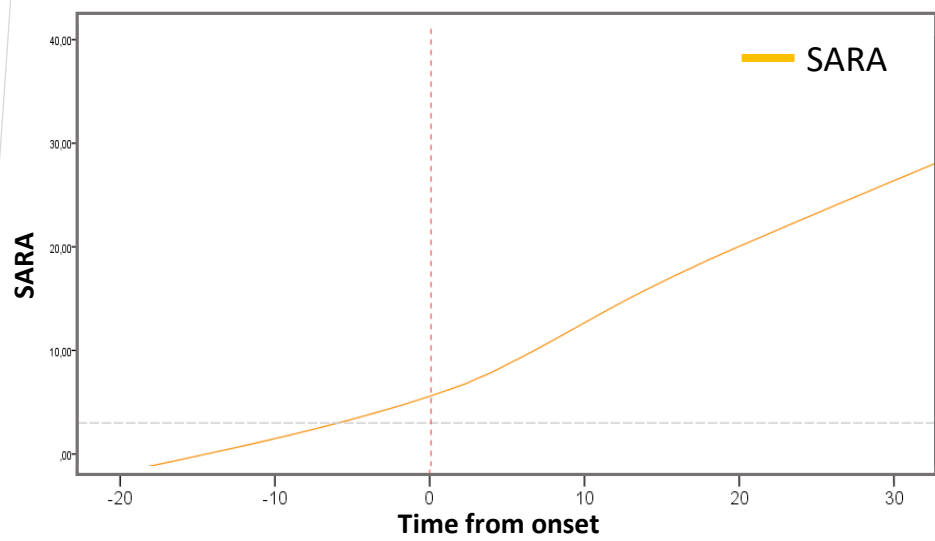
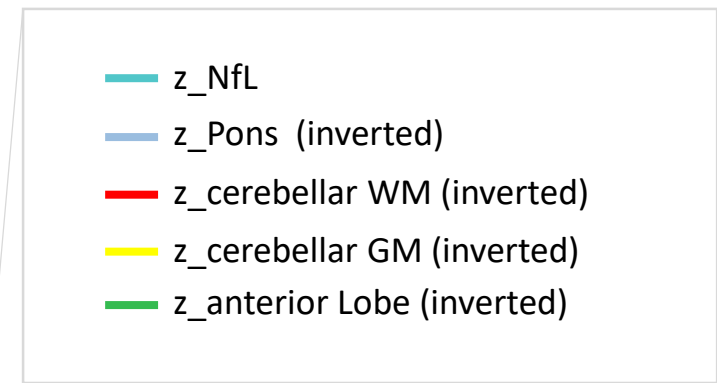
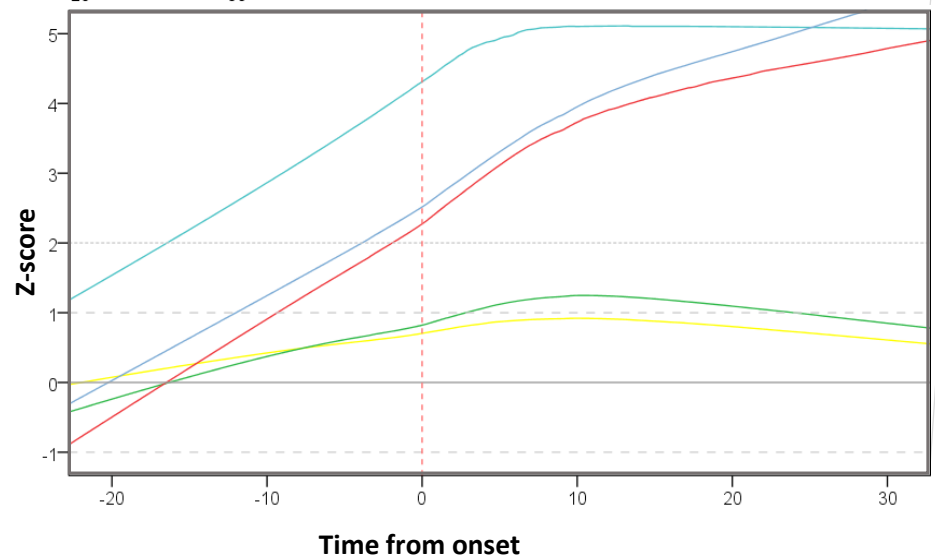
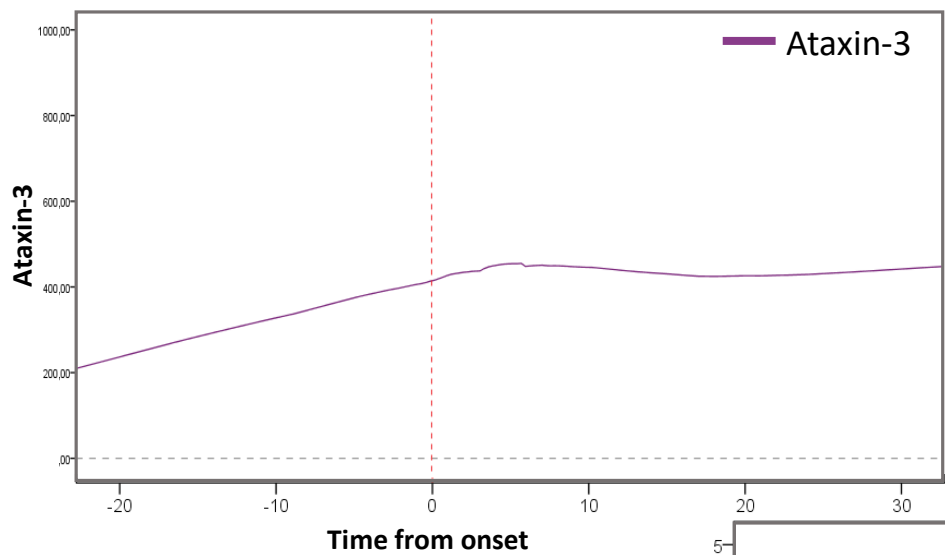


