SCA GLOBAL CONFERENCE

SCA Global

NAF National Ataxia Foundation
www.ataxia.org

March 27—29, 2019

FLAMINGO HOTEL AND CASINO

Las Vegas, Nevada

SCA GLOBAL CONFERENCE

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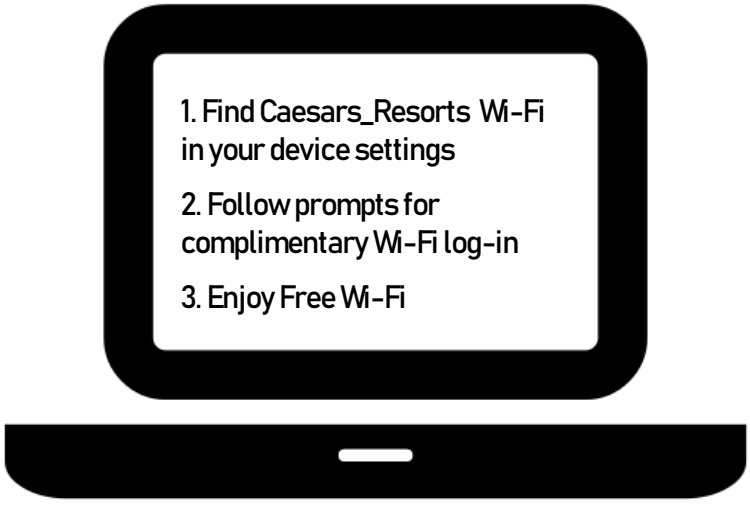

SCA Global

March 26, 2019

Dear 1st SCA Global Conference Attendees,

On behalf of the Organizing Committee and my Co-Chair Dr. Thomas Klockgether, we are delighted to welcome you to the inaugural SCA Global Conference. It has been a quarter of a century since the identification of the first SCA mutation in SCA1, and ataxia researchers have since found over 40 SCA genes to date. Meanwhile, understanding the disease-causing mechanism of some of these SCAs has advanced to the stage where therapeutic strategies based on strong scientific premise can be formulated. Many efforts are currently taking sure steps toward clinical trials of promising new drugs. However, since all SCAs are rare disorders, we must develop worldwide collaborations to make decisive clinical trials possible with sufficient statistical power.

We are here today to tackle this task of kickstarting the Global SCA initiative. There are a number of issues that make international clinical studies challenging. These issues include not only genetic diversity among people in various parts of the world but also differences in natural and cultural environment that may have an influence on the clinical outcome of the disease gene. Furthermore, regulatory restrictions, despite their good original purposes, have made international sharing of data and biological samples across borders difficult. Finally, there is an urgent need to harmonize assessment protocols, imaging procedures and biosampling. We must overcome these hurdles to accomplish our common goal to establish seamless ataxia research infrastructures. We are excited to see many people are attending this conference with a willingness to work hard to advance toward our common goal while developing mutual trust and commitment.

This conference is attended by junior investigators, including students, postdocs and other early career professionals as well as accomplished investigators. These investigators have diverse backgrounds in scientific disciplines. They are from not only academic institutions but also industry, government and patient support organizations of various countries. We are hoping that this conference becomes a venue for an international academic family of these investigators.

We would like to thank the National Ataxia Foundation (NAF) for fostering this SCA Global initiative by providing significant financial and invaluable non-monetary contributions. We also thank government and industry sponsors for their generous support. We are particularly keen about active participation of junior investigators, women and underrepresented minorities. Our staff are prepared to help anyone who have physical limitations. Last but not least, please make the most out of the opportunities to interact with patients and their family members who are attending the Annual Ataxia Conference.

I look forward to stimulating discussions and an engaging conference as we move towards a new era of ataxia therapeutics.

Kind regards,


Thomas Klockgether, M.D. and Tetsuo Ashizawa, M.D.

National Ataxia Foundation
Connecting Ataxia families, researchers, clinicians and the community
www.ataxia.org

March 27, 2019

Dear SCA Global Conference Attendees,

On behalf of the National Ataxia Foundation (NAF) Board of Directors, Medical Research Advisory Board members, the NAF staff, and the families who we serve: Welcome to the first **SCA Global Conference**. We anticipate an exciting two- and one-half-day conference that will engage researchers in advancing the field toward development of therapies for those with ataxia. A conference such as the one we are about to begin will encourage and galvanize the entire ataxia community. Researchers provide the hope that our families so desperately need. Thank you for participating in this historical conference.

Attendees at this conference are from across the globe and represent the following countries: Australia, Austria, Brazil, Canada, China, France, Germany, Hong Kong, Italy, Japan, Netherlands, Poland, Portugal, Switzerland, Taipei, UK and USA. Thank you to each speaker, poster presenter, sponsor and theme chair. Thank you to Cameryn Cobb, who will provide a welcome from her perspective of being affected with SCA7. We applaud her bravery and willingness to tell her story.

We are especially grateful to the members of the SCA Global Conference Organizing Committee members, Dr. Thomas Klockgether and Dr. Tetsuo Ashizawa, Principal Investigators, Julie Greenfield, Ph.D. and Holm Graeßner, Ph.D., M.B.A. Thank you for the many hours spent to create the stellar agenda for the conference.

The SCA Global Initiative Steering committee includes those on the Conference Organizing Committee as well as Alexandra Dürr, M.D., Ph.D., Laura Jardim, M.D., Ph.D., Bing-wen Soong, M.D., Ph.D., and David Szmulewicz, M.D., Ph.D. We look forward to the leadership that these individuals will provide to guide the future efforts of this significant initiative.

Dr. Susan Perlman, NAF's Medical Director, stated the following about the conference, "Since the founding of the National Ataxia Foundation, the past three generations of ataxia patients and families, as well as staff and clinicians, have been waiting and hoping for the door to definitive clinical trials to open. SCA Global will help make this happen."

We look forward to the exciting new partnerships that will be developed because of this SCA Global Conference and how that will bring us closer to treatments and a cure for ataxia.

Sincerely,

Sue Hagen
Patient and Research Services Director
National Ataxia Foundation

SCA GLOBAL—CONFERENCE SCHEDULE

Wednesday, March 27, 2019

8:15a - 8:20a	Welcome	Tetsuo Ashizawa, MD
8:20a - 8:35a	Patient Welcome & Expectations	Cameryn Cobb, Affected with SCA7
8:35a - 9:05a	Keynote: *Scientific premise for treatments of polyglutamine SCAs*	Henry L. Paulson, MD, PhD

Theme 1 Existing cohorts and natural history of SCAs — *Chairs: Thomas Klockgether, MD, Tetsuo Ashizawa, MD*

9:05a - 9:35a	Keynote: *Enroll-HD*	Bernhard Landwehrmeyer, MD
9:35a - 9:55a	SCAs in Europe	Thomas Klockgether, MD
9:55a - 10:15a	READISCA	Tetsuo Ashizawa, MD
10:15a - 10:35a	SCA3 in Brazil	Laura Jardim, MD, PhD
10:35a - 10:50a	**Morning break** (*Posters available for viewing)*	
10:50a - 11:10a	SCAs in Australia	David Szmulewicz
11:10a - 11:30a	Taiwanese SCA cohorts	Bing-wen Soong, MD, PhD
11:30a - 11:50a	Chinese SCA	Hong Jiang, MD, PhD
11:50a - 12:10p	SCAs in Japan	Hidehiro Mizusawa, MD, PhD
12:10p - 12:20p	Evolution of ataxia in risk persons for SCA	Heike Jacobi, MD
12:20p - 12:30p	Progression of balance dysfunction as a disease biomarker	Anna Sobanska, MD
12:30p - 1:30p	**Lunch** (*Posters available for viewing)*	

Theme 2 Standards for clinical assessment, brain imaging & biosampling — *Chairs: Chris Gomez, MD, PhD, Gülin Öz, PhD*

1:30p - 2:00p	Keynote: *Fluid biomarkers & ARCA Global*	Matthis Synofzik, MD
2:00p - 2:20p	Magnetic resonance biomarkers	Gülin Öz, PhD
2:20p - 2:40p	Clinical scales and functional tests	Alexandra Dürr, MD, PhD
2:40p - 3:00p	ENIGMA	Ian Harding, MD
3:00p - 3:20p	**Afternoon break** (*Posters available for viewing)*	
3:20p - 3:40p	Wearable sensors to measure ataxia	Christopher Gomez, MD, PhD
3:40p - 4:00p	NIH perspective & International Collaboration	Daniel Miller, PhD (NINDS)
4:00p - 4:15p	Industry perspective	Moore Arnold, PhD (Biogen)
4:15p - 4:30p	Industry perspective	Gregg Keaney, PhD (Cadent)
4:30p - 4:40p	Serum neurofilaments in SCA 3	Carlo Wilke, MD, PhD
4:40p - 4:50p	Brain and spinal cord structural alterations	Jennifer Faber, MD
4:50p - 5:00p	Blood biomarker quantification in SCA 3	Hector Garcia-Moreno, MD, PhD student
5:00p - 6:00p	Panel Discussion	
6:00p - 7:30p	SCA Global **Social Reception**	
7:30p - 9:30p	ARCA Global Inaugural Meeting	Matthis Synofzik, MD

SCA GLOBAL—CONFERENCE SCHEDULE

Thursday, March 28, 2019

Theme 3 Enhancing clinical trial readiness *Chair: Alexandra Durr, MD, PhD*

8:30a - 9:00a	Keynote: *Clinical Trials*	Melissa Beiner, MD, Biohaven
9:00a - 9:20a	Trial design	Sophie Tezenas du Montcel, PhD
9:20a - 9:40a	Biomarker/outcome measure certification and drug approval	TBD
9:40a - 10:00a	Regulatory requirements for resource sharing	Johan Wisenborn
10:00a - 10:20a	**Morning break**	
10:20a - 11:45a	Guided Poster Session	
11:45a - 12:05p	Identification of an Intronic AAGGG repeat expansion in CANVAS and late-onset ataxia	Henry Houlden, MD, PhD
12:05p - 1:15p	**Lunch**	

Working groups (parallel sessions)

1:15p - 1:30p	Defining tasks and Introduction of working groups	
1:30p - 1:45p	Charging each working group for specific goals	
1:45p - 5:30p	Working Group Facilitated Sessions	
	Clinical outcomes	Thomas Klockgether, MD
	MR Biomarkers	Gülin Öz, PhD
	Standard of Biosampling	Puneet Opal, MD, PhD
	SCA Global policies	Holm Graeßner, PhD, MBA

Friday, March 29, 2019

7:30a	Continental breakfast from AAC	
8:00a - 8:30a	Multiple system atrophy -Global harmonization for the natural history and clinical trials	Shoji Tsuji, MD, PhD

Plenary session (with presentation of working group results) *Chair: Holm Graeßner, PhD, MBA*

8:30a - 9:00a	Clinical outcomes	Thomas Klockgether, MD
9:00a - 9:30a	MR biomarkers	Gülin Öz, PhD
9:30a - 10:00a	Standard of biosampling	Puneet Opal, MD, PhD
10:00a - 10:15a	Break	
10:15a - 10:45a	SCA Global policies	Holm Graeßner, PhD., MBA
10:45a - 11:00a	Action plans and closing remarks	Thomas Klockgether, MD

