



# 9<sup>th</sup> INTERNATIONAL SYMPOSIUM ON NBIA

October 17-19, 2024  
Istanbul University, Central Campus  
BEYAZIT - ISTANBUL

## 9TH INTERNATIONAL SYMPOSIUM ON NBIA PROGRAM BOOKLET



October 17-19, 2024



Website: [>> more information <<](#)



BEYAZIT /ISTANBUL  
Istanbul University Central Campus

Dear friends and colleagues,

It is a great pleasure and honor for me to be able to welcome you on behalf of the Organizing Committee to our 9th International Symposium on NBIA here in Istanbul, Türkiye. This is the first time we are holding the meeting in Istanbul, a magical seal that unites Europe and Asia together through rich multicultural history. With the scientific program meticulously created by the doyens in the field of NBIA, we will not only learn about the developments in this field but also find ourselves in research areas that will expand our horizons.

In the Presymposium Course of NBIA that will take place just before the main symposium, as a half-day meeting, clinical information about the disease will be presented by experts. While the diagnostic algorithm and treatment challenges (treatment with medication, deep brain stimulation, botulinum toxin) will be discussed, case experiences will enrich our perspective.

The main symposium will cover basic and translational research including mysterious pathways of the diseases' mechanisms, and the recent advances unraveling these mechanisms. We are excited to discuss and develop new solutions to the group of NBIA diseases seen in all ages (from infancy to old age). In the context of translational neuroscience, it's a privilege of the NBIA to bring together a wide variety of scientists. We hope you will join us for this high-level educational symposium and excellent networking opportunity.

I would like to thank the members of the scientific program committee, the international and local organizing committee, the faculty, our attendees, and our corporate partners for making this meeting possible. This is a huge joint effort to bring this meeting together.

In autumn 2024, you are all expected to come to Istanbul, where you can enjoy a 3,000-year-old cultural heritage, friendliness, and great cuisine.

Have a fantastic symposium here in Istanbul!

Professor Zuhal YAPICI  
On behalf of the Organizing Committee

Please note that the contents in the booklet may not be cited or used in any kind of verbal or written scientific correspondence with third parties without explicit permission of the authors.





# 9th International Symposium on NBIA



October 17-19, 2024



BEYAZIT / İSTANBUL  
Istanbul University, Central Campus

## Symposium Organizing Committees

### Scientific Committee (in alphabetical order by last name)



Bülent Elibol  
(Türkiye)



Murat Emre  
(Türkiye)



Susan Hayflick  
(The USA)



Thomas Klopstock  
(Germany)



Manju Kurian  
(The UK)



Susanne Schneider  
(Germany)



Valeria Tiranti  
(Italy)



Patricia Wood  
(The USA)



Zuhâl Yapıcı  
(Türkiye)

### International Organizing Committee (in alphabetical order by last name)



Fatemeh Mollet  
(President at NBIA Suisse)



Patricia Wood  
(President of the NBIA Disorders Association)

### Local Organizing Committee (in alphabetical order)



Murat Dilek  
(Türkiye)



Cem İsmail Küçükali  
(Türkiye)



Özgür Öztop Çakmak  
(Türkiye)



Murat Terzi  
(Türkiye)



Zuhâl Yapıcı

### Poster Coordinators (in alphabetical order)



Murat Gültekin



Pervin İşeri



Yıldız Değirmenci



# 9th International Symposium on NBIA



October 17-19, 2024




BEYAZIT / İSTANBUL  
Istanbul University, Central Campus

## Scientific Program of NBIA 2024


### PRESYMPOSIUM COURSE ON NEURODEGENERATION WITH BRAIN IRON ACCUMULATION (NBIA)

October 17, 2024 (Thursday)

10:00	<b>Registration</b>
12:10	<b>Opening of the Course</b> Bülent Elibol, Murat Terzi ( <i>President of Turkish Neurological Society</i> )
	<b>1. Session: General Perspective of Neurodegeneration with Brain Iron Accumulation (NBIA)</b> <i>Chairs: Bülent Elibol, Murat Emre</i>
12:20 - 12:50	<b>Introduction of NBIA</b> Zuhal Yapıcı
12:50 - 13:20	<b>Clinical Pearls: Recognizing NBIA Patients</b> Kailash Bhatia (UK)
13:20 - 13:50	<b>Clinical Characteristics and Longterm Follow-up of MPAN</b> Okan Doğu
	<b>2. Session: Medical Treatment and Botulinum Toxin in NBIA</b> <i>Chairs: Bülent Elibol, Sibel Ertan</i>
13:55 - 14:20	<b>Case Discussions</b> Banu Özen Barut, Zeliha Matür, Gençer Genç
14:20 - 14:40	 <b>Coffee Break</b>
	<b>3. Session: Deep Brain Stimulation (DBS) in NBIA</b> <i>Chairs: Cenk Akbostancı, Atilla Yılmaz</i>
14:40 - 15:00	<b>DBS in NBIA from a Neurosurgeon's Perspective</b> Atilla Yılmaz
15:00 - 15:15	<b>Presentation of Turkish Cohort of NBIA with DBS</b> Özgür Öztop Çakmak
	<b>4. Session: DBS Round Table and Case Discussions</b> <i>Chairs: Bülent Elibol, Ersoy Kocabıçak</i>
15:15 - 16:30	Özgür Öztop Çakmak, Ayşegül Gündüz, Bilge Koçer, Gül Yalçın Çakmaklı, Pınar Topaloğlu, Zeynep Tüfekçioğlu, Esra Erkoç Ataoğlu
	<b>5. Session: Electrophysiological Aspects of NBIA</b> <i>Chairs: Barış Baslo, Nerses Bebek</i>
16:30 - 16:50	<b>Peripheral Nervous System Involvement and EMG Findings in NBIA</b> Sadıka Özdemir
16:50 - 17:00	<b>Case Presentation:</b> Sezin Baslo
17:00 - 17:20	<b>Epilepsy and EEG in NBIA</b> Ayşe Deniz Elmali
17:20 - 17:40	<b>Highlights and Closing of the NBIA Course</b>
18:30 - 22:00	<b>Welcome Reception for the 9th INTERNATIONAL SYMPOSIUM on NBIA</b>

# 9th INTERNATIONAL SYMPOSIUM ON NEURODEGENERATION WITH BRAIN IRON ACCUMULATION (NBIA)

October 18, 2024 (Friday)

07:00	<b>Registration</b>
08:00	<b>Welcome Address</b> Zuhal Yapıcı and Thomas Klopstock
08:30 - 10:00	<b>Neurodegeneration with Brain Iron Accumulation (NBIA): General</b> <i>Chairs: Murat Emre, Thomas Klopstock</i>
	<b>From Eponyms to Mechanisms: A Century of NBIA Research</b> Guest of Honor: Adrian Danek (Germany)
	<b>Entering the Therapeutics Era for NBIA Disorders</b> Susan Hayflick (USA)
	<b>The TIRCON Registry – Current State and Future Prospects</b> Thomas Klopstock (Germany)
10:00 - 10:30	 <b>Coffee Break</b>
	<b>Poster Sessions</b> <i>Chair: Pervin İşeri</i>
	<b>Group A</b>
	<b>NBIA Diagnosis: Lessons from Ten Year Experience in A French Reference Lab</b> <i>EP1 Valeria Gioiosa</i>
	<b>Transcranial Sonography in Neurodegeneration with Brain Iron Accumulation Disorders</b> <i>EP2 Elahe Amini</i>
	<b>Estimation of Ambulation and Survival in Neurodegeneration with Brain Iron Accumulation Disorders</b> <i>EP3 Mohammad Rohani</i>
	<b>Changes in Oxytocin and Oxytocin Receptor Levels in the NBIA Cell Model</b> <i>EP4 Magdalena Žabiřka</i>
	<b>Evaluation of Carrier Frequency of Neurodegeneration with Brain Iron Accumulation (NBIA) Disorders in A Middle Eastern Patient Population Based on Data from 17,868 Exome Sequences</b> <i>EP5 Hasan Bař</i>
	<b>Group B</b>
	<b>The Significance of Peroxisomal Dysfunction in the Pathogenesis of NBIA</b> <i>EP6 Karolina Wiřniewska</i>
<b>Survey of NBIA Caregiver Perspectives to Identify Relevant QoL Outcomes for Caregivers/Patients</b> <i>EP7 Janani Ramamurthy</i>	
<b>The Significance of Ferroptosis Dysregulation in The Pathogenesis of NBIA</b> <i>EP8 Karolina Pierzynowska</i>	
<b>Initiation and Elongation of the Autophagy Process in Different Types of NBIA</b> <i>EP9 Aneta Szulc</i>	
<b>Is There Any Correlation Between Amount of Iron Measured by Quantitative Susceptibility Mapping and the Clinical Features in NBIA?</b> <i>EP10 Özge Uygun</i>	
10:30 - 12:00	<b>PLA2G6-Associated Neurodegeneration (PLAN)</b> <i>Chairs: Murat Emre, Manju Kurian</i>
	<b>The Phenotype and Genotype of PLA2G6-Related Parkinsonism</b> Kailash Bhatia (UK)
	<b>Preparing for Gene Therapy for PLAN</b> Manju Kurian (UK)
	<b>Animal Models for the Investigation of Gene Therapy in INAD</b> Ahad Rahim (UK)

12:00 - 13:00



Lunch

**Pantothenate Kinase-Associated Neurodegeneration (PKAN)**

*Chairs: Thomas Klopstock, Ody Sibon*

**From Fruit Flies to Patients in Less Than 5 Years**

Ody Sibon (The Netherlands)

**PKAN hiPS-derived Astrocyte Models Highlight the Molecular Mechanism of Iron Accumulation**

Sonia Levi (Italy)

**Validating Clinical and Ophthalmology Outcome Measures for PKAN**

Robert VV Spaul (UK)

**Clinical Aspects of PKAN and Possible Treatment Based on Deep Brain Stimulation**

Giovanna Zorzi (Italy)

**Exploring New PKAN Therapies: Current Efforts & Challenges**

Choukri Ben Mamoun (USA)

13:00 - 14:50



Coffee Break

**Poster Sessions**

*Chair: Pervin İşeri*

**Group A**

**Pank Activators for the Treatment of Pantothenate Kinase-Associated Neurodegeneration. (Withdrawn)**

EP11 Jessica Regan

**Genetic Architecture of Neurodegenerative Disorder and Its Association with Consanguinity in Pashtoon Population**

EP12 Shoaib Ur Rehman (Withdrawn)

**The Identification of A 4'-Phosphopantetheine Transporter in *S. Cerevisiae***

EP13 Jouke Jan Wedman

**Investigating Copan in Mice: From Patho-mechanisms to Therapeutic Approaches**

EP14 Chiara Cavestro

14:50 - 15:20

**Group B**

**A Surprising Presentation of Atypical Pantothenate Kinase Associated Neurodegeneration Disorder: Metamorphopsia**

EP15 Elahe Amini

**The Effect of Genistein on the Autophagy Process in a Cellular Model of Pantothenate Kinase-Associated Neurodegeneration**

EP16 Eстера Rintz

**Neurodegeneration with Brain Iron Accumulation Disorders and Retinal Neurovascular Structure**

EP17 Elahe Amini

**Olfactory Status in Neurodegeneration with Brain Iron Accumulation Disorders**

EP18 Elahe Amini

**Beta-Propeller Protein-Associated Neurodegeneration (BPAN)**

*Chairs: Bülent Elibol, Sibel Uğur İşeri*

**Human WIPI  $\beta$ -Propeller Function in Autophagy and Neurodegeneration**

Tassula Proikas-Cezanne (Germany)

**Modulating Iron Homeostasis, Autophagy and Oxidative Stress Pathways in BPAN-derived fibroblasts: Active Compounds for Potential Therapy**

Petek Ballar Kırmızıbayrak (Türkiye)

**Cardiac Glycosides for the Treatment of BPAN and Delineation of the Radiological Phenotype of BPAN**

Apostolos Papandreou (UK)

15:20 - 16:30



Coffee Break

Poster Sessions

Chairs: Yıldız Değirmenci, Murat Gültekin

Group A

**Investigating Respiratory Chain Complex I Deficiency in IPSCS-Derived Dopaminergic Neurons and Astrocytes from BPAN Individuals**

EP19 Gemma Gasparini

**Characterizing the Molecular Mechanisms of Wipi2 and Wipi4 Mutations in BPAN and Neurodevelopmental Disorders**

EP20 Eleanor Attridge

**Genistein as an Autophagy Stimulation in Beta-Propeller Protein-Associated Neurodegeneration (BPAN)**

EP21 Zuzanna Cyske

**Establishing of Drosophila Model for BPAN Disease**

EP22 Celle Marion

Group B

**Autophagy and Neurodegeneration: Discovering Critical Insights and Innovative Therapeutic Strategies Using a Novel Human Neuron Model of BPAN**

EP23 Hetavi Zaveri

**Beta-Propeller Protein Associated Neurodegeneration (BPAN): Electroencephalographic Characterization of a Cohort Of 16 Patients**

EP24 Alejandra Darling

**Altered Autophagy Involved in Neurodevelopment and Neurodegeneration: Study of A Cohort of Patients with BPAN (Beta-Propeller Protein-Associated Neurodegeneration), New Insights and Phenotypes**

EP25 Alejandra Darling

**Aceruloplasminemia**

Chairs: Thomas Klopstock, Sonia Levi

**Protein Replacement and Gene Therapy Approaches in Aceruloplasminemia: Studies in Ceruloplasmin KO Mice**

Massimo Alessio (Italy)

**A Plasma-Derived Ceruloplasmin from the Optimization of Plasma Fractionation**

Andrea Caricasole (Italy)

**Recombinant Ceruloplasmin as a Tool to Study the Prevalence of Aceruloplasminemia in GnomAD**

Nicole Ziliotto (Italy)

**Travel and Poster Awards**

Patricia Wood, Fatemeh Mollet

**End of the Day: Urgent Needs and Next Steps**

Thomas Klopstock



Dinner

# 9th INTERNATIONAL SYMPOSIUM ON NEURODEGENERATION WITH BRAIN IRON ACCUMULATION (NBIA)

October 19, 2024 (Saturday)

08:30 - 09:15	<b>Kufor-Rakeb Syndrome (KRS) and Fatty Acid Hydroxylase-Associated Neurodegeneration (FAHN)</b> <i>Chair: Bülent Elibol</i>
	<b>Cellular Aspects of Iron Accumulation in Kufor-Rakeb Syndrome Patients with Different Type of <i>ATP13A2</i> Mutations</b> Arzu Karabay (Türkiye)
	<b>Patient Led Research Advances in Fatty Acid Hydroxylase-Associated Neurodegeneration (FAHN/SPG35)</b> Sunita Venkateswaran (Canada)
09:15 - 10:25	<b>Mitochondrial Membrane Protein-Associated Neurodegeneration (MPAN)-I</b> <i>Chair: Iwona Kurkowska-Jastrzebska</i>
	<b>Alteration of Autophagy and Lipid Metabolism in MPAN: What We Know and Still Don't Know</b> Arcangela Iuso (Germany)
	<b>Elucidating the Role of <i>C19ORF12</i> in Triglyceride Homeostasis</b> Rajnish Bharadwaj (USA)
	<b>Putative Involvement of Neuroinflammation in MPAN and Potential for Immunotherapy</b> Erdem Tüzün (Türkiye)
 <b>Coffee Break</b>	
<b>Poster Sessions</b> <i>Chairs: Yıldız Değirmenci, Murat Gültekin</i>	
<b>Group A</b>	
10:25 - 10:45	<b>Modeling <i>C19orf12</i> Deficiency in Zebrafish (Withdrawn)</b> <i>EP26 Barbara Gnutti</i>
	<b>Early-Onset Dementia in a Case of Late-Onset MPAN</b> <i>EP27 Hatice Yüksel</i>
	<b>Autophagy Disturbation in Fibroblasts Derived from Patients Suffering from Mitochondrial Membrane Protein-Associated Neurodegeneration (MPAN), A Type of Neurodegeneration with Brain Iron Accumulation (NBIA)</b> <i>EP28 Grzegorz Wegrzyn</i>
	<b>Mitochondrial Membrane-Protein Associated Neurodegeneration (MPAN) Presenting with Parkinsonism Findings: Case Report</b> <i>EP29 Irem Aydın</i>
<b>Group B</b>	
	<b>Mitochondrial Membrane Protein-Associated Neurodegeneration Presenting with Parkinsonism: A Case Report</b> <i>EP30 Miray Erdem</i>
	<b>Clinical Profile of Kufor-Rakeb Syndrome and Evaluation of Quantitative Sensitivity Analysis</b> <i>EP31 Ibrahim Kamaci</i>
	<b>A Case of NBIA with Iron Accumulation Not Detected by Conventional Genetic Testing</b> <i>EP32 Malika Egemberdiyeva</i>
	<b>First Close Look at Proteasome in Neurodegeneration with Brain Iron Accumulation Patients</b> <i>EP33 Lidia Gaffke</i>

10:45 - 11:15	<b>Mitochondrial Membrane Protein-Associated Neurodegeneration (MPAN)-II</b> <i>Chair: Thomas Klopstock</i>
	<b>MPAN/PKAN Biomarkers</b> Iwona Kurkowska-Jastrzębska (Poland)
	<b>Validated Scale for Neurological Status Assessment in MPAN Patients</b> Marta Skowronska (Poland)
11:15 - 11:40	<b>New Insights from MRI Research in NBIA</b> <i>Chair: Zuhai Yapıcı</i>
	Petr Dušek (Czech Republic)
11:40 - 12:30	<b>COASY Protein-Associated Neurodegeneration (CoPAN)</b> <i>Chair: Valeria Sonia Tiranti, Giovanna Zorzi</i>
	<b>Deciphering COASY-Induced Neurodegeneration: New Variants, New Phenotypes and Insights into the Transcriptomic Profile of Patient Fibroblasts</b> Valeria Sonia Tiranti (Italy)
	<b>COASY-Associated Diseases in Mouse: Not Just a Matter of Neurodegeneration</b> Ivano Di Meo (Italy)
	<b>Zebrafish Models of PKAN and COPAN</b> Dario Finazzi (Italy)
12:30 - 12:45	<b>End of the Day: Urgent Needs and Next Steps</b> Valeria Sonia Tiranti
12:45 - 13:00	<b>Highlights and Closing Remarks</b>





## POSTER SESSIONS

Electronic posters will be displayed on two separate screens in the poster area according to the ranking order in Groups A and B. The dates and times for the presentations are provided in the table below.

