ATAXIA GLOBAL INITIATIVE

worldwide platform for clinical research in ataxias

Ataxia Global Online Symposium
‘Getting ready for clinical trials’

22 & 23 November 2021

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Meeting Platform (Zoom)

You have received an email from Zoom with the link to the conference and will be sent a reminder an hour before the meeting starts on Monday 22 November. With that link you can join the conference on both meeting days at any time – also you can use that link when you have to leave the meeting at any time during the conference.

For the business meeting, all AGI members have received an email with a separate link. Please use this link to join on Monday 22 November at 15.50 CET. Note that the business meeting is only accessible for people that have applied to be an AGI member.

If you would like to make yourself familiar with the Zoom webinar functionalities as an attendee we recommend to have a look here: https://support.zoom.us/hc/en-us/articles/115004954946-Joining-and-participating-in-a-webinar-attendee-Stay

We would like to thank the members of the organizing and program committee:
Tetsuo Ashizawa, Bernard Brais, Alexandra Durr, Brent Fogel, Holm Graessner, Julie Greenfield, Susan Hagen, Laura Jardim, Thomas Klockgether, Osamu Onodera, José Luiz Pedroso, Annemarie Post, Bing-Wen Soong, Matthis Synofzik, David Szmulewicz, Birte Zurek.
(in alphabetical order)

Sponsors

Agenda | Ataxia Global Online Symposium 2021

22 & 23 November 2021 | online, Berlin time (CET)

Monday 22 November 2021

Session 1: Genetics & New Targets/Pathways

14.00 - 14.05 CET: Welcome

14.05 - 14.35: Keynote lecture – **Challenges and opportunities in ataxia genomics**
Stephan Züchner (University of Miami)

14.35 - 14.55: AGI Working Groups - **WG6: Next-generation ataxia genomics and platforms**
Matthis Synofzik (University of Tübingen)

14.55 - 15.15: AGI Projects - **Genetic modifiers in CANVAS and other repeat expansion disorders**
Henry Houlden (University College London)

15.15 - 15.35: AGI Projects - **Rapid generation of knock-out stem cell models of ARCAs**
Ricardo Schnekenberg (University of Oxford)

Session 2: AGI Business Meeting (members and partners only)

AGI members and partners have received a separate link to join this meeting on 16 November. If you would like to join, apply for membership via this link (until 21 November)

15.50 - 16.05 CET: Introduction
Thomas Klockgether (Chair of the AGI Steering Committee, University of Bonn)

16.05 - 16.25: Business presentation
Holm Graessner (Head of the AGI office, University of Tübingen)

16.25 - 16.35: Role of patient organizations in AGI
Sue Hagen (National Ataxia Foundation)
Julie Greenfield (Ataxia UK)

16.35 - 16.45: Trial readiness services
Birte Zurek (AGI office, University of Tübingen)

16.45 - 16.55: Collaboration with CPTA
Terina Martinez (CPTA)

16.55 - 17.25: Next actions and discussion
Annemarie Post (AGI office, University of Tübingen)

Tuesday 23 November 2021

Session 3: Biomarkers and natural history

19.30 - 19.35 CET: Welcome

19.35 - 20.00: Keynote lecture - **Regulatory aspects in neurodegenerative disorders**
Karl Broich (Federal Institute for Drugs and Medical Devices Germany)

20.00 - 20.17: AGI Working Groups - **WG3: MR biomarkers**
Gülin Öz (University of Minnesota)

20.17 - 20.29: AGI Projects - **Identification and characterization of biomarkers from blood plasma and CSF of spinocerebellar ataxia-1 (SCA1) patients**
Puneet Opal (Northwestern University)

20.29 - 20.41: AGI Projects - **PROSPAX: an integrated multimodal progression chart in spastic ataxias (ARSACS, SPG7)**
Rebecca Schüle (University of Tübingen)

20.41 - 20.53: **PAHAN survey on the care for ataxias in the Americas and the Caribbean**
Laura Bannach Jardim (Federal University of Rio Grande do Sul)

Session 4: Therapy

21.00 - 21.30: Keynote lecture - **ASO therapies in Huntington's disease**
Fabricio Pio (The University of British Columbia)

21.30 – 22.00: Keynote lecture - **Gene therapy for polyQ SCAs**
Nathalie Cartier (INSERM)

22.00 – 22.15: AGI Working Groups - **WG1: Clinical outcomes**
Thomas Klockgether (University of Bonn)