SCA Global Adjourns

Lunch n' Learn Session with the NAF Annual Ataxia Conference participants

11:30a - 12:30p	Open Discussion with Q&A	Thomas Klockgether, MD

SCA GLOBAL—POSTER SESSIONS

1) Laura Bannach Jardim, MD, PhD — **Universidade Federal do Rio Grande do Sul** — **Brazil**
Clinical scales and vestibulo-ocular reflex show changes in time since the pre-clinical phases in Machado-Joseph disease/ spinocerebellar ataxia type 3 (BIGPRO Study)

2) Eduardo De Mattos, PhD * — **University of Groningen** — **Netherlands**
The molecular chaperone DNAJB6 as a phenotypic modulator of spinocerebellar ataxia type 3/ Machado-Joseph disease.
(* *Poster presented by Laura Bannach Jardim, MD, PhD*)

3) Karina Donis, MD — **Hospital de Clinicas de Porto Alegre** — **Brazil**
Body mass index and peripheral sensitivity to insulin in Spinocerebellar Ataxia Type 3/Machado-Joseph Disease (BIGPRO study)

4) Chandrakanth Reddy Edamakanti, PhD — **Northwestern University** — **United States**
Characterization of Cerebellar Exosomes from SCA1 Mice: Facilitating Biomarker Development for Patients

5) Marcus Grobe-Einsler, MD — **University of Bonn** — **Germany**
SARAhome – a new clinical tool for assessing ataxia at home

6) Tomer Hillel, PhD — **Israeli MJD Association** — **Israel**
Can lifestyle affect SARA scale results

7) Henry Houlden, MD, PhD — **Institute of Neurology** — **United Kingdom**
Identification of Genetic Modifiers of Age at Onset and Disease Progression in the Spinocerebellar Ataxias

8) Richard Joules, PhD — **IXICO** — **United Kingdom**
Development of a fully automated method for MRI volumetry in ataxia

9) Marta Antonia Manes, MD — **University of Brescia** — **Italy**
Long-term efficacy of Docosahexaenoic acid (DHA) for Spinocerebellar Ataxia 38 (SCA38) treatment: an open label extension study

10) Marta Antonia Manes, MD — **University of Brescia** — **Italy**
Randomized, double-blind, sham-controlled, crossover trial of cerebello-spinal tDCS in ataxia

11) Maria Luiza Saraiva-Pereira, PhD — **Universidade Federal do Rio do Sul** — **Brazil**
Polymorphisms at ATXN3 gene: from ancestral haplotypes to functional variants in a comprehensive study in Brazilian patients with Machado-Joseph disease.

12) Thorsten Schmidt, PhD — **University of Tuebingen** — **Germany**
The haplotype status of SCA3 patients impacts the pathophysiology of SCA3

13.) Matthis Synofzik, MD — **Hertie Institute** — **Germany**
Quantifying ataxic gait characteristics as an outcome parameter in upcoming clinical SCA trials: From preclinical movement changes to free-living gait

14) Luis Pereira de Almeida* — **University of Coimbra** — **Portugal**
Characterization of the Coimbra Cohort of Machado-Joseph Disease Patients for Future Clinical Trials

(* *on behalf of the European SCA3/MJD Initiative (ESMI) consortium*)

SCA GLOBAL—CONFERENCE ATTENDEES

Moore Arnold, PhD
Principal Scientist
Biogen

Tetsuo Ashizawa, MD
Houston Methodist Hospital

Georg Auburger, MD
Frankfurt, Germany

Katie Beattie, MS, CGC
Certified Genetic Counselor
GeneDx

Jennifer Beecham, MS
Manager
Reata Pharmaceuticals

Melissa Wolfe Beiner, MD
Medical Director
Biohaven Pharmaceuticals

Rob Berman, MD
Chief Medical Officer
Biohaven

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Khalaf Bushara, MD
University of Minnesota

Hannah Casey, BS
University of Chicago

Edwin Chan, PhD
The Chinese University Of HK
Hong Kong

Cameryn Cobb
Patient Attendee

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Murdoch Children's Research Institute
Parkville, Australia

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Mike Curtis, PhD
Cadent Therapeutics

Bob Dagher, MD
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Cadent Therapeutics

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SCA GLOBAL—CONFERENCE ATTENDEES

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Braga, Portugal

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Portocannone, Italy

Lucy Manheim, PhD
Patient Attendee

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Johns Hopkins University

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Theresa Zesiewicz, MD
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SCA GLOBAL—BIOGRAPHIES

Tetsuo Ashizawa, M.D.

Dr. Ashizawa is a physician-scientist whose research interest is in genetic neurodegenerative ataxia. His laboratory found the first pentanucleotide repeat disorder (SCA10) which led to subsequent discoveries of an increasing number of similar disorders. Using single molecule real time (SMRT) sequencing, which can produce long reads of the repeat, he found interrupting repeats within the expanded repeats in patients' genomic DNA. Genotype-phenotype correlations and corresponding transgenic animal models support the hypothesis that these heterogeneous repeat sequences determine the clinical phenotypes and repeat instability of SCA10. He also investigates the RNA-gain-of-function pathogenic mechanism of SCA10 and other repeat expansion disorders. As a physician, he has provided healthcare to many SCA patients and established the US and international consortia of SCA investigators who treat and study SCA patients. He was a leader of the NIH-funded Clinical Research Consortium for Spinocerebellar Ataxia studies and continues to contribute to the group. Dr. Ashizawa is serving as corresponding PI of NIH U01 funded "READISCA" project, which includes investigators from 18 US and 2 European institutions, working toward clinical trial readiness focusing on SCA1 and SCA3. He is now working on the SCA Global with Dr. Thomas Klockgether who initiated the organization. He also has extensive research, clinical and educational administrative experiences as former Chairman of the Neurology Departments at University of Texas Medical Branch (UTMB) and the University of Florida, and as Executive Director of the McKnight Brain Institute. He is currently Director of the Neuroscience Research Program at the Houston Methodist Research Institute (HMRI).

Melissa Wolfe Beiner, MD

Dr. Melissa Beiner was formerly a pediatrician in private practice prior to joining Biohaven in 2017. Dr. Beiner conducted pre-clinical research in neuroscience, focusing on spinal cord injury and neuronal regeneration both at the Yale School of Medicine Neurosurgical Research Laboratories and at The Miami Project to Cure Paralysis. In her current role at Biohaven, Dr. Beiner is the Director of Research and Development and holds lead responsibility for the ataxia clinical program. Dr. Beiner also leads a clinical study in trigeminal neuralgia and supports the OCD program. Dr. Beiner completed her residency in Pediatrics at the Yale New Haven Children's Hospital and earned her medical degree at Yale University School of Medicine.

Cameryn Cobb

Cameryn Lauren Cobb was diagnosed with SCA-7 in November 2015. Although the ataxia diagnosis has taken many things away, she's accomplished so much including her Girl Scout Gold Award, walking across the stage for her high school graduation and successfully completing college courses. Cameryn volunteered at a day care center working with 2-3-year olds but is now focusing her time on learning American Sign Language since she hopes to be a social worker at a school for the hearing impaired. Cameryn's personal mantra is a quote from P.T. Barnum "No One Ever Made a Difference by Being Like Everyone Else." Cameryn lives in a Chicago suburb with her parents, 15 year old brother and there is no family history of ataxia.

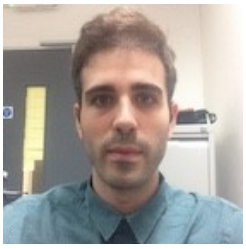
Alexandra Dürr, M.D., Ph.D.

Alexandra Durr is a Professor of Neurogenetics in the Genetic Department at the Pitié-Salpêtrière University Hospital in Paris- France. She has specialization in neurology and genetics and has been developing translational neurogenetics for 25 years, based on a thorough clinical expertise that allowed her to identify the molecular bases of many pathologies. She worked with premanifest individuals, i.e. mutation carriers without clinical signs of the disease, since 1992, pioneering the first presymptomatic structure for neurogenetic diseases in France. Genetic advances are used by her team at the ICM (Institut du Cerveau et de la Moelle épinière https://icm-institute.org) to understand pathophysiology and to set up innovative therapies. In order to prepare this new era of genetic therapeutics, Alexandra Durr is taking advantage of the pre-manifest phase of neurodegenerative diseases and is developing progression markers to determine the best therapeutic window, that will insure that the disease does not develop further. She is coordinating the SPATAX network https://spatax.wordpress.com.

SCA GLOBAL—BIOGRAPHIES

Jennifer Faber, MD

Dr. Jennifer Faber is resident physician at the Department of Neurology, University Hospital Bonn, Germany, and clinical investigator and research assistant at the German Center of Neurodegenerative Diseases (DZNE) in the group of Prof. Thomas Klockgether. She received a prediploma in Mathematics from Bonn University, and graduated from Bonn University Medical School with an M.D. and a Doctor of Medicine degree. After a research stay at the Department of Psychology of Stanford University, she continued her postdoctoral training at the DZNE. Dr. Faber's research focuses on MR imaging of ataxias. In particular, she uses diffusion tensor imaging to assess structural alterations of the white matter beyond atrophy patterns. She received the second prize of the Mähler-Linke-Foundation for an imaging study in sporadic adult-onset ataxias. Within the ongoing European Spinocerebellar Type 3/Machado-Joseph Disease Initiative (ESMI) she co-leads the longitudinal collection of standardized multimodal MRI. Here, the particular focus lies on mapping structural alterations over the whole course of the disease including the pre-ataxic stage.



Hector Garcia-Moreno, MD

Dr. Hector Garcia-Moreno works as a Clinical Research Associate and Honorary Clinical Assistant in the Ataxia Centre, UCL Queen Square Institute of Neurology and National Hospital for Neurology and Neurosurgery, London (United Kingdom). He graduated from Universidad Autonoma in Madrid (Spain) with MD degree in Medicine. Subsequently, he accomplished his specialization in Neurology in Clinico San Carlos Hospital (Madrid, Spain). In 2016, he joined the Ataxia Centre and started his PhD in UCL. Dr Hector Garcia-Moreno is involved in research projects aimed at describing new biomarkers for autosomal and recessive forms of cerebellar ataxias. In London, he is the leading clinician for the ESMI project (European Spinocerebellar Ataxia Type-3/Machado-Joseph Disease Initiative), and he is particularly focused on the characterization of novel blood and CSF biomarkers. He is also participating in other research projects for polyglutamine SCAs (EUROSCA), Friedreich's ataxia (EFACTS), xeroderma pigmentosum or ARSACS.