Presenter	Abstract Title
<b>Poster Session-I NBIA General</b>	
October 18, 2024 (Friday) 10.00 - 10.30	
<b>Group A</b>	
EP1 Valeria Gioiosa	NBIA Diagnosis: Lessons from Ten Year Experience in A French Reference Lab
EP2 Elahe Amini	Transcranial Sonography in Neurodegeneration with Brain Iron Accumulation Disorders
EP3 Mohammad Rohani	Estimation of Ambulation and Survival in Neurodegeneration with Brain Iron Accumulation Disorders
EP4 Magdalena Żabińska	Changes in Oxytocin and Oxytocin Receptor Levels in the NBIA Cell Model
EP5 Hasan Baş	Evaluation of Carrier Frequency of Neurodegeneration with Brain Iron Accumulation (NBIA) Disorders in A Middle Eastern Patient Population Based on Data from 17,868 Exome Sequences
<b>Group B</b>	
EP6 Karolina Wiśniewska	The Significance of Peroxisomal Dysfunction in the Pathogenesis of NBIA
EP7 Janani Ramamurthy	Survey of NBIA Caregiver Perspectives to Identify Relevant QoL Outcomes for Caregivers/Patients
EP8 Karolina Pierzynowska	The Significance of Ferroptosis Dysregulation in The Pathogenesis of NBIA
EP9 Aneta Szulc	Initiation and Elongation of the Autophagy Process in Different Types of NBIA
EP10 Özge Uygun	Is There Any Correlation Between Amount of Iron Measured by Quantitative Susceptibility Mapping and the Clinical Features in NBIA?
<b>Poster Session-II PKAN/CoPAN/NBIA systemic</b>	
October 18, 2024 (Friday) 14.50 - 15.20	
<b>Group A</b>	
EP11 Jessica Regan	Pank Activators for the Treatment of Pantothenate Kinase-Associated Neurodegeneration. <b>(Withdrawn)</b>
EP12 Shoaib Ur Rehman	Genetic Architecture of Neurodegenerative Disorder and Its Association with Consanguinity in Pashtoon Population <b>(Withdrawn)</b>
EP13 Jouke Jan Wedman	The Identification of A 4'-Phosphopantetheine Transporter in S. Cerevisae
EP14 Chiara Cavestro	Investigating Copan in Mice: From Patho-mechanisms to Therapeutic Approaches
<b>Group B</b>	
EP15 Elahe Amini	A Surprising Presentation of Atypical Pantothenate Kinase Associated Neurodegeneration Disorder: Metamorphopsia
EP16 Estera Rintz	The Effect of Genistein on the Autophagy Process in a Cellular Model of Pantothenate Kinase-Associated Neurodegeneration
EP17 Elahe Amini	Neurodegeneration with Brain Iron Accumulation Disorders and Retinal Neurovascular Structure
EP18 Elahe Amini	Olfactory Status in Neurodegeneration with Brain Iron Accumulation Disorders
<b>Poster Session-III BPAN</b>	
October 18, 2024 (Friday) 16.30 - 17.00	
<b>Group A</b>	
EP19 Gemma Gasparini	Investigating Respiratory Chain Complex I Deficiency in IPSCS-Derived Dopaminergic Neurons and Astrocytes from BPAN Individuals
EP20 Eleanor Attridge	Characterizing the Molecular Mechanisms of Wipi2 and Wipi4 Mutations in BPAN and Neurodevelopmental Disorders
EP21 Zuzanna Cyske	Genistein as an Autophagy Stimulation in Beta-Propeller Protein-Associated Neurodegeneration (BPAN)
EP22 Celle Marion	Establishing of Drosophila Model for BPAN Disease
<b>Group B</b>	
EP23 Hetavi Zaveri	Autophagy and Neurodegeneration: Discovering Critical Insights and Innovative Therapeutic Strategies Using a Novel Human Neuron Model of BPAN
EP24 Alejandra Darling	Beta-Propeller Protein Associated Neurodegeneration (BPAN): Electroencephalographic Characterization of a Cohort Of 16 Patients
EP25 Alejandra Darling	Altered Autophagy Involved in Neurodevelopment and Neurodegeneration: Study of A Cohort of Patients with BPAN (Beta-Propeller Protein-Associated Neurodegeneration), New Insights and Phenotypes
<b>Poster Session-IV MPAN/KRS</b>	
October 19, 2024 (Saturday) 10.25 - 10.45	
<b>Group A</b>	
EP26 Barbara Gnutti	Modeling C19orf12 Deficiency in Zebrafish <b>(Withdrawn)</b>
EP27 Hatice Yüksel	Early-Onset Dementia in a Case of Late-Onset MPAN

<i>EP28 Grzegorz Wegrzyn</i>	Autophagy Disturbation in Fibroblasts Derived from Patients Suffering from Mitochondrial Membrane Protein-Associated Neurodegeneration (MPAN), A Type of Neurodegeneration with Brain Iron Accumulation (NBIA)
<i>EP29 Irem Aydin</i>	Mitochondrial Membrane-Protein Associated Neurodegeneration (MPAN) Presenting with Parkinsonism Findings: Case Report
<b>Group B</b>	
<i>EP30 Miray Erdem</i>	Mitochondrial Membrane Protein-Associated Neurodegeneration Presenting with Parkinsonism: A Case Report
<i>EP31 Ibrahim Kamaci</i>	Clinical Profile of Kufor-Rakeb Syndrome and Evaluation of Quantitative Sensitivity Analysis
<i>EP32 Malika Egemberdiyeva</i>	A Case of NBIA with Iron Accumulation Not Detected by Conventional Genetic Testing
<i>EP33 Lidia Gaffke</i>	First Close Look at Proteasome in Neurodegeneration with Brain Iron Accumulation Patients



## From Eponyms to Mechanisms: A Century of NBIA Research

Guest of Honor:

### Adrian Danek

Neurologische Klinik und Poliklinik, Klinikum der Universität  
München, LMU, Munich Germany

While their deeds in the Nazi era must be damned, Julius Hallervorden (1882-1965) and Hugo Spatz (1888-1969) cannot be separated from the history of research into neurodegeneration with brain iron accumulation (NBIA) as their careers teach relevant lessons, in both science and its ethics. The two had met at the "German Research Institute of Psychiatry" in Munich, founded by Emil Kraepelin (1856-1926), holder of the psychiatry chair. He aimed at working out "natural disease entities" among the manifold affections of mind and brain with the help of disease signatures that were to be identified through studies e.g. of individual disease courses, of heredity, of body fluids or brain tissue. Spatz, in Munich since 1909, had recently concentrated on iron stains of the brain while Hallervorden with a background in asylum psychiatry had acquired neuropathology skills on his own. Active in Landsberg an der Warthe (now Gorzów Wielkopolski, Poland) as of 1913, he also took the district physician exam - thus enabled to conduct post mortem studies. While in Munich, the self-taught neuropathologist intensively studied one case from his collection. "Martha S." had died in 1919 and Hallervorden had also secured tissue of her sister "Alma" who had died in Landsberg in 1914. Martha's brain most conspicuously showed "dark rust-brown discoloration" of globus pallidus and substantia nigra pars reticulata. Microscopic analysis was likely done in Munich and Hallervorden and his mentor published their observations in 1922. Two years later, he published the sister's case on his own. "Hallervorden's disease" qualified for handbook entry in 1936 as more cases were recognized with shared clinical features, course, heredity, and neuropathology. For years, however, this novel entity remained among those rare diseases to be diagnosed with certainty only post mortem. Hallervorden was able to fully concentrate on neuropathology as of 1929 and became a professor at the brain research institute in Berlin-Buch under the direction of Spatz in 1938. In the "Third Reich", he joined the Nazi party and embraced its eugenic ideas.

[Click to see the rest of the Abstract here.](#)



Adrian Danek is emeritus Professor of Cognitive Neurology at the University of Munich Neurology Department.

- He initiated the Munich Brain Course (<http://www.munichbraincourse.eu/>).
- He is a member of the core faculty of the LMU Graduate School of Systemic Neurosciences (<https://www.gsn.uni-muenchen.de>).
- Participates in the CASLMU Research Group "Tools for Transnational Neuropsychiatric Research" (<https://www.cas.lmu.de/en/programs/cas-research-groups/tools-for-transnationalneuropsychiatric-research>) and serves as a trustee of the Advocacy for Neuroacanthocytosis Patients (<https://naadvocacy.org/>).
- Apart from his interest in cerebral structure-function relationships, in particular in neurodegenerative dementia, he also focuses on "bulk lipid transfer diseases" where he has contributed to gene identification of VPS13A disease (chorea-acanthocytosis; ChAc) and of XK disease (McLeod syndrome; MLS).

He is also interested in the history of the neurosciences, particularly in the "Munich school" of Gudden's and Alzheimer's. His most recent works include a novel interpretation of "Ockham's razor" (10.1093/brain/awac159) and a pocket book for bedside cognitive testing (ISBN 978-3-17-043054-9).



## Neurodegeneration with Brain Iron Accumulation (NBIA): General

[↑ Back to Scientific Program](#)

### Entering the Therapeutics Era for NBIA Disorders

#### Susan J. Hayflick

Oregon Health & Science University, Professor and Chair  
Departments of Molecular and Medical Genetics, Pediatrics, and Neurology  
U.S.A.

The era of Mendelian disease gene discovery has largely ended. For the NBIA disorders, more than 95% of patients can be diagnosed with a specific genetic etiology. Genetic delineation of the NBIA disorders has enabled the development of natural history datasets, animal disease models, biological insights into etiologies, and robust family advocacy communities.

Still, treatment for these disorders is strictly symptomatic and largely unchanged from decades ago. That is about to change. We are on the cusp of interventions that hold enormous potential for a disease-modifying outcome. Therapeutics programs in PKAN and PLAN that are based on robust studies of animal disease models are the most advanced, and experience with these will inform work to develop treatments for all NBIA disorders. We have moved into the era of therapeutics for the NBIA disorders.



Dr Hayflick has worked on the NBIA disorders since 1991.

- Her research team, with collaborators worldwide, identified the genes for PKAN, PLAN, and BPAN, delineated their associated phenotypes including molecular, cellular and biochemical pathophysiologies and clinical histories, developed new clinical molecular diagnostics, created animal models of disease, and developed rational therapeutics for the NBIA disorders.
- She is clinically active as a medical geneticist in direct patient care and laboratory diagnostics and jointly leads the OHSU Center of Excellence in NBIA Research and Clinical Care.



## Neurodegeneration with Brain Iron Accumulation (NBIA): General

[↑ Back to Scientific Program](#)

### The TIRCON Registry – Current State and Future Prospects

Thomas Klopstock

Professor of Neurology University of Munich  
Germany



Professor of Neurology at LMU Munich, Germany. Long-standing clinical and scientific expertise in mitochondrial and other neurogenetic disorders including neurodegeneration with brain iron accumulation (NBIA). Speaker of German network for mitochondrial disorders (mitoNET) and of international collaborative project TIRCON (Treat Iron-Related Childhood-Onset Neurodegeneration). Member of German Center for Neurodegenerative Diseases (DZNE), Munich Excellence Cluster for Systems Neurology (SyNergy), and board of directors of Munich Center for Rare Diseases (MZSE). Ample experience in clinical trials in neurogenetic diseases. Author of >350 peer-reviewed publications. Main goal is contributing to disease-modifying treatments of mitochondrial diseases, NBIA and other neurogenetic disorders.



## PLA2G6-Associated Neurodegeneration (PLAN)

[↑ Back to Scientific Program](#)

### Preparing for Gene Therapy for PLAN

#### Manju Kurian

Professor Manju Kurian is a Professor of Neurogenetics at UCL-Great Ormond Street Institute of Child Health.  
U.K

There are currently no disease-modifying treatments for PLA2G6-associated neurodegeneration (PLAN). Development of precision therapies is therefore an unmet clinical need and constitutes research priority. Whilst our efforts are underway to develop a gene therapy approach for PLAN, in tandem we are seeking to be 'trial ready' in order to have meaningful outcome measures to gauge both safety and efficacy.

Here we will present our work in undertaking a retrospective natural history study for PLAN, as well as the development of radiological and blood/CSF biomarkers and a PLAN focused disease-rating scale. Robust and meaningful clinical outcome measures will be of the utmost importance when clinical trials are planned and designed, as well as for regulatory approval in the longer term.



Her current research encompasses gene discovery for childhood neurological disorders, including early onset epilepsy, neurodegeneration and movement disorders.

Her lab uses mainly cell models to investigate the underlying pathological basis of disease.

She works closely with UCL Gene Therapy groups to develop novel therapeutic strategies for children with pharmacoresistant movement disorders.

Her long-term goal is to translate her research for patient benefit, through improved clinical diagnosis and precision medicine approaches.



PLA2G6-Associated Neurodegeneration  
(PLAN)

[↑Back to Scientific Program](#)

## Animal Models for the Investigation of Gene Therapy in INAD

Ahad Rahim

Professor of Translational Neuroscience, University College London, Pharmacology  
U.K





## Pantothenate Kinase-Associated Neurodegeneration (PKAN)

[↑ Back to Scientific Program](#)

### From fruit flies to patients in less than 5 years

#### Ody Sibon

C.M. University Medical Center Groningen, Department of Biomedical Sciences, Groningen, The Netherlands

After our discovery in 2015 that the vitamin B5 derivative 4'-phosphopantetheine works protective in a *Drosophila* model for PKAN, my research group together with collaborators used this fundamental knowledge to explore possibilities to generate bypass molecules for defective CoA biosynthesis steps, like the vitamin B5 derivative "4'-phosphopantetheine" and successfully tested them in PKAN animal models. After crucial promising results in a CoA-biosynthesis impaired mouse model, (research group of prof. Hayflick and prof. Hogarth at the Oregon Health and Science University (OHSU), USA), we developed 4'-phosphopantetheine further into a medical product which fulfils all the standards allowing testing in a clinical trial. As a result, at the OHSU, a clinical trial with 4'-phosphopantetheine is now successfully finished and currently, my team is coordinating the first PKAN clinical trial in the Netherlands with 4'-phosphopantetheine. Our goal is to finally bring 4'-phosphopantetheine to the market as a cost-effective product for PKAN. My lecture is about the challenges, hurdles, milestones and future steps of this mission.



- Her PhD in molecular cell biology (University of Utrecht, The Netherlands, 1990-1994) and postdoctoral training in biochemistry and *Drosophila* genetics (State University of Stony Brook, NY, USA, 1994-1997) provided her with a background in fundamental cell and developmental biology.
- In 1998, she started as a P.I. at the University Medical Center Groningen, The Netherlands.
- Two early career starting grants of the Dutch Organization for Scientific Research, allowed her to perform curiosity driven fundamental research. This resulted in the discovery of a novel link between coenzyme A (CoA) metabolism, neurodegeneration and cardiac diseases. It was because of this unforeseen outcome that her lab entered the CoA field.





## Pantothenate Kinase-Associated Neurodegeneration (PKAN)

[↑ Back to Scientific Program](#)

### PKAN hiPS-derived Astrocyte Models Highlight the Molecular Mechanism of Iron Accumulation

#### Sonia Levi

Full Professor of Biology, School of Medicine, Vita-Salute San Raffaele University and Head of the Proteomic of Iron Metabolism Unit, Division of Neuroscience, DIBIT, IRCCS-OSR. Italy

We utilized human-induced pluripotent stem cell (hiPSC)-derived astrocytes to model PANK2-associated neurodegeneration (PKAN). This disorder is characterized by progressive neurodegeneration and significant iron accumulation in the globus pallidus of patients. It is caused by mutations in PANK2, coding for the first enzyme in Coenzyme A biosynthesis. Previous co-culture experiments using hiPS-derived neurons and -astrocytes demonstrated the neurotoxic nature of PKAN astrocytes. Further analysis of iron metabolism in PKAN astrocytes exhibited cytosolic iron accumulation, altered iron metabolism, and changes in mitochondrial morphology. They also showed a propensity to develop a stellate-like phenotype, with the degree of stellation correlating with the amount of up-taken iron loaded transferrin. This suggests potential impairments in membrane dynamics, which may underlie the observed iron overload. Analysis of constitutive exo-endocytosis, a crucial route for cellular iron intake and vesicular dynamics, using the activity-enriching biosensor SynptoZip, revealed a general impairment in constitutive endosomal trafficking in PKAN astrocytes. Super-resolution (SRFF) experiments, combining live pulse & chase with fluorescent transferrin and retrospective immunolabeling of external mitochondrial walls, showed significantly fewer transferrin-enriched vesicles contacting mitochondria in PKAN astrocytes, indicating an impaired intracellular fate of cargo endosomes. Analysis of mitochondrial iron homeostasis and tubulin feature reveal that mitochondria display an iron deficiency status caused by an impairment of iron deliver to mitochondria due to alteration of tubulin acetylation. This mitochondrial iron deficiency caused cytosolic iron overload due to the restriction of the metal to iron-dependent mitochondrial biosynthesis that affect iron-protein regulation. The findings underscore the crucial role of mitochondria in iron homeostasis and their involvement in the pathogenesis of CoA deficiency disorders. The impairment in iron delivery to mitochondria triggers cytosolic iron overload and mitochondrial dysfunction, contributing to neurodegeneration. This study highlights potential therapeutic targets for NBIA disorders through the modulation of mitochondrial iron metabolism and tubulin acetylation.



- Employment: - 1989/2002- Fondazione Centro San Raffaele del Monte Tabor, Milano-Researcher - 2003-present time- Fondazione Centro San Raffaele del Monte Tabor, Milano- Proteomic of Iron Metabolism Unit-Head of the Unit. - 2005-2019 Associate Professor of Biology, School of Medicine, Vita-Salute San Raffaele University, Milano - 2019-present time Full Professor of Biology, School of Medicine, Vita-Salute San Raffaele University, Milano

- Scientific interest: - She has a solid track record in iron metabolism and, in particular, a long experience in the characterization of structure and function of ferritins, the iron storage proteins, both in vitro and in cellular models. - She was involved in the first discovery of Mitochondrial ferritin, an iron storage protein localized in mitochondria. She developed prokaryotic and eukaryotic cellular models to overexpress iron proteins and analyze their biological functions. - Her recent research interest is focused to clarify the relationship between iron and neurodegeneration.