22.15 - 22.30: AGI Projects - **CACNA1A-related ataxia: functional characterization of clinically severe variants for drug repurposing**
Ginevra Zanni (Bambino Gesù Children's Hospital)


IONIS

Conference speakers & abstracts

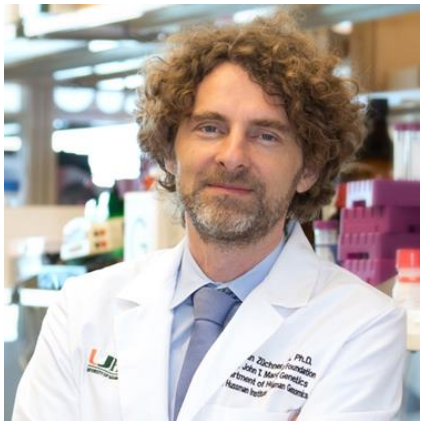
Keynote speakers

Challenges and opportunities in ataxia genomics

Stephan Züchner, University of Miami

Abstract

Genetic forms of ataxias and related disorders are extremely heterogeneous. Despite many known genes and loci, the relatively low diagnostic yield for many ataxias suggests additional important genetic factors to be identified. This presentation will use specific examples to discuss a number of strategies on how to close the diagnostic gap through activities in the AGI. International collaboration and shared data analysis opportunities have been very successful. Recent advances in bioinformatics of short-read sequencing data allow for higher fidelity of repeat expansion detection, including the non-coding chromosomal space. Long-read sequencing technologies are becoming more mature and affordable and will contribute significantly to a better understanding of structural changes in ataxias. Other promising developments in our work include machine learning for variant pathogenicity and statistical approaches in large datasets. Finally, as most rare monogenic disorders tackle similar problems, the field will benefit from lessons learned in related neurodegenerative disorders. As genetic therapies are evolving quickly, it is an imperative to improve genetic diagnostics for ataxia patients in order for them to benefit from such developments.



Stephan Züchner, M.D., Ph.D., M.D. (h.c.), FAAN, is a Professor of Human Genetics and Neurology at the University of Miami Miller School of Medicine. He serves as the Chairman of the Dr. John T. Macdonald Foundation Department of Human Genetics and the Co-Director of the Hussman Institute for Human Genomics. Dr. Züchner's research interests are focused on identifying genetic variation associated with disease. His lab is internationally renowned for being highly successful in identifying several dozen genes for Mendelian disorders, especially axonal neuropathies, ataxia, and spastic paraplegia; and also evaluated risk factors for complex genetic conditions, including Alzheimer disease, Parkinson disease, and obsessive-compulsive disorder. His group is amongst the pioneering groups that have promoted genome sequencing methods and advanced bioinformatics for disease gene identification in humans, mice, worm, and drosophila. By utilizing in house developed software solutions, such as the widely used GENESIS platform, he is currently pursuing large - scale collaborative exome and genome analysis in multiple Mendelian neurodegenerative disorders to map their complex genetic architecture, including modifier genes. Finally, therapeutic applications based on genetic approaches are being developed in his group.

Regulatory aspects in neurodegenerative disorders

Karl Broich, Federal Institute for Drugs and Medical Devices (Germany)

Prof. Dr. med. **Karl Broich** is president of the Federal Institute for Drugs and Medical Devices in Germany since 2014. Additionally, he is honorary professor at the medical faculty of the Rheinische Friedrich-Wilhelms-Universität Bonn. Prof. Dr. Broich's scientific focus is on clinical psychopharmacology; advanced imaging in neurodegenerative diseases, biomarkers, dementia, and methodology of clinical trials. He is member of the European Medicines Agency's Management Board (EMA MB), chair of the EU Telematics Management Board (EU TMB), member of the Central Nervous System Working Party (CNSWP), and chair of the Heads of Medicines Agencies (HMA) Management Group, as well as member of numerous societies. Prof. Dr. Broich is author and co-author of over 220 essays (original scientific papers, reviews, book contributions).

ASO therapies in Huntington's disease

Fabricio Pio, The University of British Columbia

Abstract

Antisense oligonucleotides (ASO) therapy has been used to treat genetic diseases such as Spinal Muscular Atrophy. ASO therapies in Huntington's disease studies have shown promising lowering of the mutant protein. In this talk we will review the hypothesis and mechanism of action of ASO therapy in Huntington's disease.