Christopher Gomez, M.D., Ph.D. Dr. Gomez began seeing patients with spinocerebellar ataxia in 1987 in the UCLA Ataxia clinic under the guidance of Susan Perlman, while working in a postdoc at Caltech. In 1990 he was recruited as assistant professor to the University of Minnesota Department of neurology where he established the U of M Ataxic Clinic and started his laboratory work on ion channel disorders and neurodegeneration. With the help of Drs Laura Ranum and Harry Orr he began to study the genetics of ataxia, eventually identifying alpha1ACT, the protein responsible for SCA6 and the gene for SCA26. In 2006 he moved to the University of Chicago and established UC ataxia clinic. In his laboratory work he identified the molecular mechanism underlying expression of the alpha1ACT and is now working with IONIS to develop anti-sense oligos to silence this protein. Dr. Gomez has been involved extensively with the clinical characterization of patients with ataxia. His recent work is focused on developing metrics for ataxia using wearable inertial sensors to increase precision in the SARA exam. It is his team's hope that the instrumented SARA, or iSARA, will increase the success of clinical trials.

Holm Graeßner, Ph.D., MBA

Dr.Graeßner has been Managing Director of the Rare Disease Centre, since 2010, at the University and University Hospital Tübingen, Germany. www.zse-tuebingen.de. He is Coordinator of the European Reference Network for Rare Neurological Diseases (ERN-RND). www.ern-rnd.eu. Together with Olaf Riess, he coordinates the H2020 Solve-RD project on "Solving the unsolved rare diseases". www.solve-rd.eu. He received his PhD "Summa cum laude" in 2004 and, then, he obtained his MBA degree in 2008. From 2003 until now, he has been coordinating and managing more than 10 EU funded collaborative projects. The main focus of these projects are rare and neurological diseases, among them EUROSCA, MEFOPA, SENSE-PARK, MULTISYN, NEUROMICS and PROOF. He has been co-leading one of the four working groups of the German Action Plan for Rare Diseases and is co-leading the program committee for the first German National Conference for Rare Diseases (Sept 2019). Since 2017, in his function as the coordinator of ERN-RND, he is a member of the Rare Disease Task Force of the European Academy of Neurology. In the Coordinator's Group of the European Reference Networks, he leads the cross-border healthcare working group.

SCA GLOBAL—BIOGRAPHIES

Julie Greenfield, PhD

Is the Head of Research for Ataxia UK, a medical research charity and patient support organization. She have been working for Ataxia UK since 2001 and in this time have gained knowledge of research in the ataxia field as well as the issues being faced by people with ataxia. Ataxia UK is a member of Euro-ataxia, the federation of ataxia charities in Europe and I play an active role within Euro-ataxia, with the aim of sharing best practice in healthcare and facilitating research. Ataxia UK also works closely with a number of other umbrella organizations such as Genetic Alliance UK (I was formerly a Trustee), Rare Disease UK and the Neurological Alliance.

At Ataxia UK I have responsibility for leading the research strategy of the charity by managing the research programme, funding grants, promoting and facilitating research on ataxia and developing numerous partnerships. I am currently a Steering Board member of the EU funded project 'European spinocerebellar ataxia type 3/machado Joseph disease initiative', as the patient group representative and on the Steering Committee of both SCA Global and ARCA global projects. I have been involved in organizing four International Ataxia Research Conferences (IARC) and have been a speaker at many events disseminating information on ataxia research and the impact of the conditions. Part of my work at Ataxia UK has also involved setting up Specialist Ataxia Clinics to improve the diagnosis and management of patients with ataxia. In addition, as a member of the Helpline team and active participant at many patient meetings, I have gained an understanding of issues that are important to people with ataxia and their families.

My background is in scientific research in the biological sciences, having completed a PhD at the University of Bristol and a three-year postdoctoral research position at the University of Manchester. Prior to joining Ataxia UK, I worked for Synergy Medical Education as a Project Manager, working on communication materials for major pharmaceutical companies.

Ian Harding, PhD

Dr. Ian Harding is a Research Fellow at the Institute of Cognitive and Clinical Neurosciences, Monash University (Melbourne, Australia). His research uses human MRI and PET neuroimaging to investigate markers and mechanisms of neurological disorders, with a focus on cerebellar and subcortical degenerative diseases. He completed his PhD in cognitive neuroscience from the University of Melbourne in 2013, before commencing a post-doc investigating the neural expression and progression of Friedreich Ataxia at Monash University. In 2016, Dr. Harding was awarded a prestigious 4-year NHMRC (Australian NIH-equivalent) early career fellowship to continue his neuroimaging work in FRDA and other cerebellar and subcortical neurodegenerative disorders. He is the founding principal investigator of the ENIGMA-Ataxia International Neuroimaging Research Consortium, and co-convener of the Monash University Dementia & Neurodegeneration Research Network, both launched in 2017.

Henry Houlden, MD, PhD

Our laboratory works on neurogenetics with a particular interest in spinocerebellar ataxia and movement disorders, particularly in diverse populations. We integrate new gene discovery such as CANVAS, SCA11, SCA15, genetics modifiers in the SCAs, using the latest genomic techniques with functional experimental validation in human tissue and other model systems. Our goal is to develop new therapeutics based on an improved understanding of disease mechanisms in children and adults. We recently established a collaborative project to genotype and carry out a GWAS in SCA patients with repeat expansions from around the world to identify genetic modifiers of age at onset and severity. As a group we are very keen to collaborate and keen to analyze further families, possible CANVAS and SCA patients in the age at onset GWAS, Email: h.houlden@ucl.ac.uk

Heike Jacobi, MD

Dr. Heike Jacobi works as consultant at the Department of Neurology, University Hospital Heidelberg, Germany. After she graduated from Cologne University Medical School with an M.D. and a Doctor of Medicine degree she successfully completed her specialist training in Neurology at the department of Neurology in Bonn. Since 10/2016 she continues her work at the Department of Neurology, University Hospital Heidelberg, Germany. Dr. Jacobi's research focuses on the clinical characteristics and natural history of the most common spinocerebellar ataxias with a special interest in the pre-ataxic stage. During her time at the Bonn University Hospital and the DZNE Dr. Jacobi coordinated two international multicenter cohort studies lead-managed by Prof. Klockgether. For her work she was awarded the German Heredo-Ataxia Price 2015 and the Hans-Jörg Weitbrecht Preis 2017.

SCA GLOBAL—BIOGRAPHIES

Laura Jardim, MD, PhD

Dr. Jardim is Full Professor at the Department of Internal Medicine, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Brazil.

She is a physician scientist who identified an important founder effect and cluster of a large population of spinocerebellar ataxia type 3, also known as Machado-Joseph disease (SCA3/MJD) in south Brazil. Thanks to her studies, SCA3/MJD is known to have a relatively high local prevalence (6: 100,000), with more than 600 live patients and approximately 1,500 people at risk in that region. Since 2001, she has been the PI of the Neurogenetics Research Group at her institution; and since 2008, she established Rede Neurogenetica (www.redeneurogenetica.ufrgs.br), a Brazilian network that allowed the diagnosis of several SCAs in Brazil.

The continued work of her research group on SCA3/MJD raised original evidence about the effect of mutation on the fecundity of carriers; the preferential segregation of the mutant allele during conception; population-specific effects that modify the age of onset regardless of causal mutation; the various neurological manifestations and their correlations with causal factors; the natural history of disease; potential biomarkers; and safety and efficacy of lithium on neurological progression in a randomized, investigator-initiated (non-industry -funded) trial. Likewise, similar approaches on other disorders due to expanded repeats and commonly found in Brazil, such as SCA2, SCA7, SCA10 and Huntington disease, are currently underway.

In summary, her aim is to help increase the knowledge on neurogenetic disorders. Because of this, training of human resources in neurogenetics is another of her goals.

Hong Jiang, MD. PhD

Prof. Hong Jiang got his bachelor's degree in Clinical Medicine at the former Hunan Medical University in 1996 and received his doctoral degree in Neurology at Xiangya Hospital of Central South University in 2004. From 2008 to 2009, he completed his postdoctoral research in Department of Neurology, University of Chicago Medical Center. He has been working as a neurologist in the Department of Neurology of Xiangya Hospital since for over 20 years. His research work mainly aims at clinical and basic research on neurodegenerative diseases and genetic diseases (spinocerebellar ataxia, hereditary spastic paraplegia, Huntington disease, multiple system atrophy, dystonia, etc.), including genetic diagnosis, molecular typing, gene cloning, pathogenesis, epigenetics and treatment research. Prof. Hong Jiang has 46 SCI papers published as the first or correspondent authors, with the total impact factor over 160. He has attained 8 National Natural Science funds, 6 provincial and ministerial achievement awards, and 2 granted patents. And he received the award of the Outstanding Young Neurologist of the Chinese Medical Doctor Association in 2016. He served as the vice chairman of the Youth Committee of the Neurology Branch of Chinese Medical Association, the vice chairman of the Youth Committee of the Neurology Physician Branch of the Chinese Medical Doctor Association, the vice chairman of the Youth Committee of the Medical Genetics Branch of the Chinese Medical Doctor Association, etc.

Thomas Klockgether, MD

Prof. Klockgether studied medicine at the University of Göttingen and during this time also carried out research at the Max Planck Institute for Experimental Medicine. After graduating, he went to Oldenburg for clinical training and then returned to the Max Planck Institute to work in basic research on Parkinson's disease. He completed his neurology training in Tübingen, where he also began to focus on degenerative ataxias, in addition to pursuing research on Parkinson's disease. These research lines evolved very successfully during his appointment in Bonn as Chairman of Department of Neurology. Prof. Klockgether has been the Dean of the Medical Faculty of the University of Bonn from 2008 to 2011. Since February 2010 he has been Speaker of the Center for Rare Diseases Bonn (ZSEB) and since May 2011 Director of Clinical Research at the DZNE.

G. Bernhard Landwehrmeyer, MD, PhD

G. Bernhard Landwehrmeyer, MD, FRCP is Full Professor of Neurology at Ulm University Hospital, Dept. of Neurology where the Central Coordination of the European Huntington's Disease Network (EHDN) is situated. 2004 he was instrumental in founding EHDN and served as chairman of the Executive Committee until 2014. EHDN serves as a platform for professionals, people affected by Huntington's disease (HD), and their relatives to facilitate working together throughout Europe and conducts large prospective natural history studies in HD, e.g. the REGISTRY study. EHDN and REGISTRY is generously funded by the CHDI Foundation (USA). He received his MD degree and Doctoral Degree from the Albert-Ludwigs-University, Freiburg. He was trained at the Royal Victoria Hospital, Queen's University, Belfast, at the Kantonsspital, Basel and worked as post-Doc from 1993 -1996 at MGH, Harvard Medical School, Boston. From 1995–1999, he was staff member at Albert-Ludwigs-University (Dept. Neurology & Psychiatry). 1999 he received Board Certification in Neurology, 2000 the Venia Legendi and full Professorship ('C3'). He served as Principal Investigator in numerous HD trials and is PI of the CHDI-sponsored Enroll-HD study, a prospective longitudinal observational study on HD and a clinical research platform with a worldwide reach that annually collects phenotypical clinical data and biomaterials.