[Click to see the rest of the CV here](#)

Santambrogio P.1, Cozzi A.1, Ripamonti M.1,2, Berno Valeria<sup>3</sup>, Cammarota Eugenia<sup>3</sup>, Moro A2., Balestrucci C2. and Levi S.1,2 1IRCCS San Raffaele Scientific Institute, Division of Neuroscience, Milano, Italy, 2Vita-Salute San Raffaele University, Milano, Italy, 3Advanced Light and Electron Microscopy Bioimaging Center ALEMBIC, IRCCS San Raffaele Scientific Institute, Milan, Italy



## Pantothenate Kinase-Associated Neurodegeneration (PKAN)

[↑ Back to Scientific Program](#)

Paediatric Neurology Clinical Research Fellow,  
Developmental Neurosciences, UCL Great  
Ormond Street Institute of Child Health

Robert VV Spaul

UCL Great Ormond Street Institute of Child Health, Developmental Neurosciences  
U.K.



- Dr Rob Spaul is a paediatric neurology doctor from the UK who undertook his medical training at the University of Oxford and Imperial College London before moving to Bristol for subspecialty training in paediatric neurology.
- Having developed an interest in neurogenetics and movement disorders, since 2020 he has been undertaking doctoral research training under the supervision of Professor Manju Kurian at University College London and Great Ormond Street Hospital.
- During his PhD on advancing precision therapies for paediatric neurogenetic conditions, Dr Spaul has undertaken projects on several conditions such as CLN2-Batten disease and AADC deficiency, but with a primary focus on PKAN. This work has focussed on using clinical scales to monitor progression, assessment of novel disease markers such as detailed ophthalmological testing, and validating these as clinical trial outcome measures.



## Pantothenate Kinase-Associated Neurodegeneration (PKAN)

[↑ Back to Scientific Program](#)

### PKAN hiPS-derived Astrocyte Models Highlight the Molecular Mechanism of Iron Accumulation

#### Giovanna Zorzi

Unit of Child Neuropsychiatry-Movement Disorder Foundation IRCCS Istituto Neurologico Carlo Besta Via Celoria 11, 20133 Milan, Italy



PKAN is one of the most common forms of NBIA, accounting for approximately half of all NBIA cases. Traditionally, PKAN patients have been divided into typical and atypical according to age at onset, but the clinical spectrum represents a continuum. Dystonia, spasticity, tremor, parkinsonism are the major motor features of the disease, in motor symptom are mainly represented by cognitive impairment, psychiatric disturbances and retinopathy; epilepsy may occur at later stage of the disease. The course of the disease is progressive, with a more rapid evolution the earlier the onset of symptoms. A dramatic deterioration (dystonic state) is a not uncommon and life-threatening complication. Treatment involves both pharmacological and surgical approaches. Pallidal deep brain stimulation is commonly used as a treatment for dystonia; however, the response is not always satisfactory and new surgical techniques and targets have been explored in recent years. The clinical features of a large single-centre case series of paediatric and adult PKAN patients with a long follow-up will be illustrated, with a focus on unusual or peculiar clinical aspects and on the outcome after surgical treatment including different approaches.

Scopus author: 6603821807; ORCID ID: <https://orcid.org/0000-0001-7041-5365>- Co-Author of 108 papers in international peer-reviewed indexed journals (PubMed, [www.ncbi.nlm.nih.gov/pubmed](http://www.ncbi.nlm.nih.gov/pubmed))  
H-index (Scopus): 34- Citation (Scopus): > 4000

- Dr. Zorzi attended the medical school at the University of Milano from 1987 to 1993. She then entered the post-graduated Specialization School of Child Neuropsychiatry at the University of Pavia and graduated in 1999

- From 2002 to 2008 she worked as child neurologist researcher in the project founded by the Ministry of Health entitled "pediatric onset movement disorders: approach for diagnosis and treatment". From 2008 she worked as a full time employer child neurologist for in and out patients at the Department of Child Neurology of the Fondazione IRCCS Carlo Besta of Milano. In 2023 she became the Head of the Child Neurology Department of the IRCCS Carlo Besta.



## Pantothenate Kinase-Associated Neurodegeneration (PKAN)

[↑ Back to Scientific Program](#)

### Exploring New PKAN Therapies: Current Efforts & Challenges.

#### Choukri Ben Mamoun

Professor of Medicine, Microbial Pathogenesis and Pathology  
Yale School of Medicine U.S.A.



Dr. Ben Mamoun is the founder of Virtus Therapeutics, a biotechnology company investigating new therapeutic strategies for PKAN and other neurodegenerative diseases.

Pantothenate Kinase-Associated Neurodegeneration (PKAN) is a devastating neurological disorder with limited therapeutic options. PKAN is caused by mutations in the PANK2 gene, which encodes a critical enzyme involved in the metabolism of coenzyme A (CoA) from vitamin B5. The resulting deficiency in CoA disrupts numerous cellular and metabolic processes, leading to neurodegeneration. In our recent research, we have identified a novel class of compounds, termed VTACs, that demonstrate potent activation of human pantothenate kinase 3 (PANK3) with AC50 values in the nanomolar range. Among these, VTAC1 and VTAC2 have emerged as leading candidates due to their favorable physicochemical properties. Preclinical studies in murine models have revealed that VTAC1 and VTAC2 possess excellent safety profiles and suitable half-lives and penetrate the central nervous system (CNS) effectively, achieving concentrations 2 to 3 times their AC50 values. This presentation will detail the discovery and characterization of VTACs, with a focus on the pharmacokinetic and pharmacodynamic properties of VTAC1 and VTAC2, as well as their safety and efficacy profiles in preclinical models. Our findings suggest that VTAC1 and VTAC2 could represent a significant advancement in the treatment of PKAN, offering hope for patients afflicted by this challenging disease.



## Human WIPI $\beta$ -Propeller Function in Autophagy and Neurodegeneration

### Tassula Proikas-Cezanne

Eberhard Karls University Tübingen Faculty of Science, Department of Biology Institute for Cell Biology (IZB) Auf der Morgenstelle 15, 72076 Tübingen, Germany



Human WIPI beta-propellers function as PI3P effectors in autophagy, with WIPI4 and WIPI3, both mutated in human neurodegenerative diseases, being able to link autophagy control by AMPK and TORC1 to autophagosome formation. WIPI4 is considered to play an important role in the formation of autophagosomal membranes together with its distinct protein interaction partner ATG2. De novo mutations in WDR45, the gene encoding human WIPI4, are causative of betapropeller-associated neurodegeneration (BPAN) hallmarked by high brain iron accumulation. The underlying mechanism how WDR45 mutations cause BPAN are unknown. We discuss a role for WIPI4 in lysosomal ferritin degradation, and how this function may be altered in the pathophysiological context of BPAN.

- Sporbeck K, Haas ML, Pastor-Maldonado CJ, Schüssele DS, Hunter C, Takacs Z, Diogo de Oliveira AL, Franz-Wachtel M, Charsou C, Pfisterer SG, Gubas A, Haller PK, Knorr RL, Kaulich M, Macek B, Eskellinen EL, Simonsen A, Proikas-Cezanne T\*. The ABL-MYC axis controls WIPI1-enhanced autophagy in lifespan extension. *Commun Biol*. 2023 Aug 24;6(1):872. doi: 10.1038/s42003-02305236-9.
- Schüssele DS, Haller PK, Haas ML, Hunter C, Sporbeck K, Proikas-Cezanne T\*. Autophagy profiling in single cells with open source CellProfiler-based image analysis. *Autophagy*. 2023 Jan;19(1):338-351. doi:10.1080/15548627.2022.2065617.
- Bakula D, Müller AJ, Zuleger T, Takacs Z, Franz-Wachtel M, Thost AK, Brigger D, Tschan MP, Frickey T, Robenek H, Macek B, Proikas-Cezanne T\*. WIPI3 and WIPI4  $\beta$ -propellers are scaffolds for LKB1-AMPK-TSC signalling circuits in the control of autophagy. *Nat Commun*. 2017 May 31;8:15637. doi: 10.1038/ncomms15637.
- Proikas-Cezanne T\*, Takacs Z, Dönnies P, Kohlbacher O. WIPI proteins: essential PtdIns3P effectors at the nascent autophagosome. *J Cell Sci*. 2015 Jan 15;128(2):207-17. doi: 10.1242/jcs.146258.
- Dupont N, Chauhan S, Arko-Mensah J, Castillo EF, Masedunskas A, Weigert R, Robenek H, Proikas-Cezanne T, Deretic V. Neutral lipid stores and lipase PNPLA5 contribute to autophagosome biogenesis. *Curr Biol*. 2014 Mar 17;24(6):609-20. doi: 10.1016/j.cub.2014.02.008.
- Pfisterer SG, Bakula D, Frickey T, Cezanne A, Brigger D, Tschan MP, Robenek H, Proikas-Cezanne T\*. Lipid droplet and early autophagosomal membrane targeting of Atg2A and Atg14L in human tumor cells. *J Lipid Res*. 2014 Jul;55(7):1267-78. doi: 10.1194/jlr.M046359. Epub 2014 Apr 28.
- van der Vos KE, Eliasson P, Proikas-Cezanne T, Vervoort SJ, van Bostel R, Putker M, van Zutphen JJ, Mauthe M, Zellmer S, Pals C, Verhagen LP, Groot Koerkamp MJ, Braat AK, Dansen TB, Holstege FC, Gebhardt R, Burgering BM, Coffey PJ. Modulation of glutamine metabolism by the PI(3)K-PKBFOXO network regulates autophagy. *Nat Cell Biol*. 2012 Aug;14(8):829-37. doi: 10.1038/ncb2536.
- Codogno P, Mehrpour M, Proikas-Cezanne T. Canonical and non-canonical autophagy: variations on a common theme of self-eating? *Nat Rev Mol Cell Biol*. 2011 Dec 14;13(12):7-12. doi: 10.1038/nrm3249.
- Mauthe M, Jacob A, Freiburger S, Hentschel K, Stierhof YD, Codogno P, Proikas-Cezanne T\*. Resveratrol-mediated autophagy requires WIPI-1-regulated LC3 lipidation in the absence of induced phagophore formation. *Autophagy*. 2011 Dec;7(12):1448-61. doi: 10.4161/auto.7.12.17802.
- Proikas-Cezanne T\*, Waddell S, Gaugel A, Frickey T, Lupas A, Nordheim A. WIPI-1alpha (WIPI49), a member of the novel 7-bladed WIPI protein family, is aberrantly expressed in human cancer and is linked to starvation-induced autophagy. *Oncogene*. 2004 Dec 16;23(58):9314-25. doi: 10.1038/sj.onc.1208331.

- Prof. Dr. Proikas-Cezanne is a German molecular biologist and an internationally recognized expert in autophagy research.

- She discovered the human WIPI genes (Proikas-Cezanne et al. *Oncogene* 2004, 23(58):9314-25), including the WDR45 gene, which encodes the autophagy protein WIPI4, and mutations of which are responsible for BPAN.

- Prof. Dr. Proikas-Cezanne studied biology at the universities of Frankfurt and Hamburg and conducted her doctoral studies at the Max Planck Institute, Max Delbrück Laboratories in Cologne, Germany.

- After postdoctoral studies at the Marie Curie Research Institute in Oxted, UK and Temple University in Philadelphia, PA, USA, Proikas-Cezanne established her independent research on autophagy at the Eberhard Karls University Tübingen, Germany.

- In recent years, Prof. Dr. Proikas-Cezanne expanded her research program on autophagy to understand the underlying mechanisms of BPAN.

## Beta-Propeller Protein-Associated Neurodegeneration (BPAN)

### Modulating Iron Homeostasis, Autophagy and Oxidative Stress Pathways in BPAN-derived fibroblasts: Active Compounds for Potential Therapy

#### Petek Ballar Kırmızıbayrak

Ege University, Faculty of Pharmacy, Department of Biochemistry. Türkiye

Sinem Yılmaz, Erdal Bedir, İbrahim Kamacı, Gül Yalçın Çakmaklı, Zuhâl Yapıcı, Petek Ballar Kırmızıbayrak Beta-Propeller Protein-Associated Neurodegeneration (BPAN) is a rare neurodegenerative disorder caused by mutations in the WDR45 gene, which plays a critical role in autophagy. Patients with BPAN experience progressive cognitive decline, motor dysfunction, and iron accumulation in the brain, leading to increased oxidative stress and cellular damage. Dysregulation of autophagy, impaired iron homeostasis, and elevated oxidative stress are key pathological features of BPAN, making these cellular processes potential therapeutic targets. Current research focuses on identifying bioactive compounds that can modulate these pathways, offering hope for treatments that could slow or alleviate the progression of BPAN. Our study evaluates the impact of several known and novel bioactive compounds, including NRF2 inducers, senotherapeutics, autophagy and proteasome inducers on iron homeostasis, autophagy markers, and oxidative stress response proteins in fibroblasts derived from BPAN patients. When comparing BPAN fibroblasts to healthy controls, significantly higher total iron levels were observed, particularly in older patients. Additionally, changes in autophagy proteins, oxidative stress-related cytoprotective proteins, and LAMP1 were detected, with no alterations in ER stress protein markers. Notably, evaluating expression levels of proteins related to iron homeostasis, such as ferritin, ferroportin and transferrin receptor revealed that ferritin levels were markedly reduced in these BPAN-derived fibroblast. By treating BPAN fibroblasts with various compounds at different concentrations, several active compounds were identified that significantly reduced total iron levels, bringing them close to control levels. Further evaluation of these active compounds revealed that they also enhanced expressions of autophagic markers, such as LC3 and p62, indicating enhanced autophagy flux in BPAN fibroblasts. Additionally, oxidative stress markers, including NRF2 and HO-1, were upregulated after treatment, suggesting activation of the antioxidant response. Importantly, the active compounds also positively affected ferritin levels, contributing to improved iron homeostasis in BPAN fibroblasts. Overall, the bioactive compounds identified in our screening effectively modulated key processes involved in BPAN pathology, including iron metabolism, autophagy, and oxidative stress, highlighting their potential therapeutic effects in addressing the dysregulation observed in BPAN cells.



•Petek Ballar Kırmızıbayrak, Ph.D., is a full professor at Ege University, Faculty of Pharmacy, Department of Biochemistry.

•She completed her undergraduate studies in Pharmacy at Ege University (2001) and earned her Ph.D. in Molecular and Cell Biology from the University of Maryland, Baltimore (2007).

•Her research primarily focuses on protein homeostasis, particularly Endoplasmic Reticulum (ER)associated protein degradation, the Ubiquitin Proteasome System, autophagy, and the Unfolded Protein Response in health and disease.

•Additionally, she conducts research on the discovery of drug candidate molecules targeting proteostasis, telomerase, and the NRF2 systems in pathologies such as aging, cancer, and neurodegeneration.

•Prof. Kırmızıbayrak has published over 60 peer-reviewed articles, mainly in the area of proteostasis, in journals like Acta Pharmaceutica Sinica B, Scientific Reports, Cells, and Free Radical Biology and Medicine.



[↑ Back to Scientific Program](#)

Beta-Propeller Protein-Associated Neurodegeneration  
(BPAN)

Cardiac Glycosides for the Treatment of BPAN  
and Delineation of the Radiological Phenotype  
of BPAN

Apostolos Papandreou  
U.K.





# Aceruloplasminemia

[↑ Back to Scientific Program](#)

## Protein Replacement and Gene Therapy Approaches in Aceruloplasminemia: Studies in Ceruloplasmin KO Mice

### Massimo Alessio

Proteome Biochemistry Unit, Center for Omics Sciences (COSR), IRCC-San Raffaele Hospital, Milano, Italy

Aceruloplasminemia (Acp) is a rare disease caused by mutations in the gene encoding for ceruloplasmin (CP), a ferroxidase playing a role in iron homeostasis. The absence of CP's activity leads to iron accumulation in several organs, including brain. This cause both systemic and neurodegenerative symptoms, together with the decrease of iron-restricted erythropoiesis. Due to its accumulation features, Acp displays an adult-onset and systemic symptoms may precede of about ten years the appearance of neurological symptoms. This time frame would be an important therapeutic window. Current therapy, based on iron chelation, partly controls systemic iron overload but is ineffective on neurological symptoms and is often discontinued due to side effects. Since CP is mainly expressed as circulating extracellular protein, secreted by the liver into the bloodstream and by choroid-plexus epithelial cells in the cerebrospinal fluid, we decided to explore the therapeutic potential of a protein replacement approach. The CP-deficient mouse (cpKO) model of Acp, was weekly administered with human CP purified from plasma for 4 months in the time frame, from 6 to 10 months of age, mimicking the therapeutic window preceding neurodegeneration. Intraperitoneal-administered CP was able to reduce iron accumulation in liver, to limit steatosis and hepatic inflammation. In addition, the mobilization of iron from organs deposition promoted the rescue of erythropoiesis. Administered CP was able to enter the brain restoring the ferroxidase activity, which in turn fosters the reduction in iron deposition and neuroinflammation, the rescue of neuronal loss, and amelioration of motor coordination. CP crosses the brain barrier systems in the cpKO mice better than in wild-type animals, and this can be associated with the iron accumulation observed in the choroid plexus, which is part of the blood-cerebrospinal fluid-barrier. Indeed, cpKO-choroid plexus epithelia cells display a defect in barrier properties associated with alterations of the cell-cell adhesion structures. To bypass the limitations of the enzyme replacement therapy, since CP is secreted in the bloodstream by the liver, we used liver-directed gene therapy aimed to establish an endogenous production of the enzyme.



- Dr. Alessio holds a degree in Biology and a PhD in Human Biology.
- At the beginning of his carrier, from 1983 to 1994, he was fellow at the Cell Biology laboratory of the University of Turin and visiting scientist at Dana Farber Cancer Institute of Boston (MS) and at the Cell Biology Laboratory, American Red Cross in Rockville (MD). During that time, he developed expertise in tumor immunology, cell biology and protein biochemistry, contributing to the biochemical and functional characterization of CD38 and CD36 molecules.
- Then, Dr. Alessio moved to the IRCCS-San Raffaele Hospital in Milano (Italy), as senior scientist in the Immunobiology Unit.
- In 2000, he became Project Leader developing his expertise in differential proteomics for biomarkers identification and characterization, and for protein post-translation modifications analysis.