Fabricio Joao Pio, MD is a neurologist and postgraduate fellow in Huntington disease at the University of British Columbia. He is involved with several studies, including Enroll-HD, Clarity-HD, Signal-HD, Natural History, Open label and Phase 3 trials. He is a member of the American Academy of Neurology, the Brazilian Academy of Neurology, the Canadian Neurological Society, the European Neurological Association and the Conselho Regional de Medicina do Estado de Santa Catarina.

Gene therapy for polyQ SCAs

Nathalie Cartier, INSERM

Abstract and CV to follow

Working Groups

WG6: Next-generation ataxia genomics and platforms

Matthis Synofzik, University of Tübingen

Abstract

The goal of this working group is to identify and enrich genetically stratified ataxia patients for trial-readiness natural history studies and treatment trials. This will be achieved by establishing a *genetic* ataxia diagnosis for as many ataxia patients as possible, in particular for genetically still undefined and "hard-to-diagnose" ataxia patients, and by prioritizing genetic ataxia conditions which are already druggable (e.g. COQ8A ataxia, Niemann Pick Type C ataxia; ataxia patients with splice mutations amenable for n-of-1 ASO treatments) or are currently being prepared for trial-readiness/druggability (e.g. ion channel SCAs, ARSACS, SPG7, etc).

This will be achieved by work on three parallel project pillars. For ataxia patients still without genetic ataxia diagnosis, pillar# 1 aims to identify mutations in known ataxia genes by (i) increasing the share of unsolved SCA/ARCA patients receiving WES/WGS, i.e. novel WES/WGS datasets (goal #1); (ii) reanalyzing existing WES/WGS datasets of patients where no causative mutation has been found so far (goal #2); and (iii) clarifying the pathogenicity of VUS in SCA/ARCA genes in still unsolved patients (goal #3). Pillar #2 aims to identify mutations in novel ataxia genes for these patients. It will here build in particular on establishing optimal and novel systematic genomic strategies to increase the yield of identifying novel ataxia genes (goal #4). Pillar #3 will implement ways to feedback these newly genetically defined ataxia patients into existing ataxia trial-readiness registries (SCA registry, ARCA registry, etc) (goal #5), and to share newly identified potentially treatable genomic mechanisms with other working groups in the AGI (goal #6).

Key to this project pillars is a readily mineable ataxia genomics NGS infrastructure. Here we will present the current progress of main NGS ataxia platforms (GENESIS, GPAP, CAGC). We outline next steps allowing AGI partners to upload existing ataxia NGS datasets in preferred ataxia NGS platform for collaborative data analysis, as well as to produce novel WES and WGS of still unsolved SCA/ARCA cohorts. Finally, we outline first novel collaborative project strategies building on these collaborative ataxia platforms which are tailored to solve still unsolved WES-negative patients and to unravel novel ataxia genes and mechanisms.

Prof. Dr. **Matthis Synofzik**, MD, is head of the research unit "Translational Genomics of neurodegenerative diseases" and senior consultant neurologist at the Hertie Institute for Clinical Brain Research & Center of Neurology, University of Tübingen, Germany. Since 2013 he is co-chair of the Ataxia outpatient clinics at the Center for Neurology, and leads the outpatient clinics for Frontotemporal Dementias and for Amyotrophic Lateral Sclerosis. He holds graduate qualifications in philosophy and in medicine and postgraduate qualifications in neurology. Matthis has received over € 4,0 million in fellowships/scholarships or grants, leading several worldwide EJP-RD consortia on recessive ataxias like "PREPARE" and „PROSPAX" as well as co-lead of the global trial-readiness platform "ATAXIA GLOBAL INITIATIVE".

He coordinates the international multicenter prospective longitudinal database on recessive ataxias ("ARCA registry"), which brings together >25 world-leading ataxia centers. Matthis has published >300 peer-reviewed PubMed-referenced papers, including manifold publications in high-rank journals like BRAIN, NATURE GENETICS, CURRENT BIOLOGY, NEURON, and NEUROLOGY. His expertise spans clinical research of disease and treatments in hereditary ataxias, frontotemporal dementias, ALS and orphan neurological diseases as well as the underlying molecular genetics and neurobiology. Using latest next-generation genomic sequencing techniques, he has been leading or involved in the identification of >10 novel ataxia genes in the last 7 years. In parallel, he has unraveled a wide range of both molecular (e.g. blood-based molecules) and digital-motor biomarkers (e.g. wearable sensors) directly facilitating trial-readiness of hereditary ataxias. Matthis has pioneered and introduced several new innovative neurorehabilitation approaches for ataxias, providing the world-first scientific evidence for the efficacy of motor training (exergames, physiotherapy, speech therapy) in degenerative ataxias.