Cerebellum GM

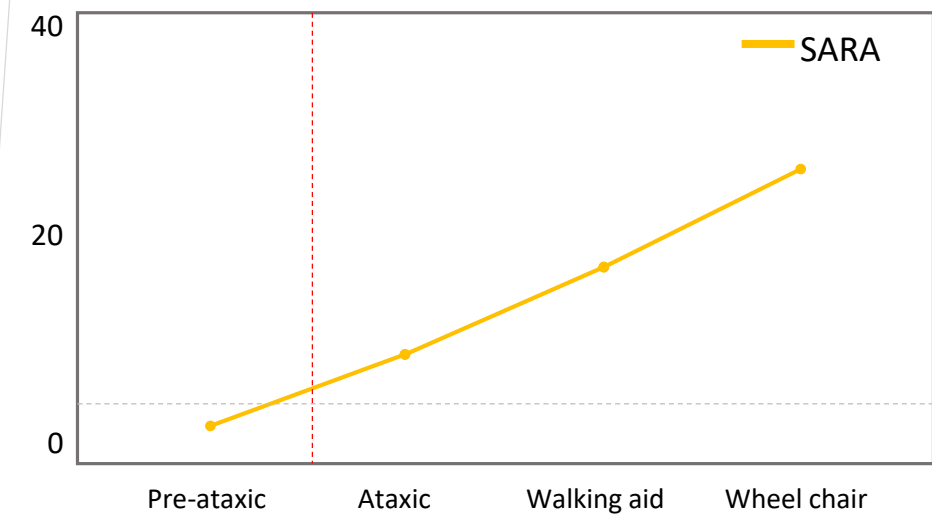
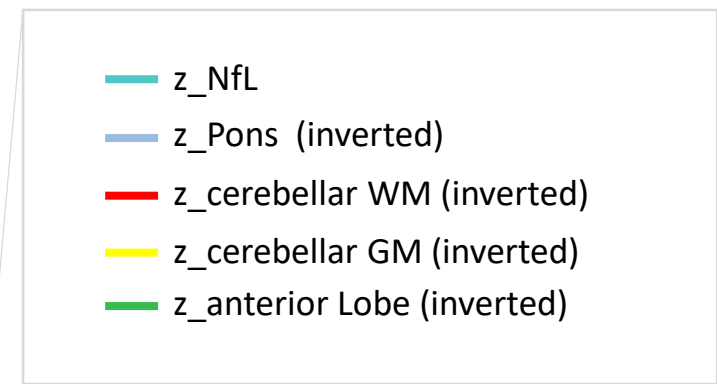