[Click to see the rest of the Abstract here](#)





# Aceruloplasminemia

## A Plasma-Derived Ceruloplasmin from the Optimization of Plasma Fractionation

Andrea Caricasole

Chief Research and Innovation Officer, Kedrion S.p.A., Lucca, Italy

Plasma-derived proteins play a crucial role in providing life-saving replacement therapies for rare conditions such as primary immunodeficiencies, autoimmune neurological diseases, and coagulation disorders like hemophilia. These proteins also have applications in critical care, such as albumin. Despite the complexity of the plasma proteome, the therapeutic potential of plasma proteins remains largely untapped. Plasma-derived therapeutics, with immunoglobulin and albumin being the most produced examples, are manufactured through an industrial fractionation process. This process involves purifying proteins from individual intermediates, some of which are left unused and discarded. From ethical, economic, and medical standpoints, developing therapeutics from these unused plasma fractionation intermediates would represent a significant innovation. To achieve this goal, we have characterized the proteome of unused plasma fractionation intermediates and identified proteins with potential as new candidate therapies for human diseases. By utilizing bioinformatics and data mining, we have prioritized proteins with the potential to serve as novel protein replacement therapies for rare and orphan conditions. One promising candidate is ceruloplasmin, a plasma ferroxidase that could be used as a therapy for aceruloplasminemia, an adult-onset ultra-rare neurological disease caused by iron accumulation due to ceruloplasmin mutations. Ceruloplasmin, purified from an unused plasma fractionation intermediate, has shown high purity and specific activity, making it suitable for preclinical efficacy studies in animal models modelling human diseases where low or absent ceruloplasmin levels lead to pathology. These findings demonstrate the feasibility of repurposing industrial waste plasma fractions as raw materials for manufacturing new candidate proteins for replacement therapies. This approach not only optimizes plasma utilization but also reduces waste generation, showcasing the potential for innovative advancements in the field of plasma-derived therapeutics.



- With a background in molecular and cell biology, Andrea Caricasole brings over 20 years of experience in the discovery and mechanistic validation of pharmacological targets, as well as in the early preclinical development of therapies for neurodegenerative conditions.
- He is a highly skilled scientist, with over 70 articles in reputable scientific journals as well as a seasoned manager, with Lead experience in multidisciplinary teams and projects in different settings.
- His international education, training and experience have enabled him to coordinate large collaborative research networks at both national and EU levels.
- His professional journey has taken him through universities, research institutes, biotech companies, pharmaceutical firms, and contract research organizations in Italy, the UK, and the Netherlands, equipping him with the toolkit to approach R&D from several perspectives.



# Aceruloplasminemia

[↑ Back to Scientific Program](#)

## Recombinant Ceruloplasmin as a Tool to Study the Prevalence of Aceruloplasminemia in GnomAD

Nicole Ziliotto

Junior Assistant Professor of Biochemistry, Department of Pharmacy, University of Pisa, Pisa, Italy Via Bonanno 6, 56126, Pisa, Italy

ACP results from mutations in the ceruloplasmin (CP) gene, which encodes the essential ferroxidase protein found in the plasma, leading to iron accumulation in organs and multisystemic phenotypic defects related to iron metabolism. However, there is currently a limited understanding of the epidemiology of ACP. Large-scale genomic population datasets, such as the gnomAD database, provide a valuable resource for better defining the prevalence of rare diseases, such as ACP. Nonetheless, the correct classification of missense variants as pathogenic or benign remains challenging. To address this, we devised a rational workflow incorporating the functional analysis of recombinant CP (rCP) mutants to validate in silico structural analyses for predicting the pathogenicity of the mutants, with the ultimate goal of assessing the prevalence of ACP in a real-world data population. Essential CP residues and ACP missense mutations were extracted from the public domain. CP missense variants found in gnomAD were filtered based on this selection of CP residues. New candidate pathogenic missense variants were identified and rationally prioritized for functional characterization. Systematic biochemical and functional analyses of representative missense variants revealed varying levels of functional impairment, with some showing no significant differences from the wild-type rCP, while others demonstrated complete loss of protein function, similar to previously identified ACP mutants. This knowledge, coupled with extensive in silico structural analysis predicting the destabilizing effects of potentially pathogenic missense mutations, allowed for an estimation of ACP prevalence in the general population, including loss-of-function mutations. The occurrence of ACP in the human population appears to be higher than previously estimated, with the presence of compound heterozygotes likely accounting for much of this increased prevalence. Given the possibility of developing a protein replacement therapy for ACP, these findings can improve the diagnosis of this condition and facilitate access to future diseasemodifying treatments for patients with ACP who might otherwise remain undetected.

[Click to see the rest of the Abstract here](#)



Dr. Ziliotto is a Junior Assistant Professor in the Department of Pharmacy at the University of Pisa (Italy).

- Her experience is in neurodegeneration/neuroinflammation, with a special focus on the clinical biochemistry of Multiple Sclerosis, Cerebral Amyloid Angiopathy, and severe traumatic brain injury, with an international experience including the Buffalo Neuroimaging Analysis Center (BNAC, USA), Cardiovascular Research Institute Maastricht (CARIM, The Netherlands), Flemish Institute for Biotechnology (VIB, Belgium), University of Ferrara (Italy), University Milano-Bicocca (Italy), and Humanitas University (Italy).

- Her current interests include mechanistic characterization of rare diseases associated with neurodegeneration.



# Aceruloplasminemia

[↑ Back to Scientific Program](#)

## Travel and Poster Awards

### Patricia Wood

Research Program Director & Founder NBIA Disorders Association  
U.S.A.



- Patricia Wood is the founder of the NBIA Disorders Association, the first patient organization for neurodegeneration with brain iron accumulation disorders that was founded in 1996.
- She served as president of the organization for 27 years, with 2.8 million raised and funding NBIA research.
- She created a world-wide NBIA community for families, and encouraged new families from other countries to start organizations and work together to fund research and promote awareness, with an end goal of treatments and ultimately cures for all NBIA disorders.
- She has helped organize, and has participated, in every NBIA symposium since the first one in 2000, as well as organizing 12 family conferences where families, researchers and clinicians came together to learn and share with each other.
- Wood stepped down as president in September, 2023, taking on a new role as Research Program Director, where she is focusing on leading research initiatives for the organization and collaborating with other NBIA patient groups.

[Click to see the rest of the CV here](#)



# Aceruloplasminemia

[↑ Back to Scientific Program](#)

## Travel and Poster Awards

Fatemeh Mollet

President of NBIA Suisse



Since 2016, I have been volunteering as the president of the NBIA Suisse association dedicated to patients affected by neurodegeneration with brain iron accumulation. My commitment stems from personal experience, as three of my nieces are affected by this rare disease. As an aunt witnessing their daily life, I felt a moral duty to get involved in this cause, not only to support my own family but also all the families affected by this ultra rare disorders.

Being in good health, I feel privileged to have the energy and resources needed to represent the interests of patients and their families and to be their voice. My goal is to advocate for better access to care, appropriate treatment and, above all, to actively contribute to the advancement of medical research in the hope of a future where the quality of life for patients is improved.

Our work at NBIA Suisse is purely voluntary. It is driven by the hope and the belief that research will one day lead to therapeutic solutions, a cure. Our association is a true pillar of support for families, while working closely with researchers and healthcare professionals to further the understanding of NBIA. We believe together we can help make hope more tangible and that is what motivates me everyday.

[Click to see the rest of the CV here](#)



## Kufor-Rakeb Syndrome (KRS) and Fatty Acid Hydroxylase-Associated Neurodegeneration (FAHN)

[↑ Back to Scientific Program](#)

### Cellular Aspects of Iron Accumulation in Kufor-Rakeb Syndrome Patients with Different Type of ATP13A2 Mutations

Arzu Karabay

Istanbul Technical University, Faculty of Arts and Sciences, Department of Molecular Biology and Genetics

Istanbul, Türkiye





## Kufor-Rakeb Syndrome (KRS) and Fatty Acid Hydroxylase-Associated Neurodegeneration (FAHN)

[↑ Back to Scientific Program](#)

### Patient led research advances in Fatty Acid Hydroxylase-Associated Neurodegeneration (FAHN/SPG35).

#### Sunita Venkateswaran

Pediatric Neurology, Department of Pediatrics Associate Professor  
Schulich School of Medicine and Dentistry, Western University Clinician  
Researcher, Children's Health Research Institute Associate Scientist, Law-  
son Health Research Institute Children's Hospital, London Health Sci-  
ences Centre 800 Commissioners Road E. London, ON N6A 5W9

As part of this symposium, I will discuss the current knowledge and steps towards further characterization of FAHN both from a clinical, imaging and biomarker perspective. In addition, there will be discussion on collaborative studies which are underway including structural biology of FA2H, status of animal modelling, iPSC models, and steps being taken towards gene therapy.



Dr. Venkateswaran is a Pediatric Neurologist, Associate Professor and Clinician Researcher at the Children's Hospital, London Health Sciences Centre, Western University, Canada. She is the current vice-president of the Canadian Association of Child Neurologists.

- She is the co-lead of the rare disease initiative in Southwestern Ontario. Dr. Venkateswaran has represented Canada as the part of TIRCON since 2016.
- Her clinical expertise is neurodegenerative and white matter disorders.
- She consults on patients from across Canada with various leukodystrophies and NBIA's with a particular interest in Fatty Acid Associated Neurodegeneration (FAHN), also known as SPG35.
- Her primary role is in understanding the natural history and developing biomarkers using various-omics and advanced neuroimaging.
- She is currently leading a consortium of international scientists studying FAHN via mouse models, structural biological studies, the development of iPSC lines and gene therapy models



## Mitochondrial Membrane Protein-Associated Neurodegeneration (MPAN)-I

[↑ Back to Scientific Program](#)

### Alteration of autophagy and lipid metabolism in MPAN: what we know and still don't know.

#### Arcangela Iuso

Institute of Neurogenomics, Helmholtz Zentrum München, Neuherberg, Germany.  
Institute of Human Genetics, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany.



Pathogenic variants in the C19orf12 gene cause Mitochondrial membrane protein-associated neurodegeneration (MPAN), a progressive neurodegenerative disorder. This study investigates the cellular mechanisms underlying MPAN pathogenesis, focusing on lipid metabolism, autophagy, and mitochondrial function. Extensive investigations in patient fibroblasts revealed no significant mitochondrial dysfunction, contrary to expectations based on the protein's mitochondrial localization. However, patient-derived fibroblasts exhibited defective autophagy activation and, when differentiated into adipocytes, showed abnormal accumulation of lipid droplets (LDs). We employ a combination of lipidomics and proteomics approaches to elucidate the relationship between impaired autophagy and LD accumulation. This research opens up novel avenues for therapeutic interventions by providing new insights into MPAN pathogenesis.

Dr. Iuso is a Senior Scientist at the Helmholtz Zentrum München and serves as the Scientific Coordinator of the International Biobank for Neurodegeneration with Brain Iron Accumulation (NBIA) at the Technical University of Munich, Germany.

- Her research focuses on neurodegenerative and metabolic disorders, with particular attention to NBIA and metabolically related conditions, including those resulting from PPCS and SLC25A42 deficiency. Dr. Iuso's work aims to understand the function of poorly characterized proteins, an approach that contributes to the exploration of rational therapeutic strategies. In her investigations, Dr. Iuso utilizes a diverse range of model systems: primary patient samples, stem cell models, genetically modified fruit flies, mouse models. This comprehensive approach allows for a thorough examination of disease mechanisms and potential treatments from multiple perspectives.

- Dr. Iuso's position at the Helmholtz Zentrum München, a leading institution for health research, facilitates her contributions to the field of neurodegenerative and metabolic disorders. Her work in basic and pre-clinical research supports the development of new insights into these complex conditions, potentially paving the way for novel therapeutic approaches.



## Mitochondrial Membrane Protein-Associated Neurodegeneration (MPAN)-I

[↑ Back to Scientific Program](#)

### Elucidating the Role of C19ORF12 in Triglyceride Homeostasis

Rajnish Bharadwaj

Department of Pathology and laboratory medicine University of Rochester Medical center Rochester, New York, USA

Mitochondrial membrane protein associated neurodegeneration (MPAN) is a familial neurodegenerative disorder associated with functional deficits and neuronal loss involving various brain regions, most prominently basal ganglia. Like other variants of Neurodegeneration with Brain Iron Accumulation (NBIA), patients with MPAN also show accumulation of iron in basal ganglia. MPAN is caused by mutations in a poorly understood gene – c19orf12. Using the model system *Drosophila melanogaster*, we have demonstrated that *Nazo*, one of the fly homologs of c19orf12 is involved in lipid homeostasis. *Nazo* is a lipid droplet associated protein and its disruption leads to extensive loss of lipid droplets in gut. *nazo* mutants have diminished whole body triglyceride reserves, due to which these mutants are sensitive to starvation and oxidative stress. *Nazo* is required for maintaining normal levels of Perilipin-2, an inhibitor of the lipase-Brummer. Overexpression of Perilipin-2 or knockdown of Brummer rescues the *nazo* loss of function phenotype. This suggests that gut LD depletion in *nazo* mutants may arise, at least in part, from diminished Perilipin-2 on lipid droplets leading to aberrant Brummer-mediated lipolysis. *Nazo*-related gut defects have profound cell nonautonomous impacts on the brain, as evidenced by significant proteomic alterations, particularly related to lipid metabolism, in the heads of *nazo* mutants.

Our findings provide novel insights into the role of c19orf12 as a possible link between lipid dyshomeostasis and neurodegeneration, particularly in the context of NBIA.



Dr. Rajnish Bharadwaj is a physician-scientist with clinical expertise in neuropathology.

- He received his MBBS from All India Institute of Medical Sciences, New Delhi and Ph.D. from University of Texas Southwestern Medical Center, Dallas.

- After finishing his graduate studies, he joined Johns Hopkins University School of Medicine as a postdoctoral fellow and worked on various problems pertaining to muscular and neuronal biology.

- Subsequently, he completed his residency in anatomic pathology and fellowship in neuropathology from University of Washington Medical Center, Seattle.

- Dr. Bharadwaj's primary research interests are in molecular mechanisms of neurodegenerative diseases.

- His ongoing research revolves around understanding the role of lipid droplet, mitochondrial and lysosomal dysfunction in neurodegeneration.

- He is currently focusing on a few genes, implicated in Parkinson's disease and a related movement disorder- Neurodegeneration with Brain Iron Accumulation (NBIA). Using the model organism *Drosophila melanogaster* as well as in vitro cell culture systems, he is trying to elucidate the roles of these genes in health and disease. To assess the broader relevance of the insights gleaned from basic research, Dr. Bharadwaj also plans to pursue translational research using postmortem brain tissue obtained from human patients.





## Mitochondrial Membrane Protein-Associated Neurodegeneration (MPAN)-I

[↑ Back to Scientific Program](#)

### Putative Involvement of Neuroinflammation in MPAN and Potential for Immunotherapy

Erdem Tüzün

Istanbul University, Aziz Sancar Experimental Medicine Research Institute  
Department of Neuroscience

Istanbul, Türkiye



Received his medical doctor and neurologist titles in Istanbul University and then worked as a postdoctoral researcher at Oxford, Texas and Pennsylvania Universities. He is currently faculty in Neuroscience Department at Istanbul University. His scientific studies are mainly focused on clinical neuroimmunology



## Mitochondrial Membrane Protein-Associated Neurodegeneration (MPAN)-II

[↑ Back to Scientific Program](#)

### MPAN and PKAN serum biomarkers.

#### Iwona Kurkowska-Jastrzębska

Neurologist and clinical pharmacologist, and the Head of the 2nd Department of Neurology in the Institute of Psychiatry and Neurology in Warsaw, Poland.



12nd Department of Neurology, Institute of Psychiatry and Neurology, 2Laboratory of Mitochondrial Biology and Metabolism, Nencki Institute of Experimental Biology Polish Academy of Sciences, 3Association NBIA Polska Blood-based biomarkers represent significant progress in the clinical assessment of neurodegenerative diseases. Specific biomarkers of neuronal degeneration, such as amyloid- $\beta$ , tau peptides, neurofilament light chain,  $\beta$ -synuclein, ubiquitin-C-terminal hydrolase-L1, and those of glial degeneration, such as glial fibrillary acidic protein, can measure key pathophysiological processes across various neurodegenerative diseases. In neurodegeneration with brain iron accumulation (NBIA), measuring synuclein pathology, and glial and neuronal degeneration, may provide important insights into the disease stage and can be used to monitor the disease and response to treatment. To identify biomarkers that can serve as indicators of disease progression and treatment effectiveness, we enrolled 25 patients with genetically confirmed MPAN and 12 patients with PKAN, along with a control group of healthy volunteers matched for age and gender. Fasting serum was collected, frozen at  $-80^{\circ}\text{C}$ , and stored until analysis. MMP-9, S100B, ICAM-1, E- and P-selectins, and total  $\alpha$ -synuclein were measured using standard ELISA techniques according to the manufacturer's instructions. Serum levels of NfL, GFAP, Tau protein, and UCH-L1 were tested using the ultrasensitive ELISA method (SIMOA Quanterix). MPAN patients exhibited higher serum levels of all biomarkers except BDNF. MMP-9, E-selectin, and P-selectin levels were 1.4 to 2 times higher than those in controls. S100B levels were ten times higher in MPAN patients, suggesting potential blood-brain barrier damage. Alpha-synuclein levels were 25 times higher, consistent with the accumulation of this protein in the brain. NfL, GFAP, and UCH-L1 levels were 8, 2, and 5 times higher, respectively. In PKAN patients, inflammatory biomarkers did not differ from controls. BDNF levels were reduced by approximately 30%, and alpha-synuclein levels were reduced by 50%. UCH-L1 and GFAP levels were not elevated compared to the control group, while NfL and Tau were significantly higher. MPAN and PKAN patients did not differ in Tau and NfL levels. Although these diseases share similar clinical and radiological features, their differing pathology is reflected in the distinct serum biomarker patterns.

She had been working for about 10 years in the Department of Experimental and Clinical Pharmacology of the Warsaw Medical University, where she was involved in basic research of neurodegenerative processes and the role of neuroinflammatory reaction in the central nervous system.

- She spent few short post-doctoral internships in the Department of Neuropathology and in the Department of Neuroimmunology of Max Planck Institute of Psychiatry in Martinsried.

- Her research interest are now concentrated on NBIA diseases as well as on neuroimmunology and demyelinating diseases of the central nervous system.

- She is a member of The Committee on Neurological Sciences of Polish Academy of Science and member of the board of the Polish Neurological Society.