WG3: MR biomarkers

Gülin Öz, University of Minnesota

Abstract

An update will be presented on the WG activities, including development of recommended MR protocols, publication plans and discussions with CPAT towards establishing a global ataxia imaging database.

Dr. **Gülin Öz** is a Professor in the Department of Radiology, Center for Magnetic Resonance Research (CMRR). Following BS degrees in Physics and Chemistry and a PhD in Biochemistry, she continued with postdoctoral training at the CMRR where she later joined the faculty. She uses high field, multi-nuclear magnetic resonance spectroscopy (MRS) to explore neurochemical and metabolic alterations in diseases that affect the brain and spearheaded utilization of neurochemical profiles to assess cerebral changes in patients with neurological diseases and their response to treatment. She focuses on applications of advanced MRS methods in neurodegenerative diseases and diabetes. She further leads efforts to facilitate the use and standardization of robust MRS methodology in the clinical setting.

WG3: Clinical outcomes

Thomas Klockgether, University of Bonn

Abstract

The goal of the working group on COAs is to define a set of data including a graded catalogue of COAs that will serve as the standard for future sharing of clinical data and joint clinical studies. To keep the hurdles for contribution of data to common analyses and studies low, it was agreed to define a mandatory dataset (minimal dataset) that can ideally be obtained during a routine clinical consultation, and a more demanding extended dataset that is useful for research purposes. The minimal dataset includes core data that provide basic information on demographics, clinical and genetic status, disability (FARS Functional Staging for Ataxia), and ataxia severity (SARA). The extended dataset includes comorbidities, medication, neurological status (INAS), activities of daily living (FARS-ADL), patient-related outcomes (PROM-Ataxia), and cognition (CCAS).

Prof. **Thomas 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. From 2011 to 2019 he has been Speaker of the Center for Rare Diseases Bonn (ZSEB) and since May 2011 Director of Clinical Research at the DZNE.

Projects

Genetic modifiers in CANVAS and other repeat expansion disorders

Henry Houlden, University College London

Abstract

CANVAS is caused by RFC1 expansions and is a frequent cause of inherited ataxia. There are other causes of recessive ataxia, where the most prevalent one is Friedreich ataxia (FRDA) caused by GAA expansions. The RFC1 expansion is an AAGGG but is as yet not known to correlate with age at onset (AAO) or clinical features and the FRDA associated GAA expansion length does correlate with severity of symptoms and inversely with age-of-onset but there are still significant AAO and clinical variability that is unrelated to the expansion size. This suggests that other contributory factors such as non-coding or coding modifying genetic variation exist.

Identifying these factors will be important in a number of ways, such as:
(1) To define the individual genetic profile of each patient to help determine disease progression, predict clinical problems and understand allele lengths and age at onset,
(2) To stratify patients more effectively for treatment trials and
(3) The modifying molecular pathways identified will certainly improve our understanding of these disorders and may in themselves be potential therapeutic targets.

Professor **Henry Houlden**, MD, PhD

Our laboratory works on neurogenetics with a particular interest in inherited ataxia in childhood and adult onset neurological disorders, as well as neuromuscular conditions, spinocerebellar ataxia, spastic paraplegia and movement disorders such as multiple system atrophy (MSA); particularly in diverse populations. We integrate new gene discovery with exome and genome sequencing identifying disease genes such as CANVAS, VWA1, SCA11, SCA15, GRIA2 and GAD1, with functional experimental validation in human tissue and other model systems. This allows us to diagnose many families to allow effective management and treatment. We have an international lab and clinical team, sharing students and young clinicians who come for exchange visits to UCL allowing joint research projects and publications. We are keen to collaborate to investigate families with neurological disorders. Our overall goal is to develop new therapeutics based on an improved understanding of disease pathways and in children and adults. We are very open to collaboration, contact: h.houlden@ucl.ac.uk.