SCA GLOBAL—BIOGRAPHIES

Daniel Miller, PhD

Dr. Daniel Miller joined NINDS in 2015 and serves as a Program Director in the Neurodegeneration Cluster. His focus is basic, translational, and clinical research on Huntington's Disease and Spinocerebellar Ataxia, as well as invertebrate neuromuscular junction research. Dr. Miller received a PhD in molecular biology from Princeton University, where he developed functional genomic approaches to study tumor virus control of cellular gene expression. He then joined the lab of Dr. Barry Ganetzky, at the University of Wisconsin-Madison, where he studied neuroprotective genes in Drosophila and developed a novel neuronal model system to probe neurodegeneration and regeneration in long-lived larvae. Most recently, as a visiting researcher at Janelia Farm (HHMI), he collaborated with Dr. Jim Truman to model the structural plasticity of injured circuits and the developmental plasticity of neuronal stem cells. Dr. Miller is also the Drosophila contact at NINDS.

Hidehiro Mizusawa, MD, PhD

Dr. Hidehiro Mizusawa is President of National Center of Neurology and Psychiatry since April 2016 after 2 years of Director General, National Center Hospital of the institute. He graduated with MD in 1976 from Faculty of Medicine of Tokyo University, where he received PhD in 1983. He moved to Tsukuba University as Assistant Professor in 1984 and became Associate Professor of Department of Neurology in 1988. He has been Professor and Chair of Department of Neurology and Neurological Sciences, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University since 1996 till 2014, where he has been Director of Center for Brain Integration Research, Director of School of Medicine, Vice Director of the Medical Hospital and Associate Managing Trustee for Research of the University.

He has contributed particularly to researches on pathogeneses of ALS, Pure Akinesia/PSP, SCA, mitochondrial neuropathy, distal myopathy and Prion disease. He has long been Chairman of Research Committees on Prion disease, Ministry of Health, Welfare and Labor, Japan since 2002 and a core member of the Research Committee on Neurodegenerative Diseases and that on Ataxic Disorders of which he was appointed as Chairman since April 2014. He has been also a member of Advisory Board of National SCA/MSA Patients' Association. Regarding the Initiative on Rare and Undiagnosed Disease, he has been the PI since 2015. He served as President of Japanese Society of Neurology since 2010 till 2014 and was President of Prion 2016 in Tokyo, President of WCN 2017 in Kyoto and Vice President of ICN 2018 in Tokyo.

Gülin Öz, PhD

Dr. Gülin Öz is Professor at the Center for Magnetic Resonance Research (http://www.cmrr.umn.edu/), University of Minnesota and specializes in magnetic resonance spectroscopy (MRS). She graduated from Bosphorus University in Istanbul, Turkey with BS degrees in Physics and Chemistry and obtained her PhD in Biochemistry at the University of Minnesota. She continued with postdoctoral training at CMRR where she joined the faculty in 2006.

Dr. Öz uses high field, multi-nuclear MRS to delineate neurochemical and metabolic alterations in diseases that affect the brain, in particular neurodegenerative diseases and diabetes. She leads a program in spinocerebellar ataxias and has studied neurochemistry in Parkinson's, Huntington's, and Alzheimer's diseases. She studies the effects of diabetes and the hypoglycemic consequences of intensive insulin therapy on brain glucose and glycogen metabolism in humans and has worked to elucidate pathogenic mechanisms of hypoglycemia unawareness syndrome using multi-nuclear MRS. Finally, she co-led an effort by the MRS Consensus Group, an international group of MR physicist and clinicians, to facilitate standardization of MRS methodology and to provide guidelines for data acquisition and analysis, quality assessment, and interpretation. She leads a multi-site Bioengineering Research Partnership (BRP) for across-platform harmonization of advanced MRS methods.

Henry (Hank) Paulson, MD, PhD

Dr. Paulson received his MD and PhD from Yale University in 1990 and then completed a neurology residency and neurogenetics/movement disorders fellowships at the University of Pennsylvania. In 2007, after a decade at the University of Iowa, he joined the Neurology faculty at the University of Michigan where he is delighted to be part of a growing group of Ataxiologists and Ataxia scientists. Dr. Paulson's research and clinical interests concern the causes and treatment of age-related neurodegenerative diseases, with a focus on Hereditary Ataxias and Alzheimer's disease. Using test tube, cell-based and animal models his lab has contributed to advances in the understanding of various neurodegenerative diseases with a particular focus on Spinocerebellar Ataxia Type3 (SCA3). Efforts in his lab increasingly are seeking to find treatment for SCA3 and related Ataxias. Nationally, Dr. Paulson has directed Ataxia courses at the Annual American Academy of Neurology meeting, has served on the scientific advisory boards of numerous disease-related organizations including the National Ataxia Foundation, and is currently Chairperson of the Board of Scientific Counselors at the National Institute for Neurological Disorders and Stroke at the National Institutes of Health. Among his awards, Dr. Paulson is a past Ellison Medical Foundation New Scholar in Aging, semifinalist for the W.M. Keck Foundation Young Scholars in Medical Research, and recipient of the Paul Beeson Physician Faculty Scholar in Aging Award from the American Federation for Aging Research.

SCA GLOBAL—BIOGRAPHIES

Anna Sobanska, MD

Anna Sobanska is a neurologist and neurophysiologist in the Department of Neurophysiology at the Institute of Psychiatry and Neurology in Warsaw, Poland. After graduating from Medical University of Warsaw in 2001, she served her internship at Miedzyleski Hospital in Warsaw and her neurology residency at John Paul II Western Hospital in Grodzisk Mazowiecki. In the same time, she cooperated with Sleep Disorders Laboratory in the Institute of Psychiatry and Neurology as well as completed training in neurophysiology, concerning electromyography and evoked potentials at Medical University of Warsaw and electroencephalography at the Institute of Psychiatry and Neurology.

In 2012 she was recruited to the Department of Neurophysiology at the Institute of Psychiatry and Neurology. Her main activities are dedicated to the diagnosis of neurodegenerative diseases. She works also in a multidisciplinary team which focusses on rare ataxias: diagnosis, follow-up, support of the patients and their families. The team has been cooperating with Ataxia Study Group for several years.

She is going to defense her PhD thesis "Analysis of postural stability in SCA1 mutation carriers by use of static posturography" this year. She studied the usefulness of force platform as a biomarker of balance dysfunction in preclinical and symptomatic SCA1 patients in the five-year-long follow-up and after short lasting intensive rehabilitation.

Bing-Wen Soong, MD, PhD

Dr. Bing-wen Soong is Professor at the Department of Neurology (http://www.cmrr.umn.edu/), Taipei Medical University and specializes in neurogenetics. He graduated from National Defense University School of Medicine in Taipei, Taiwan with MD degree in 1978 and obtained his PhD in Molecular Biology at the National Yang-Ming University, Taipei, Taiwan, in 1992. He received Neurology training at Washington University School of Medicine at St. Louis, Missouri, and University of Texas Health Science Center at Dallas, Texas and Genetics training at the National Institutes of Health (NINCDS) between 1982 and 1987.

Dr. Soong published a report of molecular and metabolic studies of patients with spinocerebellar ataxia (SCA) in 1997. In the following years, he completed many important studies on patients with SCA2, SCA3, SCA6, SCA17, SCA31, SCA35, SCA36 and multiple system atrophy. His lab is one of the first in the world to report parkinsonism as the presenting feature of SCA2. In 2003, his lab successfully mapped the locus for SCA22, followed by identification of the first mutation in KCND3 as the cause of SCA19/22 in 2012. In 2013, his lab identified the first mutations in GNB4 as the cause of a dominant intermediate Charcot-Marie-Tooth disease. His lab has put in a lot of efforts designing therapies for cerebellar ataxia, including a clinical trial with allogeneic transplantation of adipose tissue-derived mesenchymal stem cells. His lab has also been generating transgenic and knock-in animal models in order to conduct mechanistic and therapeutic studies of ataxia.

Matthis Synofzik, MD

Dr. Matthis Synofzik is Professor at the Hertie Institute for Clinical Brain Research & Center for Neurology (https://www.hih-tuebingen.de/en), University of Tübingen, Germany. He completed his medical thesis in the field of cognitive neuroscience on the perceptual and motor faculties of the cerebellum in 2008.
His post-doctoral research and clinical career has since then been fully dedicated to the genetics and biomarkers in hereditary ataxias, with specific training and expertise in next-generation genomics, deep-phenotyping, biomarkers and translational studies, as reflected by now >180 PubMed listed peer-reviewed publications on hereditary ataxias, frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS) and other neurogenetic conditions. His research includes a strong focus on unravelling the genetic and molecular basis of both autosomal-dominant and autosomal-recessive ataxias, identifying novel biomarkers, running deep-phenotyping studies and designing and establishing innovative treatments for these ataxias. This is facilitated by his function as the PI or co-PI of several global consortia, e.g. PREPARE, EarlyOnset-Ataxia Network GENFI, DZNE FTD and the new ARCA GLOBAL platform.

David Szmulewicz, MD

David Szmulewicz is an Australian Neurologist, Neuro-otologist and medical researcher. He holds a PhD from the University of Melbourne and his clinical and research interests include balance and coordination disorders that affect the cerebellum, vestibular system and the combination of the two. David is the head of the Balance Disorders & Ataxia Service at the Royal Victorian Eye & Ear Hospital, founder of the Alfred Hospital Cerebellar Ataxia Clinic, neurologist to the Monash Health Friedreich's Ataxia Clinic and Lecturer at Melbourne University. David's research activities include lead investigator on a project to develop objective ataxia metrics, research defining a novel ataxia – Cerebellar Ataxia with Neuropathy and Vestibular Areflexia Syndrome (CANVAS), as well as the development of an objective oculomotor test of imbalance - the video VVOR.

SCA GLOBAL—BIOGRAPHIES

Sophie Tezenas, MD, PhD

Sophie Tezenas du Montcel is a public health doctor (Assistance Publique-Hôpitaux de Paris) with a PhD in genetic Epidemiology. She has an expertise in biostatistics and epidemiology. She works in a Biostatistics department which encloses the Biostatistics team of the clinical research unit. The unit is involved in all the clinical trials involving academic sponsors at Sorbonne University. For the past 15 years, she has analyzed data concerning SCA patients and related disorders (Friedreich ataxia, Huntington disease). Since then she has developed collaborations locally and internationally. As part of these collaborations, she has developed a quantitative tool to evaluate the severity of the cerebellar syndrome, the CCFS (Cerebellar Composite Functional Score) and a semi-quantitative clinical scale for cerebellar assessments, SARA (Scale for the Assessment and Rating of Ataxia). She analyzes the EUROSCA natural history, a large multinational European cohort of SCA patients, and the genetic modifier study of the EUROSCA study. She also analyzes the RISCA cohort, a European cohort of SCA for at-risk subjects. As part of the READISCA study, granted by the NIH, she is in charge to design the best trial for SCA patients and to analyze the clinical data.

Shoji Tsuji, MP, PhD

Dr. Shoji Tsuji is Professor at Department of Molecular Neurology, The University of Tokyo and specialized in genomic research on neurological diseases. He graduated from the University of Tokyo. He received his MD and PhD from The University of Tokyo. He served his residency in Neurology at Jichi Medical School. In 1984, he moved to NIH and elucidated molecular basis of Gaucher disease. In 1987 he moved to Niigata University, Japan and was appointed as Professor of Neurology and Director at Brain Research Institute, Niigata University. In 2002, he moved to The University of Tokyo.