## Mitochondrial Membrane Protein-Associated Neurodegeneration (MPAN)-II

[↑ Back to Scientific Program](#)

### Validated scale for neurological status assessment in MPAN patients.

Marta Skowrońska

2nd Department of Neurology, Institute of Psychiatry and Neurology, Warsaw, Poland

Rating scales for clinical symptoms severity are an important part of patient management as they represent a way to assess disease severity, any improvement or deterioration, and impact treatment decisions. Developing scales for specific diseases is necessary to address the spectrum of clinical symptoms. After scale development, it has to be validated before it is used in clinical practice. The MPAN Disease Rating Scale is divided into three parts. The first part – for daily living activities - had been pre-tested with patients (so-called: cognitive pre-testing) with patients' suggestions for the answers. The second part of the scale is testing dementia – mostly memory and thinking, as visual and motor problems might impact the result. The third part is for neurological assessment. Each assessed item had been given instructions for the assessment and the answer options across the scale are unified.



I'm a neurologist specializing in rare movement disorders with brain metal accumulation: Wilson's Disease and NBIA.

- I also specialize in neurosonology - TCS – ultrasound technique for neurodegeneration and dystonia treatment with botulinum toxin administration under ultrasound control.
- My research interest is mainly focused on MPAN and PKAN.
- I'm looking into the clinical course of the disease, but also for the laboratory biomarkers of disease progression.
- I'm also involved in research on metabolic abnormalities in NBIA.



## New Insights from MRI Research in NBIA

### Petr Dusek

Department of Neurology and Center of Clinical Neuroscience, Department of Radiology; First Faculty of Medicine, Charles University and General University Hospital in Prague, Czechia



- Petr Dusek is an Associate Professor at the Department of Neurology and Center of Clinical Neuroscience, First Faculty of Medicine, Charles University, and General University Hospital in Prague.
- His main expertise lies in Movement Disorders and Neuroimaging. Between 2013 and 2016, he worked as a post-doc researcher at the Department of Neuroradiology, University Medicine Göttingen, Germany.
- Currently, his primary research interests focus on biomarkers of the early stages of neurodegeneration and the relationship between cerebral accumulation of metals, neuroinflammation, and neurodegeneration. In the field of neuroimaging, he investigates potential clinical applications of iron-sensitive MR techniques, such as quantitative susceptibility mapping, and works on ex-vivo validation of novel MR markers. For instance, in collaboration with the Institute of Psychiatry and Neurology in Warsaw, Poland, he developed and validated the Semiquantitative Scale for Assessing Brain MRI Abnormalities in Wilson Disease.
- His research has been supported by several significant grants, including those from the Czech Research Council, and he has collaborated on the EU's Horizon 2020 program. He also leads the Movement Disorders section of the Czech National Institute for Neurology Research.

## COASY Protein-Associated Neurodegeneration (CoPAN)

### Deciphering COASY-Induced Neurodegeneration: New Variants, New Phenotypes and Insights into the Transcriptomic Profile of Patient Fibroblasts

Valeria Sonia Tiranti

Unit of Molecular Genetics and Neurogenetics Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

COASY, the gene encoding the bifunctional enzyme CoA synthase, which catalyses the last two reactions of cellular de novo coenzyme A (CoA) biosynthesis, has been associated with two extremely rare autosomal recessive disorders, namely COASY protein-associated neurodegeneration (CoPAN), a form of neurodegeneration with brain iron accumulation (NBIA), and pontocerebellar hypoplasia type 12 (PCH12). We have identified five new individuals with new COASY variants. While one case had classic CoPAN features, the others showed atypical symptoms such as deafness, speech and autism spectrum disorders, brain atrophy, and microcephaly. All patients suffered from epilepsy, emphasising the potential prevalence of this condition in COASY-related disorders. Transcriptomic profiling of fibroblasts revealed impaired expression of genes associated with mitochondrial respiration, oxidative stress response, transmembrane transport, various cellular signalling pathways, and protein translation, modification and trafficking. Bioenergetic analysis revealed an impairment of mitochondrial oxygen consumption in COASY fibroblasts. Despite comparable total CoA levels to control cells, the levels of mitochondrial 4'phosphopantetheinylated proteins were significantly reduced in COASY patients. These results not only extend the clinical phenotype associated with COASY variants but also indicate a continuum between CoPAN and PCH12. The intricate interplay of altered cellular processes and signalling pathways provides valuable insights into the pathogenesis of COASY-associated diseases.



- Education: Unit of Molecular Genetics and Neurogenetics Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy - University of Milan – Biology degree cum laude: 1989.- University of Milan – Specialization in Medical Genetics cum laude: 2001

- Present Position:- Responsible for the Lab of Molecular Pathology of Mitochondrial Disorders, Unit of Medical Genetics and Neurogenetics, Deputy Scientific Director at Fondazione IRCCS, Istituto Neurologico C. Besta, Milan.

- Research interests:- Dr. Valeria Tiranti has a long-standing expertise in mitochondrial and metabolic disorders, including identification of disease genes, biochemical evaluation of the respiratory chain activities, molecular and cellular biology, and identification of pathogenic mechanisms of diseases. - Her group performed the characterization of different mouse models and attempted pharmacological treatments in some of them. - She joined the NBIA field some years ago and she is trying to elucidate the role of mitochondria in neurodegeneration by studying cellular and animal models.

- Organization:- Fondazione IRCCS Neurological Institute C. Besta is an internationally recognized leading Centre in neuroscience; it diagnoses and treats neurological diseases in adults and children and carries out basic and clinical research in Neurology. - The Unit of Medical Genetics and Neurogenetics is dedicated to research and advanced diagnostic activities to offer a service of excellence to patients, and make progress toward the elucidation of the causes and mechanisms leading to mitochondrial diseases. The Unit is also devoted to the molecular genetics diagnosis of NBIA and other neurodegenerative diseases, such as Parkinson's disease.



## COASY Protein-Associated Neurodegeneration (CoPAN)

[↑ Back to Scientific Program](#)

### COASY-associated diseases in mouse: not just a matter of neurodegeneration

Ivano Di Meo

Unit of Medical Genetics and Neurogenetics Fondazione IRCCS Istituto Neurologico Carlo Besta Via Temolo 4, 20126, Milano, Italy

COASY protein-associated neurodegeneration (CoPAN), a form of neurodegeneration with brain iron accumulation (NBIA), and pontocerebellar hypoplasia type 12 (PCH12) are two extremely rare autosomal recessive disorders that have been linked to COASY, the gene encoding the bifunctional enzyme CoA synthase, which catalyzes the last two reactions of cellular de novo coenzyme A (CoA) biosynthesis. Understanding why the different symptoms emerge in these disorders and what determines the development of one syndrome over the other is still not achieved. To unravel the contribution of different brain cell types to the pathogenesis of these diseases, as well as to elucidate the mechanisms linking CoA metabolism, iron dyshomeostasis, and neurodegeneration, we generated conditional, tissue-specific mouse models lacking Coasy gene in neurons or in astrocytic lineage, using the Cre-loxP system. Neuronal-specific Coasy null mice showed a clinical phenotype similar to those of CoPAN patients, characterized by neurological impairment, progressive sensorimotor defects, dystonia-like movements, and reduced lifespan. Interestingly, besides the alteration of iron homeostasis neurodegenerative neuropathology, we also found a broad neuroinflammation, characterized by microglial activation, astrocytes hyper-proliferation, and higher expression of pro-inflammatory cytokines in the brain of ko mice. Likewise, the ablation of the Coasy gene in the astrocytic lineage induces a similar clinical phenotype and astrogliosis, but histological analysis also reveals severe congenital cerebral and cerebellar cortical hypoplasia, indicating a crucial role of Coasy during neurodevelopment. All together, these data suggest that neuroinflammation could play an important role in the pathogenesis of the human disease, representing a potential target for future therapeutic interventions. Moreover, Coasy ablation in specific cell types triggers abnormal neuronal development, offering new insights into disease mechanisms.



Ivano Di Meo is a senior scientist in the Unit of Medical Genetics and Neurogenetics at the Foundation Institute of Neurology “Carlo Besta” in Milan, where he leads preclinical studies in the fields of Neurodegeneration with Brain Iron Accumulation (NBIA) and mitochondrial disorders.

- He obtained his PhD in Translational and Molecular Medicine and the specialization in Medical Genetics at the University of Milan.
- After a postdoc at the Mitochondrial Biology Unit at Cambridge University, UK, he returned to Milan, where, he developed his own group and line of investigation through a young researcher grant from the Italian Ministry of Health.
- The focus of his research is the generation and characterization of new disease models, the elucidation of molecular and biochemical pathomechanisms, and the implementation of experimental pharmacological and molecular therapeutic approaches.



## COASY Protein-Associated Neurodegeneration (CoPAN)

[↑ Back to Scientific Program](#)

### Zebrafish Models of PKAN and COPAN

Dario Finazzi

Department of Molecular and Translational Medicine

Coenzyme A (CoA) is an essential cofactor in all living organisms, functioning either as an activator of molecules with carbonyl groups or as a carrier of acyl moieties. CoA biosynthesis involves five highly conserved enzymatic steps. In humans, defects in genes encoding the CoA biosynthesis enzymes cause ultrarare inherited disorders. While mutations in phosphopantothenoylcysteine synthetase (PPCS), catalyzing the second enzymatic step, are associated with an autosomalrecessive form of dilated cardiomyopathy, sequence variations in pantothenate kinase 2 (PANK2) and coenzyme A synthase (COASY), the first and last enzymes of the biosynthetic pathway, are found in patients affected by rare forms of neurodegeneration with brain iron accumulation (NBIA), PKAN and CoPAN, respectively. These disorders share similar clinical features, including dystonia, parkinsonian traits, and cognitive impairment. In the most recent years, we explored the potential of the zebrafish (*Danio rerio*) animal model to investigate the role of these genes in neurodevelopment and elucidate the biological mechanisms leading to neurodegeneration. We generated zebrafish lines with partial or complete abrogation of *pank2* and *coasy* function. The phenotypic characterization of *pank2* morphants and mutants revealed anomalies in the development of venous vascular structures and of germinal cells. Adult fish showed testicular atrophy and altered behavioural response in an anxiety test, but no evident signs of neurodegeneration. The down-regulation of *coasy* expression perturbed the dorso-ventral patterning and severely altered neuronal development in zebrafish embryos; the complete disruption of *coasy* gene lead to larval lethality, with death occurring around 15 dpf. Mutant embryos showed a dilated heart and significant changes in lipid content, but apparently no evident signs of neurodegeneration.



Viale Europa, 11 25123 Brescia, Italy

- Dario Finazzi got his MD degree at the University of Brescia, where he completed the Specialization School in Biochemistry and Clinical Chemistry.

- He is now an Associate Professor in Molecular Biology at the University of Brescia, Italy.

- His expertise comprises a peculiar and synergistic combination of skills and longtime experience in molecular and cell biology.

- His training experience started at the Biotechnology Laboratory at the University of Brescia and continued as a visiting fellow at the Cell Biology and Metabolism Branch, National Institutes of Health, Bethesda, USA, where he studied the mechanisms involved in the regulation of the intracellular protein trafficking.

- He became a clinical researcher at the University of Brescia/Spedali Civili di Brescia, and started to work on the biological functions of proteins involved in the pathogenesis of Alzheimer's disease, to investigate genetic aspect of neurodegenerative disorders and the processes controlling the systemic and cellular iron homeostasis and their involvement in neurodegeneration.

- He got interested in the study of the molecular mechanisms associated with neurodegenerative processes characterized by extensive iron accumulation in the brain.

[Click to see the rest of the CV here](#)



# POSTER SESSIONS

## NBIA GENERAL GROUP A

[↑ Back to Scientific Program](#)

[↑ Back to Poster Session](#)

### EP1

#### NBIA DIAGNOSIS: LESSONS FROM TEN YEARS EXPERIENCE IN A FRENCH REFERENCE LAB

*<sup>1</sup>Valeria Gioiosa, <sup>2</sup>Chloe Angelini, <sup>1</sup>Isabelle Coupry, <sup>3</sup>Julie Deforges, <sup>2</sup>Patricia Fergelot-Maurin, <sup>4</sup>Jean-Paul Lasserre, <sup>3</sup>Claudio Plaisant, <sup>1</sup>Giovanni Stevanin, <sup>1</sup>Cyril Goizet*

<sup>1</sup>French Reference Center for Rare Diseases – Neurogenetics, Medical Genetic Department, Pellegrin Hospital, CHU Bordeaux, Bordeaux, France, University of Bordeaux, CNRS, INCIA, UMR 5287, NRGGen Team, Bordeaux, France

<sup>2</sup>French Reference Center for Rare Diseases – Neurogenetics, Medical Genetic Department, Pellegrin Hospital, CHU Bordeaux, Bordeaux, France, University of Bordeaux, CNRS, INCIA, UMR 5287, NRGGen Team, Bordeaux, France, Reference Laboratory for NBIA Diagnosis, Molecular Genetics Laboratory, Pellegrin

<sup>3</sup>Reference Laboratory for NBIA Diagnosis, Molecular Genetics Laboratory, Pellegrin Hospital, CHU Bordeaux, Bordeaux, France

<sup>4</sup>University of Bordeaux, CNRS, INCIA, UMR 5287, NRGGen Team, Bordeaux, France

**Introduction:** Neurodegeneration with Brain Iron Accumulation (NBIA) is a group of inherited disorders characterized by abnormal iron accumulation in brain's basal ganglia (1). NBIAs are extremely rare diseases, and heterogeneous, with variable clinical presentations and ages of onset. The common feature of NBIA is the accumulation of iron in the basal ganglia, which is visible on specific sequences of brain MRI. To date, fifteen genes are known to be responsible for NBIA, with various modes of inheritance, predominantly autosomal recessive but also autosomal dominant and X-linked.

**Materials and Methods:** The DNA of 319 patients with clinical and MRI characteristics compatible with a diagnosis of NBIA was examined. The sample of the patients were referred by various French specialists to the molecular biology laboratory at the University Hospital Center (CHU) of Bordeaux. A brain MRI was requested for each patient and clinical data were collected using a specific information sheet. A panel Next Generation Sequencing of 9 genes was performed, including: ATP13A2, CP, DCAF17, FA2H, FTL, C19orf12, PANK2, PLA2G6, and WDR45. For patients with negative NBIA panel, the referring physicians were contacted so they could offer their patients a trio exome or genome analysis.

**Results:** Among these 319 patients, the molecular diagnosis of NBIA could be established for 72 (23 %). The distribution according to the involved gene is summarized in Figure 1. For each subtype, the age of onset of the first symptoms, the nature of these symptoms, and the main clinical manifestations were evaluated. Such a large sample of patients allowed us to highlight atypical characteristics in the modes of transmission and clinical presentations. Actually, 4 families presented with dominant MPAN, including mosaic carriers of the familial variant displaying late onset presentation in two of them. They are the only demonstrated mosaic cases reported to date in the C19ORF12 gene (3). Post-zygotic mosaicism could also explain the presence in our cohort of two male monozygotic twins, where only one of them is symptomatic for a WDR45 variant. We have also identified an atypical form of Woodhouse Sakati syndrome, with a patient carrying composite heterozygous variants with the first description of a missense variant, in trans with a classical non sense variant, and an attenuated phenotype.

**Conclusion:** Our work aims to provide a precise clinical, radiological, and genetic description of patients affected by NBIA, based on the series established at the genetic laboratory at Bordeaux University Hospital for over ten years, and to identify new genetic causes of iron accumulation through trio exome and genome sequencing. Working with large samples also provides substantial support to further research.





# POSTER SESSIONS

EP2

## TRANSCRANIAL SONOGRAPHY IN NEURODEGENERATION WITH BRAIN IRON ACCUMULATION DISORDERS

<sup>1</sup>*Seyed Amir Hassan Habibi, <sup>1</sup>Zahra Azad, <sup>1</sup>Elahe Amini, <sup>1</sup>Narges Yazdi, <sup>1</sup>Maziar Emamikhah, <sup>1</sup>Mohammad Rohani*

<sup>1</sup>*Iran University of Medical Sciences School of Medicine, Tehran, Iran*

**Introduction:** Transcranial Sonography (TCS) is a non-invasive technique that has been used as a diagnostic tool for a variety of neurodegenerative disorders. However, the utility and potential application of this technique in neurodegeneration with brain iron accumulation (NBIA) disorders is scarce and inconclusive. Objectives: This study aims to describe the TCS characteristics in NBIA disorders and to determine the potential utility of this technique in diagnosing NBIA disorders.

**Materials and Methods:** In this cross-sectional retrospective case-control study, the echogenicity of Substantia Nigra (SN), Lentiform Nucleus (LN), and Diameter of the Third Ventricle (DTV) were assessed by TCS in genetically confirmed NBIA patients referring to the movement disorder clinic. The normal echogenicity area of SN was defined based on the 90th percentile of an age-and-gender- matched control group. NBIA patients underwent neurologic examination at each visit, but their brain magnetic resonance imaging (MRI) and demographics were extracted from electronic records.

**Results:** Thirty-five NBIA patients of four subtypes with a mean disease duration of 10.54 years and 35 controls were enrolled. The normally defined SN echogenicity in controls was 0.23 cm<sup>2</sup>. DTV and SN echogenicity areas were significantly higher in patients compared to the controls ( $P = 0.002$  and  $< 0.001$ , respectively). Around 85% and 63% of the patients showed LN and SN hyperechogenicity at least on one side, respectively. Disease duration was positively correlated with DTV ( $r = 0.422$ ,  $p = 0.015$ ). Cases with Pantothenate Kinase Associated Neurodegeneration (PKAN,  $n = 23$ ) also had significantly higher DTV and SN echogenicity area compared to the controls.

**Discussion:** In this study, TCS findings of 35 genetically confirmed NBIA patients of four NBIA subtypes, including PKAN, Mitochondrial membrane Protein-Associated Neurodegeneration (MPAN), Kufor Rakeb Syndrome (KRS), and adult-onset Phospholipase A2-Associated Neurodegeneration (PLAN), were reported. Hyperechogenicity is assumed to be a reflection of metal ions, iron-binding partners like neuromelanin, and/or structural changes. Our preliminary findings were suggestive of different hyperechogenicity patterns among the evaluated NBIA subtypes. Hyperechogenicity was often seen in LN in MPAN, SN and LN in PKAN, and SN in KRS in this study population. Skowronska et al. suggested that different reported patterns in the literature could be used as a discriminative tool between the NBIA subtypes. However, we assume that much more descriptive studies are necessary to achieve this purpose due to the ultra-rarity of NBIA disorders. In this study, we also detected that different NBIA subtypes, arising from different underlying genetic variants, were heterogeneous in SN echogenicity in comparison to the control group. Although the very limited sample size (especially in KRS and PLAN) does not allow us to interpret our findings, we cannot deny the role of the genetic factors and different disease pathomechanisms in the diversity of SN echogenicity that we observed between PKAN and MPAN, and between each of them and the control group.