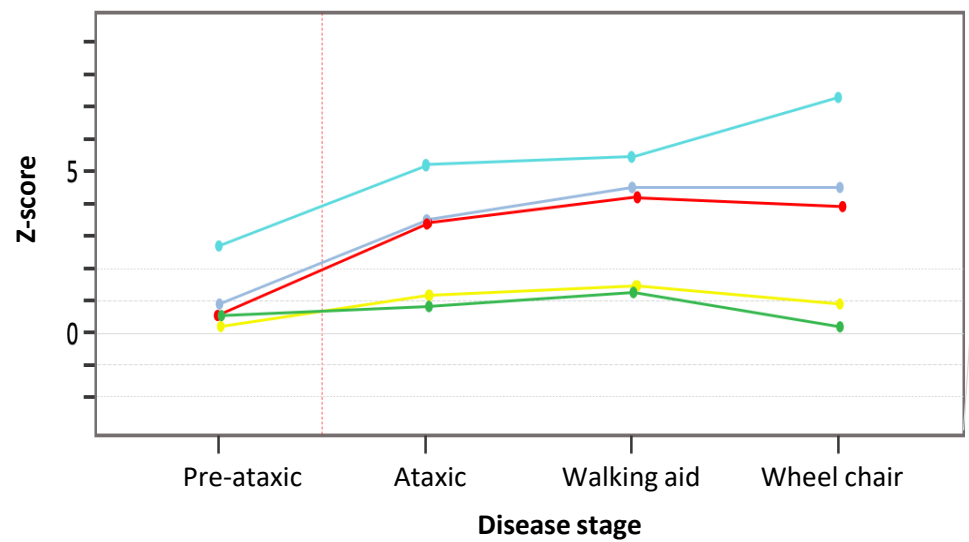
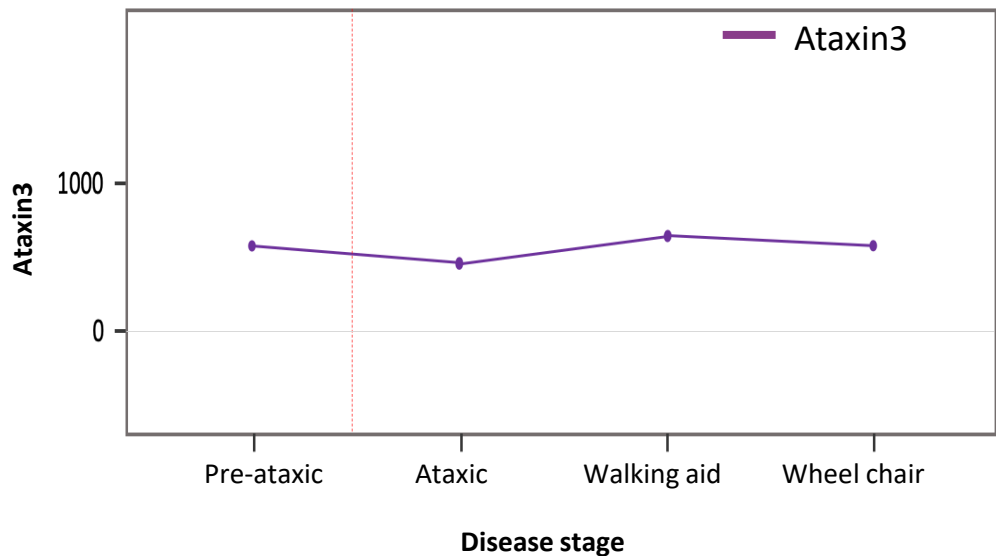