Rapid generation of knock-out stem cell models of ARCAs

Ricardo Schnekenberg, University of Oxford

Abstract

The underlying molecular pathogenic mechanisms in many ARCAs remain unclear. Recent technological advances have enabled the differentiation of pluripotent human stem cells into a variety of neuronal sub-types (including cerebellum) that can be studied in vitro, avoiding invasive human testing or using animal models. Patient cells (usually fibroblasts) containing a mutation must be reprogrammed (iPSCs) or wild type iPSCs have mutations introduced. These can be mutation specific, but are relatively expensive and labor-intensive options.

An alternative is to use a human embryonic stem cell (hESC) line, and introduce mutations using CRISPR/CAS9 gene editing. We have developed a protocol that can generate knock-out mutations in H9 hES cells using high-fidelity SpCas9 in a matter of weeks. This protocol provides a cost-effective, rapid and scalable method for screening the cellular phenotypes of recessive ataxias and for screening of potential therapeutic agents.

We illustrate this work with pilot data in which we have generated several knock-out cell lines of ITPR1 using this protocol.

Ricardo Parolin Schnekenberg, MD, is a Clarendon scholar and Domus scholar at the University of Oxford. He focuses on genomic and functional investigation of neurodevelopmental disorders in the group of Prof. Andrea Nemeth. He developed a CRISPR-based system for rapid and affordable generation of stem cell models of genetic diseases. He also created ITPR1 knockout human embryonic stem cell lines and differentiated them to cortical neurons. He has been focused on ataxia research since 2012.

Identification and characterization of biomarkers from blood plasma and CSF of spinocerebellar ataxia-1 (SCA1) patients

Puneet Opal, Northwestern University

Abstract

With new therapies on the horizon, there is a pressing need for developing biomarkers to follow disease onset and progression for the spinocerebellar ataxias (SCAs). Toward this end we wish to use the interactions of the ataxia global network to get a sufficient number of patient samples for each of the SCA subtypes. Our initial focus will be on SCA1, the most rapidly progressive SCA. The samples that we envisage studying will include samples from the CRC-SCA and READISCA cohorts with additional samples from additional sites aligned with the mission of ataxia global. This will allow us to use some sites as a discovery cohort—and others as a validation cohort. We will be use techniques including single molecule array technology (SIMOA) and meso-scale discovery (MSD) methods to identify candidate biomarker proteins from the plasma and CSF of healthy controls and SCA1 patients, along with high-throughput discovery platforms. The long-term goal will be to use these liquid biomarkers aligned with MRI based imaging to provide multi-modal markers to test for disease onset and progression that will be important for future interventional studies.

Puneet Opal, MD, PhD is a Professor of Neurology at Northwestern University Feinberg School of Medicine. His research efforts are dedicated toward elucidating the cellular and molecular basis of genetic movement disorders particularly those causing cerebellar ataxias. In the clinic he runs the Northwestern Ataxia clinic dedicated to multidisciplinary care for ataxic patients.

Dr. Opal has received research awards from the NIH, the American Cancer Society, the National Ataxia Foundation, the National Organization for Rare Disorders, and the Brain Research Foundation. He has mentored students from high school, undergraduates, graduate and post-docs to physicians at various levels of training in research projects, and is a director of the Northwestern University Physician Scientist Training Program. He is an elected member of the American Neurological Association and the American Society of Clinical Investigators.

PROSPAX: an integrated multimodal progression chart in spastic ataxias (ARSACS, SPG7)

Rebecca Schüle, University of Tübingen

Abstract

Spastic ataxias (SPAX) present an expanding group of >100 rare neurodegenerative diseases with joined damage of cerebellum and corticospinal tract (CST). While rapid genetic stratification facilitates current development of molecular therapies, effective trial-planning for SPAX is hampered by a lack of valid outcome measures and natural history studies. Building on the AGI network as well as other pre-existing networks, PROSPAX will establish a paradigmatic IRDiRC-guided integrated trial-ready model of disease progression and mechanistic evolution in SPAX, focusing paradigmatically on ARSACS and SPG7. This endeavor will allow to track and understand selective as well as overlapping dysfunction of the cerebellum and CST. In a 2-year transatlantic natural history study of each ARSACS and SPG7 we will longitudinally validate clinician- and patient-reported, digital and molecular outcomes. In addition, PROSPAX will improve on existing and develop new outcome parameters that show superior sensitivity to change. These include a novel clinical SPAX composite score, a smartphone mHealth toolbox combining remote assessment of daily living by wearable sensors with app-based patient-entered outcomes (SPAX.app), and multimodal MRI radiomics with an innovative machine learning approach for multisite MRI analysis, including in particular the infratentorial space. Longitudinal validation of targeted fluid biomarker candidates will be complemented by single-cell multi-omic studies in ARSACS and SPG7 mouse which will allow to identify shared pathways and vulnerabilities between cerebellar and corticospinal neurons and will unravel new molecular biomarkers. By focusing on these two most prevalent recessive SPAX (SPG7, ARSACS), PROSPAX will create a paradigmatic trial-readiness pathway for charting disease progression and multimodal outcome measures that will be applicable to many of the >100 SPAX diseases as well as other AGI diseases alike.