**Conclusion:** Despite most NBIA patients displayed increased DTV and higher SN and LN hyperechogenicity than healthy controls, the discriminatory role of TCS on different NBIA subtypes remains to be determined.



# POSTER SESSIONS

EP3

## ESTIMATION OF AMBULATION AND SURVIVAL IN NEURODEGENERATION WITH BRAIN IRON ACCUMULATION DISORDERS

<sup>1</sup>Elahe Amini, <sup>1</sup>Mohammad Rohani, <sup>2</sup>Anthony E Lang, <sup>1</sup>Zahra Azad, <sup>1</sup>Seyed Amir Hassan Habibi, <sup>3</sup>Afagh Alavi, <sup>1</sup>Gholamali Shahidi, <sup>1</sup>Maziar Emamikhah, <sup>4</sup>Ahmad Chitsaz

<sup>1</sup>Iran University of Medical Sciences, Tehran, Iran

<sup>2</sup>University of Toronto, Toronto, Canada

<sup>3</sup>The University of Social Welfare and Rehabilitation Sciences, Tehran, Iran

<sup>4</sup>Isfahan University of Medical Sciences, Iran

**Introduction:** Neurodegeneration with Brain Iron Accumulation (NBIA) disorder is a group of ultra-orphan hereditary diseases with very limited data on its course.

**Objectives:** To estimate the probability of preserving ambulatory ability and survival in NBIA.

**Materials and Methods:** In this study, the electronic records of the demographic data and clinical assessments of NBIA patients from 2012 to 2023 were reviewed. The objectives of the study and factors impacting them were investigated by Kaplan–Meier and Cox regression methods.

**Results:** One hundred and twenty-two genetically-confirmed NBIA patients consisting of nine subtypes were enrolled. Twenty-four and twenty-five cases were deceased and wheelchair-bound, with a mean disease duration of  $11 \pm 6.65$  and  $9.32 \pm 5$  years, respectively. The probability of preserving ambulation and survival was 42.9% in 9 years and 28.2% in 15 years for classical Pantothenate Kinase-Associated Neurodegeneration (PKAN, n=18), 89.4% in 7 years and 84.7% in 9 years for atypical PKAN (n=39), 23% in 18 years and 67.8% in 14 years for Mitochondrial Membrane Protein-Associated Neurodegeneration (MPAN, n=23), 75% in 20 years and 36.5% in 33 years for Kufor Rakeb Syndrome (KRS, n=17), respectively. The frequencies of rigidity, spasticity, and female gender were significantly higher in deceased cases compared to surviving patients. Spasticity was the only factor associated with death ( $p$ -value = 0.03).

**Discussion:** In our study, classical PKAN patients had a rapid course to become wheelchair-bound. In the Kaplan–Meier statistical model, progression to loss of walking ability and death have almost the same patterns, except for MPAN, in which the ability to walk disappears with a steep slope close to the classical PKAN subtype. This finding aligns with previous studies, which showed that MPAN and classical PKAN have a similar clinical progression regarding gait disorders. The most common symptoms of MPAN patients in our study were gait disorder (90%), spasticity (80%), cognitive impairment (50%), and speech disorder was also significantly frequent (82%). Visual loss and optic atrophy are common findings in MPAN that can intensify gait dysfunction. Around half of the MPAN cases in this study had optic atrophy. Furthermore, adulthood onset MPAN patients had a shorter disease duration to non-ambulatory status compared to the childhood onset MPAN patients. However, we could not compare them statistically because of the limited number of adult-onset patients. KRS patients had the best survival and the longest ambulation period. The slow progression of KRS has been observed previously. Our deceased cases died due to septicemia resulting from swallowing dysfunction and severe motor restriction. Additionally, spasticity was found to be a determining factor of death in our NBIA patients, which was more prevalent in patients with classic type than atypical PKAN cases.

**Conclusion:** KRS had the best survival with the most extended ambulation period. The classical PKAN and MPAN cases had similar progression patterns to loss of ambulation ability, while MPAN patients had a slower progression to death. Spasticity was revealed to be the most determining factor for death.



# POSTER SESSIONS

EP4

## CHANGES IN OXYTOCIN AND OXYTOCIN RECEPTOR LEVELS IN THE NBIA CELL MODEL

<sup>1</sup>*Magdalena Żabińska, <sup>1</sup>Karolina Wiśniewska, <sup>1</sup>Aneta Szulc, <sup>1</sup>Lidia Gaffke, <sup>1</sup>Grzegorz Węgrzyn, <sup>1</sup>Karolina Pierzynowska*

<sup>1</sup>*University of Gdansk, Poland*

**Introduction:** Neurodegeneration with Brain Iron Accumulation (NBIA) refers to a group of rare, inherited metabolic disorders where specific mutations affect the function of proteins involved in iron homeostasis in tissues. These disorders can occur in both children and adults, and diagnosis is often based on the observation of increased iron concentrations in the basal ganglia on magnetic resonance imaging (MRI) [1]. Oxidative stress is believed to play a significant role in these disorders, leading to brain tissue degeneration. NBIA is characterized by movement disorders, painful dystonia, parkinsonism, intellectual disability, and premature death. While NBIA tends to be resistant to therapeutic strategies, some interventions may provide significant symptomatic relief for selected patients [2,3]. There are a few main types of NBIA: pantothenate kinase-associated neurodegeneration (PKAN), mitochondrial membrane protein-associated neurodegeneration (MPAN), and beta-propeller protein-associated neurodegeneration (BPAN) [1]. Oxytocin (OXT), along with its receptor (OXTR), plays essential roles in cells. Commonly associated with social behaviors, oxytocin is not only responsible for human bonding and emotional regulation, but disturbances in OXT levels or OXTR activity and their impacts on cellular and organismal functions have been observed in various human diseases [4]. Scientific sources also suggest that OXT interacts with PPAR gamma, which influences peroxisome biogenesis in NBIA. This is particularly important as peroxisomes are crucial for lipid metabolism and protecting cells from oxidative stress [5].

**Aim:** Investigate the function of oxytocin in cells (including OXTR and OXT levels) and peroxisome levels in cells derived from NBIA patients and healthy controls. **Materials and Methods:** Cell lines used include NBIA types (MPAN, BPAN, PKAN) and control lines (K27, K13). The study utilized automated western blot (WES), dot blot, and immunofluorescence techniques.

**Findings:** Our research demonstrated alterations in both the receptor for oxytocin and oxytocin itself in MPAN, BPAN, and PKAN cells compared to control cells. Additionally, the OXTR receptor formed aggregates in all of these NBIA types, losing its native conformation. Both OXTR and OXT levels were abnormal in NBIA cells.

**Conclusions:** The formation of OXTR aggregates in cells derived from NBIA patients may lead to changes in oxytocin levels, resulting in dysregulation of important cellular processes. Abnormal OXT levels, in turn, may negatively affect the number of peroxisomes, as oxytocin seems to regulate peroxisome biogenesis. A deficiency of peroxisomes increases the risk of secondary cellular disturbances, including elevated oxidative stress, which may exacerbate NBIA symptoms.

### References:

- (1) Marupudi N, Xiong MP. Genetic Targets and Applications of Iron Chelators for Neurodegeneration with Brain Iron Accumulation. ACS Bio Med Chem Au. doi:10.1021/acsbiomedchemau.3c00066
- (2) Svetel M, Dragašević N, Petrović I, et al. NBIA Syndromes: A Step Forward from the Previous Knowledge. doi:10.4103/0028-3886.329603
- (3) Hayflick SJ, Kurian MA, Hogarth P. Neurodegeneration with brain iron accumulation. Handb Clin Neurol. doi:10.1016/B978-0-444-63233-3.00019-1
- (4) Pierzynowska K, Gaffke L, Żabińska M, et al. Roles of the Oxytocin Receptor (OXTR) in Human Diseases. Int J Mol Sci. doi:10.3390/ijms24043887
- (5) Moslemi M, Motamedi F, Asadi S, Khodagholi F. Peroxisomal Malfunction Caused by Mitochondrial Toxin 3-NP: Protective Role of Oxytocin. Iran J Pharm Res. 2019;18(1):296-307



# POSTER SESSIONS

EP5

## EVALUATION OF CARRIER FREQUENCY OF NEURODEGENERATION WITH BRAIN IRON ACCUMULATION (NBIA) DISORDERS IN A MIDDLE EASTERN PATIENT POPULATION BASED ON DATA FROM 17,868 EXOME SEQUENCES.

*Hasan Baş<sup>1</sup>, Hasan Öztürk<sup>1</sup>, Zuhâl Yapıcı<sup>2</sup>, Fatma Dereli Devrez<sup>1</sup>, Muhammed Burak Yılmaz<sup>1</sup>, Mine Öca<sup>1</sup>, Başak Rana Çakır<sup>1</sup>, Harun Ba<sup>1</sup>, Serdar Ceylaner<sup>1</sup>*

*1 Intergen Genetics and Rare Diseases Diagnosis Center, Ankara, Türkiye*

*2 Department of Neurology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Türkiye*

**Aim:** In addition to enabling the diagnosis of disease groups, exome sequencing also reveals secondary findings of medical significance. In populations with high rates of consanguineous marriages, identifying carriers of recessive disorders is essential for informing families and shaping public health policies. Neurodegenerative diseases, such as NBIA, despite their rarity, have severe impacts on quality of life, and genetic testing supports their clinical diagnosis. Therefore, in this study, screening the carrier frequency in this patient group has been targeted.

**Materials and methods:** The screening of variants in the PANK2, PLA2G6, C19orf12, CoASY, ATP13A2, CP, DCAF17, FA2H, CRAT, and REPS1 genes, which are known to be associated with recessively inherited NBIA, has been conducted using whole exome and clinical exome sequencing data from patients referred to our center for routine management. Duplicate data, multiple cases from the same family, and data with low quality were removed from the study to obtain the most suitable dataset possible. Variants in the specified genes were extracted from the VCF data using the developed software. All of the detected variants were evaluated according to ACMG variant classification criteria, if they have a read depth greater than 20. The read quality of pathogenic and likely pathogenic variants was evaluated using IGV and fake variants were eliminated. The carrier frequency was analyzed based on the remaining variants.

**Findings:** A total of 17,868 (clinical exome sequencing: 2290, whole exome sequencing: 15578) exome sequencing data were interpreted. The gene with the highest carrier frequency was identified as PLA2G6, with a rate of 0.36% (~1/300). Additionally, 13 novel variants that have not been previously reported in the literature or population databases and are likely to be disease-causing and specific to the population we studied have been identified in this gene. The second most frequent was PANK2-related NBIA carrier status, identified in approximately 0.2% (~1/500) of the cases. Eight novel variants were also found in this gene. "When all genes were evaluated together, the carrier frequency for NBIA group diseases in the population was found to be approximately 1 in 100.

**Conclusion:** The study results suggest that when NBIA diseases are evaluated together, they may represent genetic disorders that are relatively common in the population. Moreover, due to the study's limitations, such as not examining copy number variations or not being able to comment on variants of uncertain clinical significance, it is believed that the actual frequency may be higher than estimated. Similar to other studies, the most frequent carriers were detected in the PLA2G6 gene, while the discovery of new and unique variants highlights the importance of studies incorporating genetic data from different populations. The scarcity of data on Middle Eastern patients in population databases further underscores the value of the study's findings.

### References:

- (1) Kolarova, H., Tan, J., Strom, T. M., & Klopstock, T. (2022). Lifetime risk of autosomal recessive neurodegeneration with brain iron accumulation (NBIA) disorders calculated from genetic databases. *EBioMedicine*, 77.
- (2) Gregory A, Hayflick S. Neurodegeneration with Brain Iron Accumulation Disorders Overview. 2013 Feb 28 [Updated 2019 Oct 21]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. *GeneReviews*<sup>®</sup> [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK121988/>
- (3) Hogarth, P., & Kurian, M.A. (2020). Neurodegeneration with Brain Iron Accumulation: Insights into Pathophysiology and Potential Therapies. *Nature Reviews Neurology*, 16(4), 199-209.
- (4) Richards S, Aziz N, Bale S, & Rehm HL; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015 May;17(5):405-24. doi: 10.1038/gim.2015.30. Epub 2015 Mar 5.



[↑ Back to Scientific Program](#)

# POSTER SESSIONS

## NBIA GENERAL GROUP B

[↑ Back to Poster Session](#)

### EP6

#### THE SIGNIFICANCE OF PEROXISOMAL DYSFUNCTION IN THE PATHOGENESIS OF NBIA

*<sup>1</sup>Karolina Wiśniewska, <sup>1</sup>Magdalena Żabińska, <sup>1</sup>Aneta Szulc, <sup>1</sup>Lidia Gaffke, <sup>1</sup>Karolina Pierzynowska, <sup>1</sup>Grzegorz Węgrzyn*

*<sup>1</sup>University of Gdansk, Gdansk, Poland*

**Introduction:** Neurodegeneration with brain iron accumulation (NBIA) is a group of genetically determined neurological disorders characterized by iron accumulation in various brain areas. Symptoms include motor disorders (such as parkinsonism, dystonia and neurodegenerative changes leading to rapid patient death), visual impairment, cognitive impairment and neuropsychiatric disorders. The etiology of NBIA appears complex and remains unclear, but a growing body of evidence suggests that iron accumulation may in fact develop secondary to an, as yet unknown, primary cause. Some studies highlight the important role of lipid profile abnormalities in brain tissues for the pathogenesis of the disease. Besides mitochondria, peroxisomes are the organelles most involved in lipid metabolism (especially very long chain fatty acids (VLCFA)). Moreover, the link between lipid metabolism and iron homeostasis has been known for years, and peroxisomes also play a key role in ferroptosis, a specific form of iron-dependent cell death.

**Aim:** The aim of this work was to investigate whether peroxisome abnormalities are present in fibroblasts from NBIA patients (MPAN, PKAN and BPAN).

**Materials and methods:** We assessed the levels of selected peroxisomal proteins (related to both structure and functions of peroxisomes) and the abundance of these organelles, using western-blotting technique and fluorescence microscopy methods, respectively.

**Findings:** Our results indicated that both the number of peroxisomes and the levels of proteins associated with VLCFA metabolism are significantly altered in cells derived from NBIA patients compared to healthy controls. We also observed elevated levels of the 5- LOX protein, which is partially dependent on peroxisome number and affects ferroptosis induction and lipotoxicity.

**Conclusions:** Our findings suggest that the peroxisome dysfunction may be an important target for the study of NBIA pathogenesis. Proper functioning of peroxisomes is extremely important for, amongst other things, the correct synthesis of lipid membranes and the neutralization of reactive oxygen species. Depending on the tissue type, peroxisomes may have more specialized functions, i.e. bile acid synthesis and detoxification in the liver or synthesis of the myelin sheath in the brain. Further research in this area may contribute to a better understanding of this group of neurodegenerative diseases and lead to new therapeutic strategies.



[↑ Back to Scientific Program](#)

[↑ Back to Poster Session](#)

# POSTER SESSIONS

EP7

## SURVEY OF NBIA CAREGIVER PERSPECTIVES TO IDENTIFY RELEVANT QOL OUTCOMES FOR CAREGIVERS/PATIENTS

*<sup>1</sup>Janani Ramamurthy, <sup>2</sup>Brittany Paul, <sup>3</sup>Richard Webster, <sup>3</sup>Deepti Reddy, <sup>4</sup>Sunita Venkateswaran*

*<sup>1</sup>Queen's University Department of Neurology, Kingston ON Canada*

*<sup>2</sup>University of Ottawa Department of Anesthesiology, Ottawa ON Canada*

*<sup>3</sup>CHEO RI, Ottawa ON, Canada*

*<sup>4</sup>CHEO RI, Ottawa ON, Canada; Western University Department of Pediatric Neurology, London ON, Canada*

**Background:** Neurodegeneration with Brain Iron Accumulation (NBIA) is a heterogenous group of disorders with the common theme of iron accumulation in the basal ganglia. These disorders typically present in childhood with progressive neurodegeneration and neuropsychiatric symptoms. Caring for an individual with NBIAs is intensive, however it is unknown what factors impact caregiver well-being and quality of life.

**Methods:** Common themes were obtained via literature review of quality of life surveys in children with neurological and chronic illnesses. Five domains were addressed: Diagnosis, Communication, Symptom Management, Clinical Experience and Resources/Support. The survey was approved by the Family Advisory Committee at the CHEO Research Institute and the CHEO REB. The survey was distributed via the Rare Connect Platform to Canadian caregivers.

**Results:** Using Likert scales and open-ended responses, common challenges were identified from the caregivers of patients with NBIA, such as: struggling to cope with diagnostic uncertainty, financial, mental and physical caregiver challenges, and difficulty navigating transitions to adult care services. A ranked analysis created from data obtained from the survey identified diagnostic uncertainty as the predominant concern affecting caregivers' quality of life. Caregivers also identified healthcare practices and discussions that they found beneficial. Suggestions for resources to provide support for caregivers of children of NBIA, including support groups and community services, were compiled.

**Conclusions:** The results of the survey will inform advocacy for caregivers (financially and informatively) through the development of NBIA management guidelines for physicians and families and direct the structure of future Canadian NBIA family conferences.



[↑ Back to Scientific Program](#)

[↑ Back to Poster Session](#)

# POSTER SESSIONS

EP8

## THE SIGNIFICANCE OF FERROPTOSIS DYSREGULATION IN THE PATHOGENESIS OF NBIA

<sup>1</sup>*Karolina Pierzynowska*, <sup>2</sup>*Karolina Pierzynowska*, <sup>2</sup>*Karolin Wiśniewska*, <sup>2</sup>*Magdalena Żbińska*, <sup>2</sup>*Aneta Szulc*, <sup>2</sup>*Lidia Gaffke*, <sup>2</sup>*Grzegorz Węgrzyn*

<sup>1</sup>*Gdańsk, Poland*

<sup>2</sup>*University of Gdansk, Gdansk, Poland*

**Introduction:** Neurodegeneration with brain iron accumulation (NBIA) is a group of genetically determined neurological disorders whose etiology is still unclear. There are currently 15 types of NBIA, with a diverse genetic background, but a common feature of all types of disorders is iron accumulation in different areas of the brain. Abnormal iron metabolism is one of the elements contributing to the pathology of different neurodegenerative diseases, like NBIA and Alzheimer's disease. An interesting and relatively newly identified phenomenon associated with iron metabolism disorders is ferroptosis - a type of cell death dependent on disturbed iron metabolism and increased lipid peroxidation.