His research focus is elucidation of molecular basis of hereditary as well as sporadic neurological diseases based on comprehensive genome analysis. In 2013, his team discovered that COQ2 gene is a susceptibility gene for multiple system atrophy (MSA), which suggested the efficacy of supplementation of a high dose CoQ10 for MSA. He organized a consortium to conduct a cohort study to obtain a natural history of Japanese MSA patients, and, has been conducting a phase 2 clinical trial for MSA this year. Very recently his team discovered noncoding repeat expansions in benign adult familial myoclonus epilepsy (BAFME).

Carlo Wilke, MD, PhD

Dr. Carlo Wilke is a neurologist and research fellow at the Hertie Institute for Clinical Brain Research (https://www.hih-tuebingen.de/en/), University of Tuebingen, Germany, and specializes in biomarker research and genetics of neurodegenerative diseases. He studied medicine in Tuebingen, Aberdeen and London.
His research is dedicated to discovering both robust and easily accessible fluid biomarkers in neurodegenerative diseases to promote early diagnosis and precise monitoring of disease progression, including the presymptomatic stage of neurodegenerative diseases. Dr. Carlo Wilke has focused on quantifying peripheral blood concentrations of biomarkers for central neurodegeneration, such as Neurofilament Light (NfL) and phosphorylated Neurofilament Heavy (pNfH), both in degenerative ataxias and other complex neurodegenerative diseases. Moreover, he has a broad background in the genetics of neurodegenerative diseases, with specific training in next-generation genetics and deep-phenotyping of degenerative ataxias.

ADDITIONAL SCA GLOBAL CONFERENCE ATTENDEES

Peter Bialek, PhD
Department Head
Triplet Therapeutics
Cambridge, MA

Jennifer Farmer, MS, CGC
Executive Director
FARA
Downingtown, PA

Astrid Rasmussen, MD, PHD
Oklahoma Medical Research
Foundation
Oklahoma City, OK

Adina Tocoian, MD, PhD, FACMG
Roche
Zug, Switzerland

Lodewijk Toonen, PhD
Research Fellow
UniQure
Amsterdam, Netherlands

SCA GLOBAL— POSTER SESSION ABSTRACTS

1) Laura Bannach Jardim, MD, PhD

Clinical scales and vestibulo-ocular reflex show changes in time since the pre-clinical phases in Machado-Joseph disease/spinocerebellar ataxia type 3 (BIGPRO Study)

Camila M. Oliveira[1], Gabriela Bolzan, [1] Gabriela Ecco[1], Amanda Henz[1], Anastacia G. Rocha[1], Nathalia Kersting[1], Mariana Rieck[2], Ana Carolina Martins[1], Vanessa B. Leotti[1,2], Maria-Luiza Saraiva-Pereira[1,2], Laura B. Jardim. [1,2]

[1] *Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil;* [2] *Hospital de Clinicas de Porto Alegre, Brazil.*

Suggested Theme: Theme 1 - Existing cohorts and natural history of SCAs.

Background and Objective: BIGPRO is a longitudinal study aiming to validate biomarkers for disease progression in spinocerebellar ataxia type 3/ Machado-Joseph disease (SCA3/MJD) since the pre-symptomatic period (bigpro.webnode.com). We report baseline findings obtained from clinical scales and vestibulo-ocular reflex (VOR).

Methods: Recruitment occurred between August 2017 and November 2018. For asymptomatic carriers (SARA < 3), time from onset (corrected by age) was estimated as described elsewhere (doi: 10.1111/ene.13779): they were divided in far from (AFF) and near (AN) (4 or less years) the predicted age at onset at birth. Genetic tests were double-blind. VOR was measured by video-oculography using EyeSeeCam system (doi: 10.3233/VES-160579).

Results: Overall characteristics of 83 subjects were:

	Symptomatic carriers (29)	Asymptomatic carriers near the predicted AO (AN) (12)	Asymptomatic carriers far from predicted AO (AFF) (23)	Related controls (19)	p
Age at evaluation (years)	39.5 (9.3)a	32.92 (9.55)	27.13 (5.66)	31.2 (9.8)b	0.0001*
CAG repeat larger allele	76 (69-81)	76 (72-81)	74 (71-78)		ns***
Time versus start of gait ataxia (years)	5 (0 to 8)	-5 (-6 to -4)	-13,00 (-29 to -7)		
NESSCA	12 (7-23)a	**7 (11-13)b**	2 (0-9)c	**2 (0-5)c**	0.0001**
SARA	7 (3-16)a	1 (0-2.5)b	0.5 (0-2.5)b	0.5 (0-1.5)b	0.0001**
ICARS	22 (8-47)a	5.5 (2-13)b	2 (0-9)b	1.00 (0-7)b	0.0001**
INAScount	5 (2-11)a	3.5 (0-7)b	1 (0-5)b	1 (0-4)b	0.0001**
SCAFI	-0.77 (0.76)a	**0.10 (0.35)b**	0.38 (0.41)c	**0.67 (0.40)c**	**0.001 ***
CCFS	1.04 (0.08)a	0.95 (0.06)b	0.92 (0.03)b	0.92 (0.05)b	0.0001 *
VOR 60	0.69 (0.27-1.10)a	**0.93 (0.36-1.06)b**	1.02 (0.89-1.14)c	**1.06 (0.77-1.16)c**	**0.0001****

* Anova; ** KW; *** t test. Tukey and Dunn tests: different letters mean significant differences.

VOR, NESSCA and SCAFI distinguished AN from controls. Time to onset correlated with NESSCA, ICARS and VOR in pre-symptomatic carriers (rho=0.60, 0.62 and -0.51, p<0.05).

Conclusion: VOR and NESSCA distinguished pre-clinical carriers near the predicted from controls and correlated with time to onset in pre-symptomatic subjects, and are good candidates for state biomarkers for this phase of life in SCA3/MJD.

Acknowledgements: CAPES, CNPq, FAPERGS, FIPE-HCPA.

References: 10.1111/ene.13779: de Mattos et al. Age at onset prediction in spinocerebellar ataxia type 3 changes according to population of origin. *Eur J Neurol.* 2019 Jan;26(1):113-120. 10.3233/VES-160579: Luis et al. Vestibulo-ocular reflex dynamics with head-impulses discriminates spinocerebellar ataxias types 1, 2 and 3 and Friedreich ataxia. *J Vestib Res.* 2016 Jul 2;26(3):327-34.

2) Eduardo De Mattos, PhD

The molecular chaperone DNAJB6 as a phenotypic modulator of spinocerebellar ataxia type 3/ Machado-Joseph disease

Eduardo Preusser de Mattos [1,2,3], Vanessa Bielefeldt Leotti [4,5], Gabriel Vasata Furtado [1,2], Márcia Polese-Bonatto [2,6], Gabriela Bolzan [1], Camila Maria Oliveira [1], Anastácia Guimarães Rocha [7], Jonas Alex Morales Saute [8,9], Harm H. Kampinga [3], Maria Luiza Saraiva-Pereira [1,2,8,10], Laura Bannach Jardim [1,8,9*]

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[9] *Departamento de Medicina Interna, Universidade Federal do Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, 90035-003, Brazil.*

[10] *Departamento de Bioquímica, Universidade Federal do Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, 90035-000, Brazil.*

Suggested Theme(s): Enhancing clinical trial readiness

Eduardo De Mattos, PhD - Continued

Background and Objective: Spinocerebellar ataxia type 3/Machado-Joseph disease (SCA3/MJD) is caused by an expanded CAG tract (CAGexp) at ATXN3, coding for ataxin-3 protein with an abnormally long polyglutamine (polyQ) stretch. Although no disease-modifying therapies are available for SCA3/MJD, several molecular chaperones modulate polyQ-induced phenotypes *in vitro* and *in vivo*, with the HSP70 co-chaperone DNAJB6 being the most prominent candidate[1,2]. The aim of the present work was to test whether protein levels of selected chaperones, especially DNAJB6a and DNAJB6b isoforms, correlate with age at onset (AO) and velocity of disease progression (VDP) in SCA3/MJD.

Methods: Early-, average-, and late-onset patients, corrected for CAGexp, were recruited in Brazil (n=27) and the Netherlands (n=21)[3]. Chaperone protein levels were measured in fibroblasts derived from skin biopsies and compared among AO groups within each cohort. VDP was estimated in the Brazilian cohort by clinical scales at baseline and 15.0 ± 4.7 (mean ± S.D.) months follow-up. Mixed linear models assessed the relationship between distinct chaperones and VDP[4].

Results: Levels of all investigated chaperones were similar among Brazilian AO groups, but HSP40/DNAJB1, DNAJB6a, HSP60, and HSPA8 levels were significantly higher in late-onset Dutch patients. On longitudinal analysis, HSP60, DNAJB6a, and DNAJB6b protein levels were significant predictors of VDP. Remarkably, both DNAJB6a and DNAJB6b levels at baseline significantly correlated with slower Scale for Assessment and Rating of Ataxia (SARA; R^2=1.000 and R^2=0.879, p<0.001, respectively) and SCA Functional Index (SCAFI; R^2=0.447, p<0.001; and R^2=0.142, p=0.016, respectively) progression.

Discussion and Conclusion: Molecular chaperones, particularly DNAJB6, seem to modulate SCA3/MJD phenotype, at least in some groups of patients. Our findings argue in favor of therapeutic strategies aiming at manipulating chaperone levels to delay AO and/or slow down VDP in this disease.

References:
[1]Hageman J, Rujano MA, van Waarde MAWH, et al. A DNAJB chaperone subfamily with HDAC-dependent activities suppresses toxic protein aggregation. Mol Cell. 2010;37(3):355-369.
[2]Kakkar V, Månsson C, de Mattos EP, et al. The S/T-Rich Motif in the DNAJB6 Chaperone Delays Polyglutamine Aggregation and the Onset of Disease in a Mouse Model. Mol Cell. 2016;62(2):272-283.
[3]Zijlstra MP, Rujano MA, Van Waarde MA, Vis E, Brunt ER, Kampinga HH. Levels of DNAJB family members (HSP40) correlate with disease onset in patients with spinocerebellar ataxia type 3. Eur J Neurosci. 2010;32(5):760-770.
[4]Jardim LB, Hauser L, Kieling C, et al. Progression rate of neurological deficits in a 10-year cohort of SCA3 patients. Cerebellum. 2010;9(3):419-428.

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3) Karina Donis, MD

Body mass index (BMI) and peripheral sensitivity to insulin (PSI) in Spinocerebellar Ataxia Type 3/Machado-Joseph disease (BIGPRO study)

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Suggested Theme(s): Theme 1 - Existing cohorts and natural history of SCAs.

Background and Objective: BMI and PSI are altered in spinocerebellar ataxia type 3/ Machado-Joseph disease (SCA3/MJD). Contradictory associations have been described with disease progression and mutation severity. We aimed to review our previous results by expanding our sample size of SCA3/MJD subjects studied so far.