Rebecca Schüle is assistant professor and group leader at the Department of Neurodegenerative Diseases at the University of Tübingen. She focuses on next-generation genomics of neurodegenerative diseases (with a main focus on hereditary spastic paraplegias, spastic ataxias and hereditary neuropathies), stem cell models of axonopathies, translational research including natural history studies, biomarker identification, and the development of clinical outcome parameters. She is the coordinating PI of the multi-national network 'Alliance for Treatment in HSP and PLS', PI of the NIH-funded motoneuron network CReATe, PI of the NIH-funded initiative 'HSP genomics'. Moreover, she is coordinator of the biobank of the Center for Neurology & Hertie-Institute for Clinical Brain Research, University of Tübingen (NeuroBiobank) and the German Center for Neurodegenerative Diseases (DZNE biobank).

PAHAN survey on the care for ataxias in the Americas and the Caribbean

Laura Bannach Jardim, Hospital de Clínicas de Porto Alegre

Abstract

Background: Access to health care is a complicated issue, especially in the case of rare diseases such as hereditary ataxias. Not much is known about it. The Pan American Hereditary Ataxia Network (PAHAN) proposed to conduct an exploratory poll between professionals of health, about the access of ataxic subjects to health care in the American continents and the Caribbean.

Methods: Invitations to participate were sent by emails to 72 known health professionals between July and October 2021. There were English, Spanish and Portuguese versions of the survey, with questions about the hereditary ataxias already identified; access of ataxics to health care; and local teaching and research on ataxia. Data from each participant center was related to a geographic region and population. The number of ataxic patients under current care per 100,000 inhabitants of each region was estimated and subtracted from the expected overall prevalence of 6/100,000. The number obtained was an estimation of the prevalence of uncovered ataxic patients per Region. The local Human Development Index (HDI) was used as an independent variable to measure socio-economic risk factors. This was an exploratory study, where Mann-Whitney U and Kruskal-Wallis tests were used with a o<0.05.

Results: 28 professionals (26 sites) contacted by email agreed to participate. Most of them worked in Latin American countries; 11 were Brazilian. HDIs of the sites varied between 0.698 and 0.944: 12 sites had very high (above 0.8), 13 had high (0.7 to 0.79) and one site had medium HDI. Participants reported on 2,841 ataxic patients under current care: 2,239 with spinocerebellar ataxias and 602 with confirmed or potential recessive forms. The number of ataxic patients under current care varied across different sites and regions, between 0.14 and 12/100,000 inhabitants. The estimation of the prevalence of uncovered ataxic patients of a given Region was inversely correlated with the HDI of the same Region (rho = -0.782, p<0.001). Access to technologies needed for the molecular diagnosis, to pre-symptomatic testing programs, and to rehabilitation among sites with very high HDI were significantly higher than those of the remaining sites (p<0.045). Twelve respondents (42%) supervise students, and 17 sites (65%) reported they were performing clinical studies on hereditary ataxias. Among the top four priorities to improve the health care of ataxic patients in her/his site, three items were common between the 11 very high HDI and the 8 not very high HDI respondent sites: the need for more and better molecular diagnostic tools, for protocols and guidelines and for professional training for ataxia care.

Discussion: As far as we know, this was the first poll on the health care status of ataxic people on the American continents and the Caribbean. Some results clearly pointed to great inequalities in access to health care among the people of our continents. The potential number of ataxic subjects who would not be receiving health care were significantly higher in cities, provinces or countries with lower HDIs. Molecular diagnosis, pre-symptomatic testing and rehabilitation raised as the facilities that are lacking among these sites. However, both rich and poor sites chose the same three items among the top 4 priorities for them: the need of more and better molecular diagnostic tools, of protocols and guidelines and of professional training. We suggest that PAHAN consortium might help with the last two tasks.