**Aim:** Due to the common feature of NBIA, which is iron accumulation and lipid disorders, being pointed out with increasing frequency as a possible cause of the disease, we decided to test whether disorders that may lead to ferroptosis are present in cells of patients with the most common types of NBIA (MPAN, BPAN, PKAN).

**Materials and methods:** Using fluorescence microscopy and western blotting, we checked, among other things, the levels of total iron and Fe<sup>2+</sup> (a form toxic to cells), the levels of proteins directly related to iron metabolism, glucose metabolism, the response against reactive oxygen species and lipid peroxidation in patients' fibroblasts.

**Findings:** Our results indicated numerous and varied, depending on the type of NBIA, disturbances in all the processes studied.

**Conclusions:** Although ferroptosis is a process still being explored, it already appears to have a significant impact on the pathogenesis of various types of neurodegenerative diseases. Our results suggest that this process may also have a role in the pathogenesis of NBIA, especially as its disruption is not only observed in cells of the nervous system. It is possible that the regulation of ferroptosis may represent a potential therapeutic target in NBIA, but further studies are needed to fully understand the importance of this process in the pathogenesis of the disease



[↑ Back to Scientific Program](#)

# POSTER SESSIONS

[↑ Back to Poster Session](#)

EP9

## INITIATION AND ELONGATION OF THE AUTOPHAGY PROCESS IN DIFFERENT TYPES OF

*<sup>1</sup>Aneta Szulc, <sup>1</sup>Karolina Wiśniewska, <sup>1</sup>Magdalena Żabińska, <sup>1</sup>Lidia Gaffke, <sup>1</sup>Karolina Pierzynowska, <sup>1</sup>Grzegorz Węgrzyn*

*<sup>1</sup>University of Gdansk, Gdansk, Poland*

**Introduction:** Neurodegeneration with brain iron accumulation (NBIA) is a rare group of neurological disorders with still unclear etiology. Characteristic neurodegeneration with iron accumulation is accompanied by symptoms such as dystonia, dysarthria, spasticity, parkinsonism, neuropsychiatric abnormalities, and optic atrophy or retinal degeneration. Currently, 15 types of NBIA have been identified, with the most common types being PKAN (mutations in the PANK2 gene), PLAN (mutations in the PLA2G6 gene), BPAN (mutations in the WDR45 gene), and MPAN (mutations in the C19orf12 gene). Although the mutations responsible for these conditions are known, the mechanisms leading to disease development are not well understood. One of the key processes essential for maintaining proper cellular and organismal function is autophagy, an evolutionarily conserved intracellular mechanism that removes damaged organelles and misfolded proteins to preserve cell homeostasis. Disruptions in this process are widely reported in the pathology of neurodegenerative diseases such as Alzheimer's disease (AD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and mucopolysaccharidoses (MPS). In many neurodegenerative diseases, potential therapeutics are being explored among compounds that stimulate the autophagy process.

**Aim:** In our study, we aimed to investigate whether fibroblasts derived from NBIA patients (types: BPAN, PKAN, MPAN) exhibit abnormalities in the autophagy process at the initiation and elongation stages.

**Materials and methods:** Patient- and healthy individual-derived fibroblast lines we used in all experiments. Cells were cultured under standard laboratory conditions. The autophagy process was investigated at the initiation stage (formation of the ULK complex), as well as at the LC3- and Atg12-dependent elongation step. We used the Western-blotting method to determine the levels of proteins involved in the formation of the ULK1 complex as well as proteins interacting with LC3 and Atg12.

**Findings:** Our results indicated that the levels of proteins involved in various stages of the autophagy process are significantly altered in cells derived from NBIA patients (types: BPAN, PKAN, MPAN) compared to healthy individuals (the control group), as well as between the different disease types.

**Conclusions:** Our findings suggest that different stages of the autophagy process are altered to varying degrees in the different types of NBIA relative to control cells derived from healthy individuals. Autophagy is a crucial process involved in the degradation of macromolecules and cellular organelles in the cytosol. Understanding the changes occurring in the autophagy process in cells derived from affected patients will allow for the identification of disruptions within this process and enable targeted stimulation to slow the progression of neurodegenerative processes. Further research may contribute to a better understanding of this group of diseases and aid in the development of new, more effective therapeutic strategies.





[↑ Back to Scientific Program](#)

[↑ Back to Poster Session](#)

# POSTER SESSIONS

EP10

## IS THERE ANY CORRELATION BETWEEN AMOUNT OF IRON MEASURED BY QUANTITATIVE SUSCEPTIBILITY MAPPING AND THE CLINICAL FEATURES IN NBIA

*<sup>1</sup>Özge Uygun, <sup>1</sup>Ozge Uygun, <sup>2</sup>Sibel Ugur Iseri, <sup>3</sup>Alpay Ozcan, <sup>4</sup>Alp Dincer, <sup>5</sup>Zuhal Yapici*

<sup>1</sup>Department of Neurology, Cerrahpasa Faculty of Medicine, Istanbul University-Cerrahpasa, Istanbul, Türkiye

<sup>2</sup>Department of Genetics, Aziz Sançar Institute of Experimental Medicine, Istanbul University, Istanbul, Türkiye

<sup>3</sup>Department of Electrical and Electronics Engineering, Bogazici University, Istanbul, Türkiye

<sup>4</sup>Department of Radiology, Acibadem Mehmet Aydınlar University, Faculty of Medicine, Istanbul, Türkiye

<sup>5</sup>Department of Neurology, Istanbul University Faculty of Medicine, Istanbul, Türkiye

**Introduction:** Neurodegeneration with brain iron deposition (NBIA) is a group of inherited disorders in which iron deposition usually occurs in the basal ganglia (BG) in the brain. The aim of this study is to measure the iron in BG with a sensitive method and to reveal the relationship between the amount of iron accumulation and some of the clinical features.

**Materials and Methods:** Patients genetically diagnosed with NBIA (9 PKAN, 3 MPAN, 2 PLAN, 2 Kufor Rakeb) and age/sex-matched healthy controls were included. 3 Tesla Magnetic Resonance Imaging (MRI) including T1, T2 and SWI sequences was performed on all of them. Quantitative iron content in all BG nuclei was evaluated by the QSM method. In addition, the BFM dystonia scale (BFMS) was used to determine clinical severity.

**Results:** The most iron accumulation in patients was found in the GP ( $p=0.008$ ). Compared to the healthy controls, PKAN patients had in GP ( $p=0.001$ ), and MPANs in GP and SN with 2.5 times more iron ( $p=0.005$ ,  $p=0.036$ ). GP iron levels upper than 0.1133 ppm shows 18 times higher risk for probability of being PKAN by ROC analysis with 95% confidence interval (sensitivity: 0.75, specificity: 0.82). When PKAN and MPAN patients were evaluated among themselves, no significant difference was observed in terms of iron accumulation. A correlation was found between iron accumulation and age in putamen in healthy controls, whereas there was correlation between age and amount of iron in putamen, substantia nigra and nucleus ruber of patients.

**Conclusion:** Iron deposition in the GP seems to play a key role in the pathology of NBIA diseases. There was no significant relationship in terms of iron accumulation between the age of onset, gender, and clinical severity.



[↑ Back to Scientific Program](#)

[↑ Back to Poster Session](#)

# POSTER SESSIONS

PKAN / COPAN/NBIA SYSTEMIC  
GROUP A

EP11

PANK ACTIVATORS FOR THE TREATMENT OF PANTOTHENATE KINASE-ASSOCIATED NEURODEGENERATION

<sup>1</sup> *Jessica Regan*, <sup>2</sup> *Anasuya Pal*, <sup>2</sup> *Choukri Ben Mamoun*

<sup>1</sup> *Virtus Therapeutics, Groton CT, USA*

<sup>2</sup> *Yale Üniversitesi, New Haven CT, USA*

WITHDRAWN



[↑ Back to Scientific Program](#)

[↑ Back to Poster Session](#)

# POSTER SESSIONS

EP12

GENETIC ARCHITECTURE OF NEURODEGENERATIVE DISORDER AND ITS ASSOCIATION WITH CONSANGUINITY IN PASHTOON POPULATION

*<sup>1</sup>Shoaib Ur Rehman*

*<sup>1</sup>University of Science and Technology Bannu, Pakistan*

WITHDRAWN



# POSTER SESSIONS

EP13

## THE IDENTIFICATION OF A 4'-PHOSPHOPANTETHEINE TRANSPORTER IN *S. CEREVISIAE*

*<sup>1</sup>Jouke Jan Wedman, <sup>1</sup>Lotte De Vries, <sup>1</sup>Bart Van Lingen, <sup>1</sup>Marianne Van Der Zwaag, <sup>1</sup>Rubén Gómez-Sánchez, <sup>1</sup>Ralph Hardenberg, <sup>2</sup>Wim Huibers, <sup>2</sup>Hjalmar Permentier, <sup>3</sup>Erick Strauss, <sup>1</sup>Michael Chang, <sup>4</sup>Fulvio Reggiori, <sup>5</sup>Anton I. De Kroon, <sup>1</sup>Ody Sibon, <sup>1</sup>Hein Schepers*

<sup>1</sup>University Medical Centre Groningen, Holland

<sup>2</sup>University of Groningen, Holland

<sup>3</sup>Stellenbosch University, South Africa

<sup>4</sup>Aarhus University, Denmark

<sup>5</sup>Utrecht University, Holland

**Introduction:** Coenzyme A (CoA) is an essential molecule required by all organisms. Canonically, CoA biosynthesis depends on the uptake of pantothenate by well-studied transporters. However, it has been known for over 70 years that alternative precursors, such as pantetheine (PanSH) and 4'-phosphopantetheine (PPanSH), can also serve as starting substrates for CoA biosynthesis. Currently, PPanSH is being studied in clinical trials as a treatment for patients with Pantothenate Kinase Associated Neurodegeneration (PKAN). PKAN is caused by a mutation in PANK2, a gene encoding a paralog of pantothenate kinase (PANK). Besides PKAN, patients with other CoA-linked diseases (PPCS-deficiency and PPCDC-deficiency) could potentially also benefit from (4'-phospho)pantetheine treatment. Although models of CoA-related diseases treated with (4'-phospho) pantetheine show promising results, it remains unclear how these molecules are taken up by cells. We aimed to identify a transporter for (4'-phospho)pantetheine, using *Saccharomyces cerevisiae* (baker's yeast) as a model organism.

**Material and Methods:** We cultured *S. cerevisiae* on synthetic media lacking pantothenate, but supplemented with pantetheine or 4'-phosphopantetheine. We observed that yeast can acquire the ability to grow on (4'-phospho) pantetheine, and used Whole Genome Sequencing to identify the responsible mutations. We used yeast strains with defects in CoA biosynthesis enzymes to determine whether growth on (4'-phospho)pantetheine bypasses these enzymes.

**Results:** After having identified the responsible mutations, we discovered the transporter of (4'-phospho) pantetheine. This transporter differs from the well-studied pantothenate transporter Fen2, and takes up (4'-phospho) pantetheine via a unique mechanism. Once pantetheine is imported, PPCS and PPCDC, previously considered essential, are bypassed. When 4'-phosphopantetheine is imported, PANK is additionally bypassed.

**Discussion:** This newly identified uptake provides new insights into non-canonical CoA biosynthesis, which is especially of interest in the context of CoA-biosynthesis-related diseases. Future research will indicate the evolutionary extent of this novel uptake mechanism.



# POSTER SESSIONS

EP14

## INVESTIGATING COPAN IN MICE: FROM PATHOMECHANISMS TO THERAPEUTIC APPROACHES

<sup>1</sup>Chiara Cavestro, <sup>1</sup>Francesca Morra, <sup>1</sup>Maria Nicol Colombo, <sup>1</sup>Marco D'Amato, <sup>2</sup>Cristina Vergara, <sup>3</sup>Laura Rodríguez-Pascau, <sup>3</sup>Pilar Pizcueta, <sup>1</sup>Valeria Tiranti, <sup>1</sup>Ivano Di Meo

<sup>1</sup>Fondazione IRCCS Neurological Institute C. Besta, Milan, Italy

<sup>2</sup>Minoryx Therapeutics BE, S.A., 6041 Charleroi, Belgium

<sup>3</sup>Minoryx Therapeutics S.L., 08302 Barcelona, Spain

**Introduction:** COASY protein-associated neurodegeneration (CoPAN) is a rare form of neurodegeneration with brain iron accumulation, caused by biallelic mutations in the COASY gene. This gene encodes for the bifunctional enzyme CoA synthase, which catalyzes the final two reactions of the cellular CoA biosynthetic pathway. Patients present a range of neurological symptoms, including Parkinsonian features, cognitive impairment, obsessive-compulsive symptoms, and MRI-detected brain iron accumulation in the basal ganglia (1). However, recent studies have identified patients with previously unreported clinical characteristics, such as pontocerebellar hypoplasia, seizures, hearing loss, strabismus, autism spectrum disorder, and neuromuscular involvement with multiple mitochondrial complex defects in muscle.

**Aim and Method:** The pathogenetic process underlying the disease remains largely unknown, and therapeutic options for its treatment are virtually absent. To better understand the mechanisms linking CoA metabolism, iron dyshomeostasis, and neurodegeneration, we generated an inducible, neuron-specific Coasy null mouse model (SLICK-Coasy). This model allows for the ablation of the Coasy gene in adulthood, thereby avoiding the effects of Coasy deficiency during developmental phases and more accurately mimicking a condition of neurodegeneration (2).

**Findings:** The mice exhibited neurological impairment, progressive locomotor defects, dystonia-like movements, and a decreased lifespan to only three months after the induction of Coasy ablation. Ex vivo evaluations revealed signs of neurodegeneration, alterations in iron homeostasis and, notably, widespread neuroinflammation characterized by microglial activation and astrocyte hyperproliferation. Additionally, we observed increased expression of pro-inflammatory cytokines in the brains of KO mice. The onset of symptoms is progressive and this characteristic made the model suitable for testing the effectiveness of potential therapeutic options. Preliminary data showed that the administration of the PPAR-gamma agonist Leriglitazone (3) at the dose of 75 mg/kg/day can improve the clinical picture of this model. Although survival remains unchanged, Leriglitazone slightly enhance the animals' motor performance, as measured by behavioral tests. Furthermore, Leriglitazone appears to ameliorate the neuroinflammatory profile by reducing astrocyte and microglia hyperproliferation and lowering the expression of pro-inflammatory cytokines.

**Conclusion:** These findings suggest that neuroinflammation may play a significant role in the pathogenesis of the disease, and that Leriglitazone could be a potentially effective therapeutic option for managing pathological conditions involving neuroinflammatory aspects related to brain iron accumulation.

### References:

- (1) Cavestro C, Diodato D, Tiranti V, Di Meo I. Inherited Disorders of Coenzyme A Biosynthesis: Models, Mechanisms, and Treatments. *Int J Mol Sci.* 2023 Mar 21;24(6):5951. doi: 10.3390/ijms24065951. PMID: 36983025; PMCID: PMC10054636.
- (2) Di Meo I, Cavestro C, Pedretti S, Fu T, Ligorio S, Manocchio A, Lavermicocca L, Santambrogio P, Ripamonti M, Levi S, Aycirix S, Mitro N, Tiranti V. Neuronal Ablation of CoA Synthase Causes Motor Deficits, Iron Dyshomeostasis, and Mitochondrial Dysfunctions in a CoPAN Mouse Model. *Int J Mol Sci.* 2020 Dec 19;21(24):9707. doi: 10.3390/ijms21249707. PMID: 33352696; PMCID: PMC7766928.
- (3) Santambrogio P, Cozzi A, Di Meo I, Cavestro C, Vergara C, Rodríguez-Pascau L, Martinell M, Pizcueta P, Tiranti V, Levi S. PPAR Gamma Agonist Leriglitazone Recovers Alterations Due to Pank2-Deficiency in hiPS-Derived Astrocytes. *Pharmaceutics.* 2023 Jan 6;15(1):202. doi: 10.3390/pharmaceutics15010202. PMID: 36678831; PMCID: PMC9862015.



# POSTER SESSIONS

## PKAN / COPAN/NBIA SYSTEMIC GROUP B

EP15

### A SURPRISING PRESENTATION OF ATYPICAL PANTOTHENATE KINASE ASSOCIATED NEURODEGENERATION DISORDER: METAMORPHOPSIA

<sup>1</sup>*Elahe Aminj, <sup>1</sup>Zahra Azad, <sup>1</sup>Reza Mirshahi, <sup>1</sup>Mohammad Rohani*

<sup>1</sup>*Iran University of Medical Sciences, Tehran, Iran*

**Introduction:** Pantothenate kinase-associated neurodegeneration (PKAN) is the most common neurodegeneration with brain iron accumulation (NBIA) subtype caused by a mutation in the PANK2 gene. Classical and atypical PKAN are two different subgroups classified according to the different ages at disease onset and the disease progression course, which is earlier and more severe in classical PKAN. Retinitis pigmentosa is a known retinal pathology in classical PKAN with a remarkable prevalence, while it is a rare symptom of atypical PKAN. Epiretinal membrane (ERM) is a pathologic membrane that lies immediately over the internal limiting membrane of the retina, evolving out of myofibroblastic cell proliferation. Although some secondary etiologies have been identified, most cases remain idiopathic. No specific predisposing genetic basis has been identified for ERM.

**Objectives:** This letter aims to report an atypical PKAN patient with evidence of bilateral ERM for the first time.

**Case summary:** A 36-year-old male complaining of recurrent fallings and mildly progressive slowness of limb movement was referred to the central movement disorder clinic. He gave a history of bilateral progressive visual distortion and nyctalopia interfering with daily activities from 6 years ago. He did not have any past medical history of diabetes mellitus, ocular surgery, or trauma. He had not undergone comprehensive medical assessments, and no medication or therapy had been received. Neurological assessments showed mild bradykinesia and hypokinesia without any evidence of pyramidal involvement. Cerebellar examinations were normal, independent of visual impairment. Ophthalmological assessments showed bilateral optic disc swelling by ophthalmoscopy and impaired retinal function with near-flat waves in electroretinography. The spectral-domain optical coherence tomography (SD-OCT) revealed a bilateral increased retinal thickness along with cystic spaces in the middle retina, and the photoreceptor as well as ellipsoid zone were disrupted outside the fovea in favor of ERM. The genetic evaluation confirmed the diagnosis of atypical PKAN. Levodopa benserazide 100/25 mg three times daily was prescribed.