Methods: we performed case–control observations in 2007 in group 1 (1) and (2); 2011-2013 in group 2 (3); and 2017-2018 in group 3, BIGPRO study (bigpro.webnode.com). BMI was calculated as [weight/(height)^2]. PSI was studied by means of HOMA2-%S, estimated by Calculator v2.2.2. For asymptomatic carriers (SARA < 3), time from onset (corrected by age) was estimated as described elsewhere (4). SARA, ICARS, SCAFI, CCFS, NESSCA, INAScount, age, age at onset, time to/after onset and the CAG repeat length at the expanded allele (CAGexp) were obtained. HOMA2-%S and CAGexp were logarithm10 transformed for parametric analyses.

Results: BMI of carriers were lower than controls - 24.9±4.6 in symptomatic (n=138) and 24.7±4.7 in pre-symptomatic (n=47) subjects and 26.8±5.3 in controls (n=109) (p=0.004, ANOVA with Tukey). Similarly, logHOMA2-%S of carriers were higher than controls – 4.76±0.39 in symptomatic (n=44) and 4.78±0.38 in pre-symptomatic (n=34) subjects and 4.51±0.43 in controls (n=39) (p=0.007, ANOVA with Tukey). No differences were found between symptomatic and pre-symptomatic subjects. Although BMI was correlated to age at onset, age, logCAGexp and HOMA2-%S on SCA3/MJD carriers, only HOMA2-%S explained BMI on linear regression (r=0.500, p<0.05). BMI was unrelated to time to/after onset or any of the clinical scales. LogHOMA-%S was not correlated with any of these variables but BMI (r=-0.48, p<0.0001) – similarly as seen in controls.

Conclusion: Although low BMI and high PSI are clearly associated with the carrier status in SCA3/MJD and are quite interrelated, they did not seem to present good potential to be used as biomarkers of neurological progression in SCA3/MJD.

References:

1) 10.1002/mds.23428: Saute JA et al. Serum insulin-like system alterations in patients with spinocerebellar ataxia type 3. Mov Disord. 2011 Mar;26(4):731-5.

2) 10.1007/s12311-011-0326-6: Saute JA et al. Body mass index is inversely correlated with the expanded CAG repeat length in SCA3/MJD patients. Cerebellum. 2012 Sep;11(3):771-4.

3) 10.1007/s12311-015-0719-z: da Silva Carvalho G. Cytokines in Machado Joseph Disease/Spinocerebellar Ataxia 3. Cerebellum. 2016 Aug;15(4):518-25.

4) 10.1111/ene.13779: de Mattos et al. Age at onset prediction in spinocerebellar ataxia type 3 changes according to population of origin. *Eur J Neurol.* 2019 Jan;26(1):113-120.

Acknowledgements:
CAPES, FIPE HCPA, CNPq.

4) Chandrakanth Reddy Edamakanti, PhD

Characterization of Cerebellar Exosomes from SCA1 Mice: Facilitating Biomarker Development for Patients

Chandrakanth Edamakanti, James Coy-Dibley and Opal P

Davee Department of neurology, Northwestern University Feinberg School of Medicine, Chicago

Suggested Theme(s): Common standards for clinical assessment, brain imaging and biosampling.

Background and Objective: Identifying objective, reliable and sensitive biomarkers is an important prerequisite to perform well-powered interventional clinical trials using fewer patients and shorter time-lines in rare spinocerebellar ataxias. There has been recent research in other degenerative syndromes (Alzheimer's, Huntington's & Parkinson's) suggesting that extracellular vesicles originating in the brain can be isolated from blood and CSF; these exosomes thus could serve as liquid biomarkers since their contents (RNA and protein) can change based on pathology. We have begun to isolate exosomes in mouse models of SCA1 as a means to identify candidate biomarkers that can be translated into the clinical arena. These experiments with SCA1 will serve as proof of principal as we expand into other SCA preclinical models.

Methods: We used $SCA1^{154Q/2Q}$/Wildtype mice (P4-P7) to isolate exosomes from cerebellar mixed cultures. Exosomes were isolated using ultra centrifugation and Exoquick methods. RNA sequencing was performed at Northwestern university NUseq Core Facility. The quality of RNA was checked using Agilent Bioanalyzer 2100. The Illumina Truseq Stranded mRNA Library Preparation kit was used to prepare sequencing libraries from total RNA.

Results: We have established protocols to isolate exosomes from cultured cerebellar neurons from mice. Transcriptional profiling of these cerebellar exosomes suggests that RNA that function in cell-cell communication, neuronal migration and synaptic organization are particularly abundant. Comparing mRNA profiles between wild type and SCA1 neurons demonstrate alteration in genes associated with a subset of these pathways. Gene ontology pathway analysis performed using MetaScape and KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway analysis performed using DAVID Bioinformatics Resources. We are now performing proteomic profiling of these exosomes as well.

Conclusion: We are optimistic that the biomarkers that we identify in preclinical models can be validated in human patients so as to pave the way for their use in human clinical trials.

5) Marcus Grobe-Einsler, MD

SARA^{home} – a new clinical tool for assessing ataxia at home

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6: University Pierre et Marie Curie, Paris, France

Theme: 3 - Enhancing clinical trial readiness

Background: The Scale for the Rating and Assessment of Ataxia (SARA) is a validated clinical tool developed for the rating of the severity of ataxia that is widely used in observational and interventional studies. SARA is applied by trained staff in an artificial clinical or research environment. Thus, it cannot be used to study ataxia under everyday conditions nor to assess day-to-day and within-day fluctuations. We are therefore developing SARA^{home}, a video-assisted rating tool applied at home by patients themselves.

Methods: Based on practicability for self-application, five SARA items (gait, stance, speech, finger-nose-test, fast-alternating hand-movements) were selected for SARA^{home}. Using data from the EUROSCA observational study, scores and progression rates of SARA and SARA^{home} were compared in linear regression models. To prospectively validate SARA^{home}, we are currently performing SARA and SARA^{home} in parallel. The prospective study is performed in 30 ataxia patients during study visits in our trial unit. Home performance is videotaped on a tablet device using a newly developed SARA^{home} app that can be integrated into pre-existing health apps. Secure data transfer and authorised data access are implemented according to current data protection regulations. SARA^{home} videos are centrally rated by experienced raters.

Results: Data of 526 SCA1, SCA2, SCA3, or SCA6 patients from the EUROSCA study were analysed. Baseline SARA and SARA^{home} scores were highly correlated ($r = 0.985$, $p < 0.001$). Progression of scores also showed a high correlation over time ($r = 0.67$, $p < 0.001$). In the ongoing prospective study, feasibility of SARA^{home} self-application was demonstrated. Implementation of data transfer in collaboration with a qualified industrial partner is ongoing.

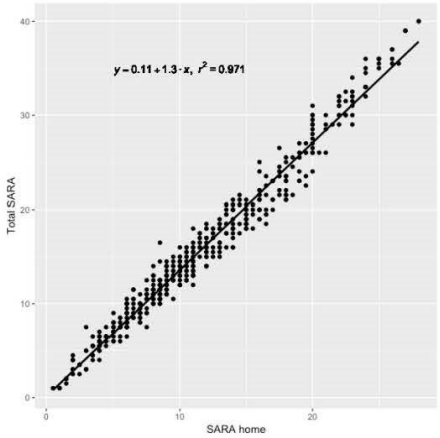

Figure: Correlation between Total SARA and SARA^{home} at baseline

Discussion and Conclusion: SARA^{home} is conceptualized as a patient-related outcome measure with a high potential to complement conventional clinical outcome measures in future trials. SARA^{home} will offer the unique opportunity to assess fluctuations of ataxia severity and to differentiate them from rater variability. SARA^{home} will be further developed by establishing automated video- and audio recording-based rating tools.

SCA GLOBAL– POSTER SESSION ABSTRACTS

6) Tomer Hillel, PhD

Can lifestyle affect SARA scale results

Tomer Hillel

Chairman, Israeli MJD Association

Suggested Theme: Theme 3 - Enhancing clinical trial readiness. **Revising lifestyle protocol**

The SARA scale is the gold standard in ataxia assessment. Moving forward into a clinical trial increases the importance of correct data analysis. Analyzing SARA results without taking into consideration lifestyle, may shift the actual drug effect. In neurodegenerative diseases lifestyle interventions can influence gene expression [1-3], which in turn triggers beneficial and supportive processes like autophagy [1, 4-6], neuron and synapse growth [7, 8], reduction of energy scavengers [9], increase cell energy production [9, 10], heat shock protein production [11, 12]. Furthermore, those processes affect/influence the disease Pathophysiology on 3 levels: system, organ and cell. Therefore, the influence of exercise [10, 13], physiotherapy [14-16], diet [17-20], nutrition [21], sleep [22, 23], detoxification and stress management [24] should be considered.

References:

1. Cunha-Santos, J., et al., *Caloric restriction blocks neuropathology and motor deficits in Machado–Joseph disease mouse models through SIRT1 pathway.* Nature Communications, 2016. **7**: p. 11445.
2. Paillard, T., Y. Rolland, and P. de Souto Barreto, *Protective Effects of Physical Exercise in Alzheimer's Disease and Parkinson's Disease: A Narrative Review.* J Clin Neurol, 2015. **11**(3): p. 212-219.
3. Musiek, E.S. and D.M. Holtzman, *Mechanisms linking circadian clocks, sleep, and neurodegeneration.* Science, 2016. **354**(6315): p. 1004-1008.
4. Komatsu, M., et al., *Loss of autophagy in the central nervous system causes neurodegeneration in mice.* Nature, 2006. **441**(7095): p. 880-884.
5. Alves, S., et al., *The autophagy/lysosome pathway is impaired in SCA7 patients and SCA7 knock-in mice.* Acta Neuropathologica, 2014. **128**(5): p. 705-722.
6. Menzies, F.M., et al., *Autophagy and Neurodegeneration: Pathogenic Mechanisms and Therapeutic Opportunities.* Neuron, 2017. **93**(5): p. 1015-1034.
7. Stangl, D. and S. Thuret, *Impact of diet on adult hippocampal neurogenesis.* Genes Nutr, 2009. **4**(4): p. 271-82.
8. Winner, B. and J. Winkler, *Adult neurogenesis in neurodegenerative diseases.* Cold Spring Harb Perspect Biol, 2015. **7**(4): p. a021287.
9. Selzer, M., et al., *Chapter 18 Neuronal death and rescue: neurotrophic factors and anti-apoptotic mechanisms*, in *Textbook of Neural Repair and Rehabilitation*. 2014, Cambridge University Press: p. 225.

Tomer Hillel, PhD—Continued

7) Henry Houlden, MD, PhD

Title: Identification of Genetic Modifiers of Age at Onset and Disease Progression in the Spinocerebellar Ataxias

1. Specific aims:

A. Collecting core and advanced clinical data on a worldwide spinocerebellar ataxia (SCA) series

Over the last 18 months we have established collaborations with a large number of neurologists and ataxia researchers around the world to share clinical data and DNA on SCA patients, in preparation for a SCA age at onset (AAO) genome-wide association study (GWAS). We have so far collected >3,733 DNA samples, stored at UCL. We have agreement with two Chinese research groups to genotype >1,600 samples in China as DNA cannot be shipped out of their country. We also have access to samples from Cuba that will be extracted and genotyped in collaboration with the Frankfurt neurology department (~1,200). We are working with other groups and Institutes/Hospitals on MTA's to obtain a further ~3,000 samples and ideally more, as many groups are happy to share samples. Based on these numbers, power calculation shows we have > 99% power, at genome-wide significance level (p=5x10^{-8}) to detect variants of similar effect size to those observed in HD AAO GWAS [1].