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

She is a clinical neurologist and geneticist who follows patients, conducts clinical studies, and supervises graduate students with a focus on neurogenetic conditions. Prof. Jardim identified the founder effect and cluster of a large population of spinocerebellar ataxia type 3, also known as Machado-Joseph disease (SCA3/MJD) in South Brazil. Since 2001, she has been the PI of the Neurogenetics Research Group at her institution. Between 2008 and 2015, Prof. Jardim led Rede Neurogenetica (www.redeneurogenetica.ufrgs.br), a network that allowed the diagnosis of several SCAs in Brazil and Peru, and also the study of the natural history and genetic characteristics of SCA2, SCA7, SCA10, Huntington disease, Friedreich disease and other neurogenetic disorders commonly found in Latin America. Dr. Jardim participates in the steering committees of AGI and PAHAN.

CACNA1A-related ataxia: functional characterization of clinically severe variants for drug repurposing

Ginevra Zanni, Bambino Gesù Children's Hospital

Abstract

Pathogenic variants in the CACNA1A gene encoding the pore-forming α1A subunit of the voltage-gated CaV2.1 (P/Q-type) Ca2+ channel underlie rare and clinically variable neurological disorders including sporadic and familial hemiplegic migraine (FHM1), Episodic Ataxia type 2 (EA2), Spinocerebellar Ataxia (SCA6) and Congenital/ Early Onset Ataxia (CA/EOA). The phenotypes are frequently overlapping and further studies are required to better define the genotype-phenotype correlations and the functional classification of CACNA1A variants. We have identified 16 ataxic patients from unrelated families with missense CACNA1A variants presenting congenital or early-onset ataxia. Most of these variants are predicted to be gain of function (GOF) by in silico tools, but specific in vitro functional characterization based on human induced pluripotent stem cells (iPSCs) models derived from CACNA1A patients, will be essential for variant-tailored therapeutic approaches.

We will develop an in vitro disease model based on induced pluripotent stem cells (iPSCs) obtained from patients carrying CACNA1A variants, and characterize the neuronal and electrophysiological phenotype to compare it with different patients' lines and clinical phenotypes in view of drug repurposing. We will also collect data in view of deep phenotyping (e.g. onset, progression, seizures and other associated features) in collaboration with other centers/networks such as: Ataxia Global Initiative Ataxia Study Group of the EPNS, NonPolyQ SCA project, PREPARE consortium, Wolfson Medical Center, CACNA1A foundation.

Ginevra Zanni, MD, PhD, is a Staff Medical and Research Scientist at the Department of Neurosciences, Bambino Gesù Children's Hospital, Rome, Italy. She is a member of the European Reference Network Rare Neurological Diseases (ERN-RND) and other international networks for the study of Ataxias. Her research focuses on the screening and identification of new genes involved in rare neurodevelopmental disorders and the characterization of physiopathological mechanisms and genotype-phenotype correlates. Currently, she mainly works on pediatric ataxias and neurodevelopmental disorders.

Ataxia Global Conference 2022

On Friday 18 & Saturday 19 March 2022, we hope to meet you all for the next in-person Ataxia Global Conference in Orlando, FL, USA. During this meeting, you can enjoy keynote talks on various topics, as well as hear the latest on progression towards trial readiness for ataxias. A preliminary program is available here. More information will follow soon.

The Ataxia Global Conference will be held in conjunction with the International Congress for Ataxia Research (15 - 18 March 2022) and the NAF Annual Ataxia Conference for ataxia patients (18 & 19 March 2022).

ABSTRACT SUBMISSION

During this conference, there is the opportunity to present your work as a poster. Additionally, 6 - 8 abstracts will be selected for an oral presentation in one of the sessions. To submit your abstract, please use this template. The **deadline for abstract submission is 30 November 2021.**

Note that abstracts intended for the Ataxia Global Conference should have a strong focus on the goal of the AGI: trial readiness for ataxias. Abstracts should not be duplicated between ICAR and AGI, if applicable.

YOUNG INVESTIGATOR TRAVEL AWARD

The AGI offers to provide up to 2,000 USD travel support for three young investigators to attend the Ataxia Global Conference and the International Congress for Ataxia Research (ICAR) in Orlando, March 2022. The three eligible young investigators (2 non-US and 1 US) are committed to ataxia research and – without financial support – would be unable to attend these conferences.

You can apply for this travel award until 30 November 2021. More information can be found here.