Disease stages

Disease Modeling



Disease Modeling



Disease Modeling

Disease stage	
Model	R ²
age, sex, CAG	0.628
age, CAG	0.607

SARA	
Model	R ²
age, sex, CAG	0.739
age, CAG	0.729

Disease stage	
Model	R ²
age, sex, CAG, Pons, NfL, anteriorLobe, ataxin3	0.671
age, sex, CAG, NfL, anteriorLobe, ataxin3	0.670
age, sex, CAG, NfL, ataxin3	0.663
age, sex, CAG, ataxin3	0.649
age, sex, CAG	0.628
age, CAG	0.607

SARA	
Model	R ²
age, sex, CAG, Pons, NfL, anteriorLobe, ataxin3	0.809
age, CAG, Pons, NfL, anteriorLobe, ataxin3	0.809
age, CAG, Pons, NfL, anteriorLobe	0.800
age, CAG, Pons, anteriorLobe	0.793
age, CAG, Pons	0.777

SCA3: Staging framework

Carrier stage

Biomarker stage

Ataxia stage

Ataxic

Walking aid

Wheelchair

Birth

Ataxia onset



SCA3: Staging framework

Carrier stage

Biomarker stage

Ataxia stage

Ataxic

Walking aid

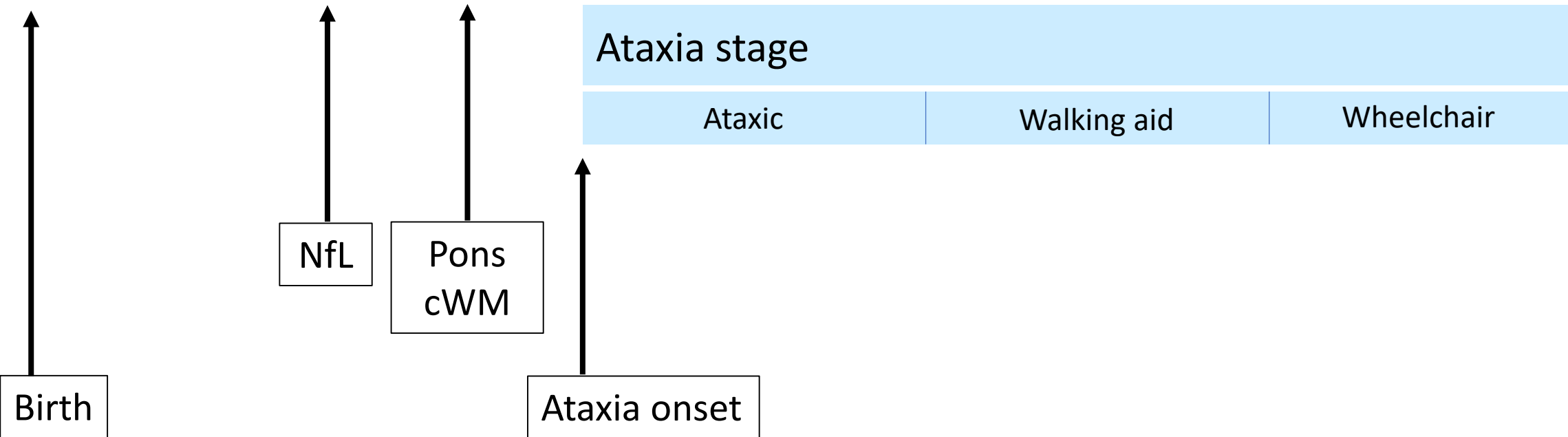
Wheelchair

NfL

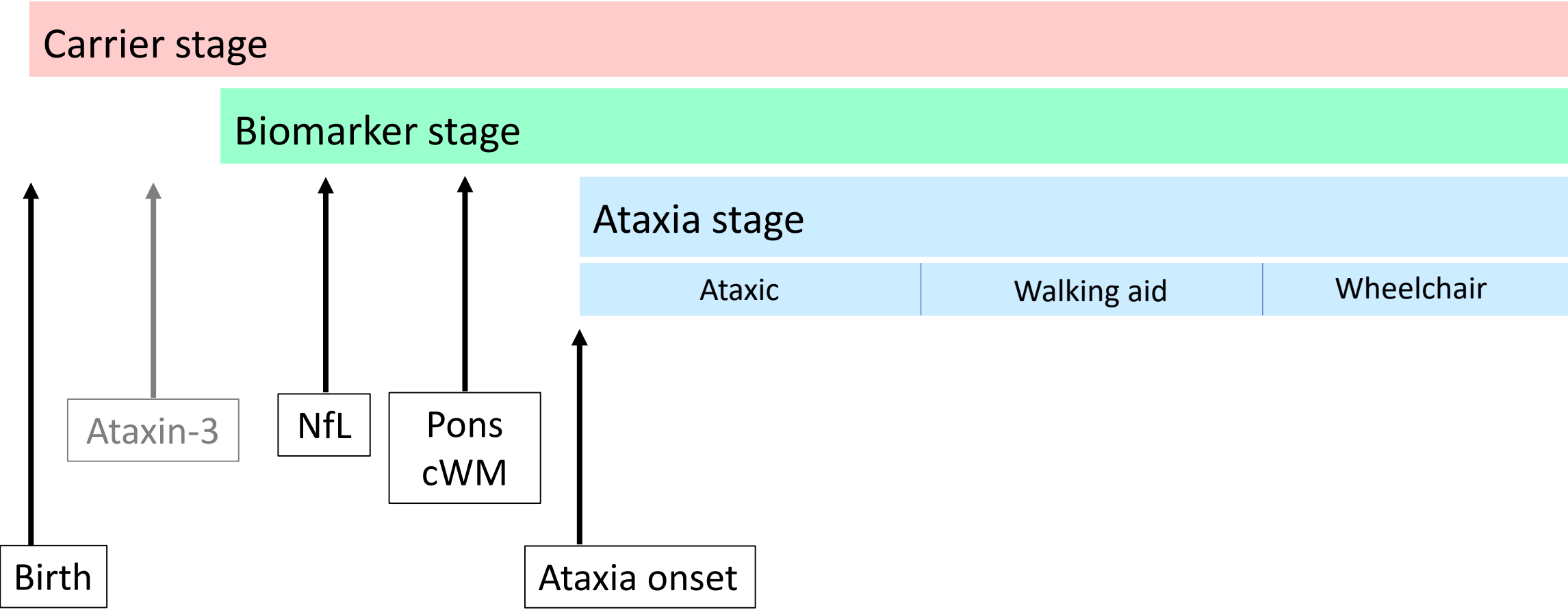
Pons
cWM

Ataxia onset

Birth



SCA3: Staging framework



Thank you for your attention!

Thomas Klockgether

Aachen, Germany
Azores, Portugal
Coimbra, Portugal
Essen, Germany
Groningen, Netherlands
Heidelberg, Germany
London, UK
Nijmegen, Netherlands
Tübingen, Germany

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Boston, USA
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NfL: Carlo Wilke, Matthis Synofzik
Hector Garcia-Moreno, Paola Giunti
Statistics: Moritz Berger, Matthias Schmid,