The core clinical feature of motor onset is available for each sample in the SCA AAO GWAS, but obtaining advanced clinical features will enhance the proposal significantly, and may allow us to identify genetic variants associated with other factors such as disease progression or age at death [2]. So far, we have core clinical features on >2,100 samples and advanced features on ~1,600. In this aim we will use the junior clinical fellow (funded by Ataxia UK), to work with clinicians and research groups, to collect the clinical data. Although this would seem a straightforward part of the proposal, clinicians and researchers are already stretched and finding the time for this is difficult without dedicated personnel. Our clinical fellow will chase clinical details, go through notes/PDF files and in some instances, visit the Institute/Hospital to obtain these data. The overall dataset will be important for the SCA AAO GWAS but will also form a framework of DNA and clinical data to build upon for future collaborative studies.

B. Identify genetic variants associated with AAO in trinucleotide repeat SCAs

In our preliminary SCA age at onset analysis, we focussed on a small number of variants in candidate genes that were found to modify the age at onset (AAO) in the Genetic Modifiers of Huntington's Disease (GeM-HD) Consortium GWAS [1]. We demonstrated [3] that these DNA variants significantly modified age at onset in a small number (~1,017) of SCA patients see preliminary data section below. However, these variants collectively account for only a small proportion of the total variance of SCA age at onset, highlighting the need for a genome wide study in a larger sample. Here we will perform a GWAS using the Illumina Infinium multi-ethnic array, described in the research plan below. As with GeM-HD data, the SCA summary data will be made publically available, linked to the clinical database.

C. Define modifier loci common to (a) multiple types of CAG related SCA as an entire group, and (b) modifiers associated with specific SCA subtypes where we have larger numbers.

We will analyze each SCA subtype separately, then all the SCA CAG repeat disorders together and finally all CAG repeat disorders together to investigate small CAG repeat genetic modifiers, using modelling techniques similar to those previously deployed [3]. Depending on sample numbers in the larger SCA subtypes such as SCA2 and SCA3 we may be able to perform a two tier analysis. We will also co-analyze with the latest HD GWAS data (available on >6000 subjects with HD, Jones unpublished data) [1] as discussed in the research plan.

D. Identify biological pathways and gene networks influencing SCA onset

Notably, the DNA repair pathways highlighted as influencing in HD AAO [1] were also found to be implicated in HD progression [4]. Since the SNPs found to be associated with SCA AAO [3] were taken from these pathways, it is important to examine whether there is association with altered SCA age at onset in the pathways as a whole extending beyond the most significant hits. In a similar way to the recent progression study [4], we will perform pathway analyzes using two complementary approaches, both implemented in MAGMA [5]. Initially, we will focus on the mismatch repair pathways highlighted in [1] and [4], but we will also perform secondary analyzes on a large pathway set taken from public databases in order to uncover novel biology. To improve coverage of poorly-annotated genes, we will augment our analyses by testing networks of genes derived from genome-wide expression and protein-protein interaction datasets.

8) Richard Joules, PhD

Development of a fully automated method for MRI volumetry in ataxia

Joules R[1], Palombit A[1], Faber J[2,3], Diedrichsen J[4], Klockgether T[2,3], Wolz R[1,5]

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Suggested Theme(s): Theme 3 - Enhancing clinical trial readiness.
Theme 2 - Common standards for clinical assessment, brain imaging and biosampling.

Background and Objective: Automated measurement of brain volumes from MRI data can provide an efficient means to assess local brain neurodegeneration, supporting clinical decision making and clinical trial efficacy analysis as well as patient selection. As new therapies in different ataxias are entering clinical development, the development and validation of image analysis pipelines optimized for the specific brain regions affected can critically support trial design and analysis.

Methods: LEAP[1] is a fully-automated brain segmentation technology based on machine learning and multi-atlas registration that has previously been optimized and validated for accurate, localized brain segmentation in Alzheimer's disease (AD), progressive supranuclear palsy (PSP) and other neurodegenerative diseases. LEAP provides a flexible framework where the method can be 'trained' to segment a given brain structure by providing a set of manually delineated reference datasets. As part of the European Spinocerebellar Ataxia Type 3/Machado-Joseph Disease Initiative (ESMI) project[2], we have extended the LEAP methodology to integrate the cerebellar sub-division provided by Diedrichsen et al[3] on 19 reference subjects into LEAP, providing a fully-automated segmentation for 27 cerebellar substructures. The automated tool was applied and its results compared to the manual cerebellar segmentations in a leave-one-out fashion to measure spatial agreement between both sets of labels as well as independently evaluated in a dataset of ataxia patients retrospectively collected within the ESMI study.

Results:
Figure 1 shows dice overlaps between manual and automated segmentations of cerebellar regions.
Overlaps show good agreement with a mean dice of 0.96 for the overall cerebellum and an average overlap of 0.70+/-0.18 for individual regions. Considered the regional variability and broad range of involved regions to be segmented, the segmentation accuracy is consistent to a recent alternative implementation with similar parcellation scheme[4].
As visually presented in Fig 1, the dice variability across subjects for corresponding regions ranged from a minimum coefficient of variation of 0.8% in cerebellar lobules I-IV up a maximum coefficient of variation of 17.0% in V. The average dice variability across subject of 10.1% suggests the automatic segmentation to have stable performances in different subjects.
The clinical validation on retrospective ESMI data shows good differentiation between ataxic mutation carriers and non-ataxic carriers for several of the cerebellar sub-regions integrated into LEAP as part of this work as well as for some of the brainstem and ventricular regions previously available in the method.
A detailed presentation of results and discussion of clinical implications is provided by Faber et al[5].

Richard Joules, PhD - Continued

Discussion and Conclusion:

A fully automated segmentation tool was developed to provide a sub-division of cerebellar brain regions and compared to gold-standard manual segmentations and validated for its clinical utility in SCA3 mutation carriers. Good agreement was obtained with manual segmentations and relevant clinical trends were measured, strengthening the hypothesis that automated MRI volumetry can support upcoming clinical trials in SCA3 and other forms of ataxia in patient selection and efficacy analysis.

References:

1 – Wolz R, et al. Neuroimage 2010 Jan 15; 49(2): 1316–1325.
2 - http://www.ataxia-study-group.net/html/studies/esmi
3 - Diedrichsen J., et al. Neuroimage 2011; 54(1):1786-94
4 – Romero J. et al., Neuroimage 2017; 147(1):916-924
5 - Faber et al, 1st SCA Global Conference, 2019, Las Vegas

Acknowledgements:

None.

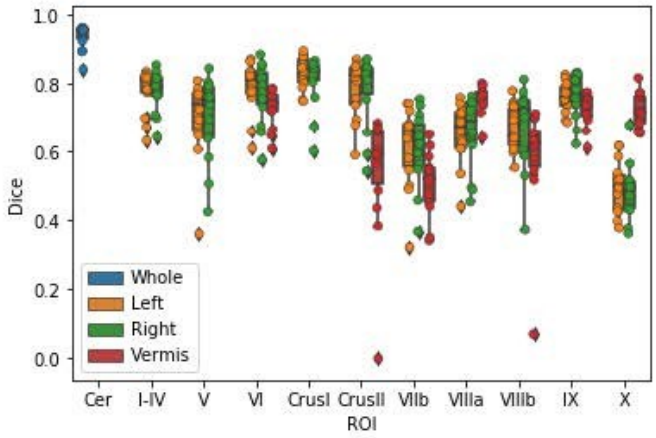

Figure 1: Boxplot representing the spatial overlap (dice) across cerebellar subregions between LEAP and manual annotations. The spatial agreement at whole cerebellum level (Whole organ) maximizes the agreement otherwise separately reported per hemisphere (respectively left and right) and vermis.

9) Marta Antonia Manes, MD

Long-term efficacy of Docosahexaenoic acid (DHA) for Spinocerebellar Ataxia 38 (SCA38) treatment: an open label extension study

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Suggested Theme: Clinical Trial results

Abstract

Background and Objective: Spinocerebellar Ataxia 38 (SCA38) is caused by *ELOVL5* gene mutation, with significant reduction of serum docosahexaenoic acid (DHA) levels. DHA supplementation has been proven effective at short-term follow-up. In the present paper, we evaluated long-term safety and efficacy of 600 mg/day oral DHA in SCA38 by a 2-year open label extension study.

Marta Antonia Manes, MD - Continued

Methods: Nine SCA38 patients underwent standardised clinical assessment at 62 (T1), 82 (T2) and 104 (T3) weeks, and compared to pre-treatment scores (T0). Brain 18-Fluorodeoxyglucose Positron Emission Tomography and electroneurography were performed at T0 and T3.

Results: We found a significant maintenance of clinical symptom improvement at each follow-up time-point (p<0.001) as compared to T0, a sustained increase of cerebellar metabolism at T3 as compared to T0 (p=0.013), and no worsening of neurophysiological parameters. No side effect was recorded.

Discussion and Conclusion: Long-term DHA supplementation is an eligible treatment for SCA38.

References:

1. Borroni B, Di Gregorio E, Orsi L, Vaula G, Costanzi C, Tempia F, et al. Clinical and neuroradiological features of spinocerebellar ataxia 38 (SCA38). Parkinsonism Relat Disord. (2016);28:80-6.
2. Manes M, Alberici A, Di Gregorio E, Boccone L, Premi E, Mitro N, et al. Docosahexaenoic acid is a beneficial replacement treatment for spinocerebellar ataxia 38. Ann Neurol. (2017);82:615-21.
3. Di Gregorio E, Borroni B, Giorgio E, Lacerenza D, Ferrero M, Lo Buono N, et al. ELOVL5 mutations cause spinocerebellar ataxia 38. Am J Hum Genet. (2014);95:209-17.

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SCA GLOBAL— POSTER SESSION ABSTRACTS

10) Marta Antonia Manes, MD

Randomized, double-blind, sham-controlled, crossover trial of cerebello-spinal tDCS in ataxia

Alberto Benussi, MD[1], Valentina Dell'Era, MD[1], Valentina Cantoni, MS[1,2], Elisa Bonetta, MS[1], Marta Manes, MD[1], Roberto Grasso, PsyD,[1] Rosa Manenti, PhD[3], Maria Cotelli, PhD[3], Alessandro Padovani, MD, PhD[1], Barbara Borroni, MD[1*]

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Marta Antonia Manes, MD—Continued

Discussion and Conclusions: A two-weeks' treatment with cerebello-spinal tDCS reduces symptoms in patients with ataxia and restores motor cortex inhibition exerted by cerebellar structures. Cerebello-spinal tDCS might represent a promising future therapeutic and rehabilitative approach in patients with neurodegenerative ataxia, a still orphan disorder of any pharmacological intervention.

11) Maria Luiza Saraiva-Pereira, PhD

Polymorphisms at *ATXN3* gene: from ancestral haplotypes to functional variants in a comprehensive study in Brazilian patients with Machado-Joseph disease.

Gabriel Vasata Furtado [1,2], Eduardo Preusser de Mattos [1,2], Tailise Conte Gheno [1], Ana Carolina de Moraes Mello [1], Fernando Regla Vargas [3], José Luiz Pedroso [4], Orlando Barsottini [4], Luis Carlos Santana da Silva [5], Clécio Godeiro [6], Pedro Braga Neto [7], Silvana Santos [8], Katia Lin [9], Maria Betânia Pereira Toralles [10], Marcial Francis Galera [11], Laura Bannach Jardim [1,12], Maria Luiza Saraiva-Pereira [1,12].

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Suggested Theme(s): Theme 1 - Existing cohorts and natural history of SCAs.

Background and Objective: Spinocerebellar ataxia type 3 or Machado-Joseph disease (SCA3/MJD) is highly prevalent in Brazil, and a comprehensive haplotype study might help to clarify its ancestral origins. Moreover, it is relevant to understand whether genetic variability at *ATXN3* modulates SCA3/MJD phenotypes, such as age of onset (AO). Hence, our aim was to describe *ATXN3* haplotypes in Brazilian patients and search for associations between haplotypes and AO of symptoms.

Methods: A total of 587 Brazilian patients (264 families) from eleven different states were enrolled in this study. AO of the first symptom was informed by the patient and/or a close relative. Fifty DNA samples from controls were also genotyped and used to infer *ATXN3* haplotypic frequencies in the general population. The minimally informative *ATXN3* haplotype (rs1048755, rs12895357, and rs7158733 variants) was initially determined, and later extended by the analysis of four STRs (rs60264948, rs72265156, rs10664277, and rs35641569).

Results and discussion: This study showed that ACA lineage was the most frequent linked to SCA3/MJD in Brazil, representing 86% of all subjects. The GGC lineage was found in one patient only in Rio Grande do Sul state but it was present in twelve families in the group of patients from other states and in several controls. In our cohort, ACA subjects carried quite larger CAGexp than GGC subjects. However, no statistically significant effect was found of the ancestral haplotype on AO, probably due to the small sample size of GGC group.

Conclusion: Data reported here shows clearly that the most frequently found haplotype in the ACA lineage of MJD/SCA3 patients in Brazil is the same found in Portugal and other European populations, following an Asian migration through North America. Moreover, this study brings a more comprehensive view on the ancestral origin of mutant *ATXN3* alleles in the Brazilian population.

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12) Thorsten Schmidt, PhD

The haplotype status of SCA3 patients impacts the pathophysiology of SCA3

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Suggested Theme(s): Theme 1 - Existing cohorts and natural history of SCAs.

Background and Objective: The *ATXN3* gene, affected in Spinocerebellar Ataxia type 3 (SCA3) or Machado-Joseph disease (MJD), contains three nonsynonymous single nucleotide polymorphisms within its coding region which cause amino acid changes or even a premature stop in the encoded ataxin-3 protein: The polymorphism A^{669}TG/G^{669}TG (in exon 8), C^{987}GG/G^{987}GG, and TAA^{1118}/TAC^{1118} (both in exon 10). In SCA3 patients, two major haplotypes of these polymorphisms can be found: the so called Flores haplotype (ACA) and the São Miguel haplotype (GGC), named after Azorean Islands (Gaspar et al., 2001). Therefore, depending on the haplotype, SCA3 patients express different versions of ataxin-3. Here we analyzed the consequences of these haplotypes on pathophysiological mechanisms in SCA3.

Methods: We examined the significance of ataxin-3 isoforms generated by alternative splicing of the *ATXN3* gene and the effect of polymorphic amino acid changes and the premature stop on major aspects of the physiological function of ataxin-3 as well as their impact on main disease mechanisms. We further determined the frequency of each haplotype in a cohort of European SCA3 patients.

Results and Discussion: At the physiological level, we show that alternative splicing and the premature stop codon alter ataxin-3 stability and that ataxin-3 isoforms differ in their enzymatic deubiquitination activity, subcellular distribution, and interaction with other proteins. At the pathological level, we found that the expansion of the polyglutamine repeat leads to a stabilization of ataxin-3 and that ataxin-3 isoforms differ in their aggregation properties. The stop codon, present in the Flores haplotype (ACA), aggrevates pathology. Interestingly, we observed functional interactions between normal and polyglutamine-expanded *ATXN3* allelic variants which modify the physiological and pathophysiological properties of ataxin-3. Our findings indicate that the haplotype, alternative splicing, and interactions between different ataxin-3 isoforms affect not only major aspects of ataxin-3 function but also SCA3 pathogenesis.

Conclusion: As the polymorphisms within ataxin-3 impact major pathophysiological mechanisms of SCA3, the haplotype status of SCA3 patients (both of the normal and the expanded allele) should be considered as disease modifier in future clinical trials involving SCA3 patients.

References: Gaspar et al. (2001) Am J Hum Genet 68:523–528

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13) Matthis Synofzik, MD

Quantifying ataxic gait characteristics as an outcome parameter in upcoming clinical SCA trials: From preclinical movement changes to free-living gait

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Theme 2 - Common standards for clinical assessment, brain imaging and biosampling.

BACKGROUND: Gait disturbances present as the first signs in most spinocerebellar ataxias (SCAs)[1] and are one of the most disabling features in the course of disease. We have demonstrated that ataxic gait can be specifically characterized by spatio-temporal variability measures in lab-based assessments, allowing to quantify disease severity[2] even at preclinical stages[3] of SCAs and to quantify treatment-induced improvements[4, 5], thus showing a high potential as both progression and treatment response outcome parameters in upcoming SCA trials. Identification of ecologically meaningful improvements, however, requires quantification of patients' motor behavior during everyday life. Yet transfer of laboratory-based measures into free-living is complicated by the facts that free-living gait is inherently far more variable and by patients' use of various compensation strategies, thus increasing the heterogeneity of walking patterns. Here, we aimed to unravel measures that allow to quantify specific features of ataxic gait in free living by wearable sensors.

METHODS: We assessed gait of 20 patients with SCA (age: 52±15, SARA: 10.2±2.9) compared to age-matched controls by 3 inertial body-worn sensors (APDM) in two conditions: (i) *constrained* walking in a clinical setting; (ii) *unconstrained walking* at home, allowing to test whether features can also be captured in free-living gait. Analysis included the identification of adequate walking bouts out of the data stream and the assessment of a compound measure of spatial step variability.

RESULTS: We were able to capture step variability in free-living gait, demonstrating a group difference (p=0.03) and a correlation with ataxia severity (r=0.86). Moreover, step variability during constrained and unconstrained walking were highly correlated, indicating validity across conditions.

CONCLUSIONS: Our algorithms allow to quantify not just unspecific features of physical activity of SCAs, but the specific component of ataxic free-living gait in everyday life, thus yielding an ecologically valid outcome measure for multi-centre natural history and treatment trials.

References

1. Globas C, du Montcel ST, Baliko L, et al. Early symptoms in spinocerebellar ataxia type 1, 2, 3, and 6. Mov Disord 2008;23(15):2232-2238.

2. Ilg W, Golla H, Thier P, Giese MA. Specific influences of cerebellar dysfunctions on gait. Brain 2007;130(3):786-798.

3. Ilg W, Fleszar Z, Schatton C, et al. Individual changes in preclinical spinocerebellar ataxia identified via increased motor complexity. Mov Disord 2016;31(12):1891-1900.

4. Ilg W, Brötz D, Burkard S, Giese MA, Schöls L, Synofzik M. Long-term effects of coordinative training in degenerative cerebellar disease. Mov Disord 2010;25(13):2239-2246.

5. Ilg W, Schatton C, Giese MA, Schols L, Synofzik M. Video game-based coordinative training improves ataxia in children with degenerative ataxia. Neurology 2012;79(20):2056-2060.

14) Luis Pereira de Almeida* (* *on behalf of the European SCA3/MJD Initiative (ESMI) consortium*)

CHARACTERIZATION OF THE COIMBRA COHORT OF MACHADO-JOSEPH DISEASE PATIENTS FOR FUTURE CLINICAL TRIALS

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Introduction: Machado–Joseph disease (MJD) is the most common of the dominantly-inherited ataxias worldwide[1]. MJD is caused by a CAG over repetition in *ATXN3* gene, which translates into a mutated ataxin-3 protein that accumulates in neurons, causing neuronal dysfunction and death. To date, there is no therapy available to stop or slow disease progression, but several potential therapeutic approaches have been developed and the field is now entering a phase of trial activity. To initiate clinical trials the availability of a large cohort of patients is mandatory. The *European Spinocerebellar ataxia type 3/Machado-Joseph disease Initiative* (ESMI) is therefore intended to set up an international large MJD cohort ready for interventional trials. In this study, we assembled and characterized the Portuguese cohort of MJD patients that integrates the ESMI project.

Methods: This study was approved by the Ethics Committee of the Faculty of Medicine of the University of Coimbra. MJD patients were enrolled in the study upon signing informed consent. Each participant was characterized using clinical (SARA, INAS and ADL) and functional tests (9HP, 8MW and PATA). This evaluation was performed at a baseline visit and after one year.

Results: 39 patients (20 male, 19 female; 50.2±12.9 years old) were enrolled in the study. Mean age of disease onset was 40.4±11.9, disease duration was 10.1±6.1 and the number of CAG repeats on expanded allele was 71.7 ± 4.6. 5% of the patients were on disease stage 0 (DS0), 59% on DS1, 15% on DS2 and 21% on DS3. Overall, at baseline, mean score for SARA scale was 13.8±10.1, whereas mean INAS count was 5.6±2.3. All patients exhibited at least one non-ataxic symptom, being pyramidal signs and oculomotor disturbances the most frequent symptoms. ADL scale mean score was 9.4±9.4 and for CCFS scale, obtained overall mean scores were 2.513±0.2. Follow-up data from DS1 patients (n=11) revealed no variations from baseline either in SARA scores (p=0.97) and INAS counts (p=0.06). ADL scores, on the contrary, were significantly higher comparing with baseline (p=0.01). Regarding functional tests, no statistically significant changes were observed in 9HP (p=0.58) and PATA (p=0.82) tests at one-year follow up, but a decrease in the performance of 8MW (p=0.006) was observed.

Conclusion: In this study, we characterized a Portuguese cohort of MJD patients. Follow-up analysis showed that early stage disease patients worsen their ability to walk and to perform daily life activities. Recognizing the most disturbed parameters affecting these patients is relevant to identify the needs for therapeutic interventions in order to improve patients' quality of life and clinical intervention. Promising gene silencing and caloric restriction mimetics for future clinical interventions will be discussed.

Abbreviations: Scale for the Assessment and Rating of Ataxia (SARA), Inventory of Non-Ataxia Signs (INAS), Activities of daily life (ADL), 9 Hole Peg test (9HP), 8 meter walking test (8MW), PATA rate test (PATA).

Keywords: Machado-Joseph disease; ESMI; Trial-ready cohort; Clinical research

References: (1) Ruano L et al. *Neuroepidemiology* **42**, 174-183 (2014)

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NOTES

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