**Discussion:** The initial symptoms of our atypical PKAN patient were unusual visual disturbances and metamorphopsia that led to recurrent falling. The neurological and ophthalmological assessments revealed he had bilateral ERM. These results were confirmed by SD-OCT and electroretinography findings. We assume that his recurrent fallings were not only caused by his mild hypokinesia but were intensified by his visual impairment as well.

**Conclusion:** Since ERM is usually an incidental finding in elderly individuals with no significant symptoms, exploring it bilaterally at a poor prognosis stage causing severe metamorphopsia in a middle-aged patient with a certain known genetic mutation contributes to the hypothesis that this genetic mutation may predispose ERM.



[↑ Back to Scientific Program](#)

# POSTER SESSIONS

[↑ Back to Poster Session](#)

EP16

## THE EFFECT OF GENISTEIN ON THE AUTOPHAGY PROCESS IN A CELLULAR MODEL OF PANTOTHENATE KINASE-ASSOCIATED NEURODEGENERATION

<sup>1</sup>*Estera Rintz, <sup>1</sup>Lidia Gaffke, <sup>1</sup>Zuzanna Cyske, <sup>1</sup>Karolina Pierzynowska, <sup>1</sup>Grzegorz Wegrzyn*

<sup>1</sup>*Department of Molecular Biology, University of Gdansk, Gdansk, Poland*

**Introduction:** Neurodegeneration with brain iron accumulation (NBIA) is a group of genetic disorders leading to the rapid development of dystonia, spasticity, and other neurological symptoms. One of these diseases is pantothenate kinase-associated neurodegeneration (PKAN), which results from mutations in the PANK2 gene<sup>1</sup>. The product of this gene is necessary for converting vitamin B5 into coenzyme A. Due to this mutation, cellular energy metabolism is disrupted, and iron accumulates in the central nervous system, particularly in the globus pallidus and substantia nigra<sup>2</sup>. Currently, no therapy exists that can cure NBIA. Process of autophagy appears to be a promising target in this regard. Autophagy is a process that degrades proteins in the cell, and its stimulation at an appropriate level could potentially contribute to the degradation of aggregates in NBIA.

**Aim:** This study describes the effect of genistein, an autophagy inducer, on the cellular localization of three autophagy-related proteins and autophagy markers in cellular model of PKAN disease.

**Materials and Methods:** In this study, we employed cell lines derived from PKAN patients, along with cell lines from healthy individuals as controls. The cells were cultured under standard conditions (37°C, 5% CO<sub>2</sub>). Protein levels of key autophagy-related markers were measured using the western blotting technique. Fluorescence microscopy was employed to examine the abundance and cellular localization of specific proteins, including LAMP2, TFEB, and BECLIN1.

**Results:** Levels of autophagy marker proteins (LC3-II, p62) were determined in PKAN cells compared to control cells. We found that autophagy process is impaired in comparison to the control cells. While genistein improve this process. Additionally, the levels and localization of proteins involved in the functioning and biogenesis of lysosomes were assessed. Obtained results indicated significant changes in levels of studied proteins. Both TFEB and LAMP2 protein levels were increased after genistein treatment in comparison to untreated PKAN cells. There was no difference in BECLIN1 protein level.

**Conclusions:** The results indicated that the autophagy process is impaired in PKAN patients. However, these defects can be corrected by utilizing autophagy stimulators such as genistein.

### References:

- (1) Schneider, et al. "Syndromes of neurodegeneration with brain iron accumulation (NBIA): an update on clinical presentations, histological and genetic underpinnings, and treatment considerations." *Movement disorders: official journal of the Movement Disorder Society* vol. 27,1 (2012): 42-53. doi:10.1002/mds.23971
- (2) Tang, Yinglu et al. "Mitochondrial quality control links two seemingly unrelated neurodegenerative diseases." *Autophagy* vol. 18,10 (2022): 2495-2497.



# POSTER SESSIONS

EP17

## NEURODEGENERATION WITH BRAIN IRON ACCUMULATION DISORDERS AND RETINAL NEUROVASCULAR STRUCTURE

<sup>1</sup>*Elahe Aminj*, <sup>1</sup>*Mohammad Rohani*, <sup>2</sup>*Alfonso Fasano*, <sup>1</sup>*Zahra Azad*, <sup>3</sup>*Shahnaz Miri*, <sup>1</sup>*Seyed Amir Hassan Habibi*, <sup>1</sup>*Maziar Emamikhah*, <sup>1</sup>*Reza Mirshahi*, <sup>1</sup>*Mohammad Taghi Joghataei*, <sup>1</sup>*Khalil Ghasemi Falavarjani*

<sup>1</sup>*Iran University of Medical Sciences, Tehran, Iran*

<sup>2</sup>*University Health Network University of Toronto, Toronto, Italy*

<sup>3</sup>*Vision Neurology Center, San Francisco, California*

**Introduction:** The unique neurovascular structure of the retina has provided an opportunity to observe brain pathology in many neurological disorders. However, such studies on neurodegeneration with brain iron accumulation (NBIA) disorders are lacking.

**Objectives:** To investigate NBIA's neurological and ophthalmological manifestations.

**Materials and Methods:** This cross-sectional study was conducted on genetically confirmed NBIA patients and an age-gender- matched control group. The thickness of retinal layers, central choroidal thickness (CCT), and capillary plexus densities were measured by spectral domain-optical coherence tomography (SD-OCT) and OCT angiography, respectively. The patients also underwent funduscopy, electroretinography (ERG), visual evoked potential (VEP), and neurological examination (Pantothenate-Kinase Associated Neurodegeneration-Disease Rating Scale [PKAN-DRS]). The generalized estimating equation model was used to consider inter-eye correlations.

**Results:** Seventy-four patients' and 80 controls' eyes were analyzed. Patients had significantly decreased visual acuity (VA), reduced inner or outer sectors of almost all evaluated layers, increased CCT, and decreased vessel densities, with abnormal VEP and ERG in 32.4% and 45.9%, respectively. There were correlations between VA and temporal peripapillary nerve fiber layer (positive) and between PKAN-DRS score and disease duration, and scotopic b-wave amplitudes (positive). When considering only the PKAN eyes, outer nuclear layer (ONL) was among the significantly decreased retinal layers, with no differences in retinal vessel densities. Evidence of pachychoroid was only seen in patients with Kufor Rakeb syndrome (KRS).

**Discussion:** Most retinal layers in NBIA patients were notably thinner, except for the inner and outer nuclear layers. However, in PKAN patients specifically, the ONL was significantly thinner than in controls. Besides, thinning was observed in the outer macular nerve fiber layer (NFL), inner ganglion cell layer (GCL), and the full retina, suggesting that ONL attenuation may be a distinguishing feature of PKAN. Macular vascular densities, including those of the superficial capillary plexus, radial peripapillary capillary, and deep capillary plexus, were significantly lower in NBIA patients compared to controls. However, these were not significantly different between PKAN patients and controls. This finding may pronounce the vascular pathologic changes in other NBIA subtypes than PKAN. Reduced vascular densities correlated with NFL and GCL thinning, implying a possible role of vascular impairment in retinal layer degeneration. Alternatively, retinal degeneration might reduce circulation demand, leading to lower vascular densities. For the first time, we evaluated CCT in NBIA patients and found it significantly increased. This could be a compensatory response to retinal changes. Pachychoroid was seen only in KRS patients, with one case showing pigment epithelium detachment, suggesting that lipofuscin accumulation might remodel the ocular venous drainage system, causing pachychoroid development. In PKAN patients, ONL degeneration correlated with more frequent abnormal ERG results compared to other NBIA subtypes. Although all PKAN cases in our study were atypical and had normal retinas on funduscopy examination, more than 50% and 26% of them showed impaired retinal and optic nerve function, respectively.

**Conclusion:** Observing pathologic structural and functional neurovascular changes in NBIA patients may provide an opportunity to elucidate the underlying mechanisms and differential retinal biomarkers in NBIA subtypes in further investigations.





# POSTER SESSIONS

EP18

## OLFACTORY STATUS IN NEURODEGENERATION WITH BRAIN IRON ACCUMULATION DISORDERS

<sup>1</sup>Elahe Amini, <sup>1</sup>Mohammad Rohani, <sup>1</sup>Maryam Jalessi, <sup>1</sup>Zahra Azad, <sup>2</sup>Franco Valzania, <sup>2</sup>Francesco Cavallieri, <sup>1</sup>Mohammad Farhadi

<sup>1</sup>Iran University of Medical Sciences, Tehran, Iran

<sup>2</sup>Azienda USL-IRCCS of Reggio Emilia, Reggio Emilia, Italy

**Introduction:** Olfactory dysfunction has been suggested as a diagnostic and discriminative biomarker in some neurodegenerative disorders. However, there are few studies regarding the olfactory status in rare diseases including neurodegeneration with brain iron accumulation (NBIA) disorders.

**Objectives:** In this study, we tried to find whether there is a difference in olfactory status among various subtypes of NBIA disorders with different pathologies.

**Materials and Methods:** Genetically-confirmed NBIA patients were enrolled. Neurological and cognitive examinations were conducted according to the Pantothenate Kinase-Associated Neurodegeneration-Disease Rating Scale (PKAN-DRS) and the Mini-Mental State Examination (MMSE) questionnaire, respectively. Olfaction was assessed in three domains of odor threshold (OT), odor discrimination (OD), odor identification (OI), and total sum (TDI) scores by the Sniffin' Sticks test. The olfactory scores were compared to a control group and a normative data set.

**Results:** Thirty-seven patients, including 22 PKAN, 6 Kufor Rakeb syndrome (KRS), 4 Mitochondrial membrane Protein-Associated Neurodegeneration (MPAN), 5 cases of other 4 subtypes, and 37 controls were enrolled. The mean PKAN-DRS score was  $51.83 \pm 24.93$ . Sixteen patients (55.2%) had normal cognition based on MMSE. NBIA patients had significantly lower olfactory scores compared to the controls in TDI and all three subtests, and 60% of them were hyposmic according to the normative data. Including only the cognitively-normal patients, still, OI and TDI scores were significantly lower compared to the controls. The Phospholipase A2-Associated Neurodegeneration (PLAN) and MPAN patients had a significantly lower OI score compared to the cognitively-matched PKAN patients.

**Discussion:** Our results, in line with previous studies, suggest that the olfactory function is impaired in NBIA patients. The only PLAN case in our study, 50% of MPAN patients, and approximately two-third of KRS patients were hyposmic based on the Sniffin' Stick test. Our data showed a negative association between cognitive status and OI. Based on the MMSE, 16 patients with normal cognition, including PKAN and KRS subtypes, had significantly lower OI and TDI scores compared to the control group. In the PKAN-DRS part 1 assessment, 21 patients with normal cognition, including PKAN, MPAN, KRS, and Woodhouse-Sakati Syndrome subtypes, also had significantly lower OD, OI, and TDI scores than the control group. The exact underlying pathogenesis of olfactory impairment in neurodegenerative diseases is not clear; Misfolded protein aggregation in the olfactory pathway is one of the most suggested pathologies. In recent studies, evidence of tau protein was detected in the brains of PKAN patients, while the accumulation of alpha synuclein protein was seen in the brains of the MPAN and PLAN patients. Our results suggest that PKAN patients performed significantly better than MPAN and PLAN patients in the OI test, while their cognition status was not significantly different. It leads to assuming that the different neuropathology existing between the different NBIA subtypes (tauopathy versus alpha synucleinopathy) may justify these results.

**Conclusion:** Olfactory impairment as a common finding in various subtypes of NBIA disorder can potentially be considered a discriminative biomarker. Better OI in PKAN compared to PLAN and MPAN patients may be related to the different underlying pathologies



# POSTER SESSIONS

## BPAN GROUP A

### EP19

#### INVESTIGATING RESPIRATORY CHAIN COMPLEX I DEFICIENCY IN IPSCS-DERIVED DOPAMINERGIC NEURONS AND ASTROCYTES FROM BPAN INDIVIDUALS

*<sup>1</sup>Gemma Gasparini, <sup>1</sup>Carolin Kraus, <sup>1</sup>Stephanie Kartika, <sup>1</sup>Nihan Özcan, <sup>2</sup>Ejona Rusha, <sup>2</sup>Tanja Orschmann, <sup>3</sup>Luisa Iommarini, <sup>4</sup>Alessandra Torracco, <sup>5</sup>Saskia B. Wortmann, <sup>5</sup>Johannes H. Mayr, <sup>6</sup>Anna Ardissonne, <sup>7</sup>Arcangela Iuso*

<sup>1</sup>Institute of Neurogenomics, Helmholtz Zentrum München, Neuherberg, Germany

<sup>2</sup>IPSC Core Facility, Helmholtz Zentrum München, Neuherberg, Germany

<sup>3</sup>Department of Pharmacy and Biotechnology (FABIT), University of Bologna, Bologna, Italy

<sup>4</sup>Laboratory of Molecular Medicine, Unit of Muscular and Neurodegenerative Disorders, Bambino Gesù Children's Hospital, IRCCS, 00146 Rome, Italy

<sup>5</sup>University Children's Hospital, Paracelsus Medical University, Salzburg, Austria

<sup>6</sup>Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

<sup>7</sup>Institute of Neurogenomics, Helmholtz Zentrum München, Neuherberg, Germany; Institute of Human Genetics, School of Medicine, Technical University of Munich, Munich, Germany

**Background:** Pathogenic variants in the gene WDR45, which encodes a protein involved in autophagy, are the cause of Beta-Propeller Protein- Associated Neurodegeneration (BPAN). This rare X-linked dominant disorder within the Neurodegeneration with Brain Iron Accumulation (NBIA) spectrum is characterized by developmental delay/intellectual disability, motor dysfunction, seizures and progressive neurodegeneration. With no curative therapy currently available for BPAN, supportive therapies are essential to manage clinical symptoms and improve patients' quality of life. Ongoing research efforts aim to deepen our understanding of the molecular mechanisms underlying the disorder to develop targeted treatments. Recent studies have identified defective respiratory chain complex I (CI) activity in the brain of a WDR45 knock out (KO) mouse model [1] and in fibroblasts from a patient carrying the pathogenic variant c. [749\_751delCCT]; [0] in WDR45[2], suggesting that mitochondrial dysfunction may play a critical role in BPAN pathogenesis. This study intends to evaluate mitochondrial function in brain cell types derived from BPAN patients.

**Methods and Preliminary Results:** We are utilizing high-resolution respirometry with a Seahorse XF analyzer to assess CI activity in permeabilized BPAN cells. This technology enables real-time measurement of cellular bioenergetics, offering a comprehensive overview of cellular metabolism through the oxygen consumption rate (OCR) parameter, which reflects mitochondrial respiration.[3] The analysis has been conducted on fibroblasts from two BPAN patients with pathogenic variants c. [830+1G>A]; [=] and c. [729-2A>T]), [=], and these results were compared with respiration in the fibroblast line confirmed to have a CI defect, carrying the variant c. [749\_751delCCT]; [0]. Preliminary data indicate a CI defect in the two previously uncharacterized fibroblast lines. Additionally, the fibroblast lines carrying the c. [729-2A>T]), [=] and c. [749\_751delCCT]; [0] variants have been reprogrammed into induced pluripotent stem cells (iPSCs). These iPSCs have been fully characterized in terms of genotype, pluripotency markers and differentiation potential. They have subsequently been differentiated into midbrain dopaminergic neurons and astrocytes, with ongoing characterization.

**Future Plans:** This study aims at elucidating whether the respiratory chain CI deficiency observed in the KO mouse model and fibroblasts from three WDR45-deficient patients is also present in brain cells, neurons and astrocytes, thereby providing a disease-relevant system for investigating human neurological disorders. Upon validation of the initial hypothesis, the fibroblasts and differentiated cells will be treated with various compounds (cAMP, Forskolin, Resveratrol) to assess their potential to rescue defective respiratory chain CI activity. In conclusion, this research project combines stem cell technology with advanced bioenergetic analysis to investigate BPAN pathology. Confirmation of CI deficiency in BPAN patients could open new avenues for therapeutic development.

#### References:

- (1) Biagosch, C. A. et al. A comprehensive phenotypic characterization of a whole-body Wdr45 knock-out mouse. *Mamm. Genome* 32, 332–349 (2021).
- (2) Ardissonne, A. et al. WDR45-related encephalopathy mimicking Leigh syndrome associated with complex I deficiency: a case report. Preprint at <https://doi.org/10.21203/rs.3.rs-4575643/v1> (2024).
- (3) Divakaruni, A. S., Rogers, G. W. & Murphy, A. N. Measuring Mitochondrial Function in Permeabilized Cells Using the Seahorse XF Analyzer or a Clark-Type Oxygen Electrode. *Curr. Protoc. Toxicol.* 60, 25.2.1–16 (2014).



[↑ Back to Scientific Program](#)

[↑ Back to Poster Session](#)

# POSTER SESSIONS

EP20

## CHARACTERISING THE MOLECULAR MECHANISMS OF WIPI2 AND WIPI4 MUTATIONS IN BPAN AND NEURODEVELOPMENTAL DISORDERS

<sup>1</sup>*Eleanor Attridge, <sup>1</sup>Sharon Tooze*

<sup>1</sup>*Francis Crick Institute, London, England*

There are four human WIPI  $\beta$ -propeller proteins, all members of the PROPPIN family. In autophagy they bind PI3P at the phagophore to recruit other interactors acting as a scaffold during autophagosome biogenesis. Specifically, WIPI2b binds ATG16L1 [1] and WIPI4 ATG2 [2]. WIPI2 and WIPI4 have been shown to interact with one another [3] but the nature and function of this interaction is unknown. We have begun characterisation of this interaction to understand the functional protein complex at the phagophore and the consequence of this interaction. Mutations in the WDR45 gene, encoding WIPI4, cause the neurodegenerative disease BPAN. The molecular mechanism of how such mutations cause disease is not clear, specifically if they cause impairment to WIPI4's function in autophagy. Mutations in the WIPI2 gene have also been linked to neurodevelopmental disorders, with milder phenotypes than BPAN. We are developing disease models from patient derived neurons to be used to study the molecular mechanisms of how WIPI2 and WIPI4 interactions and mutations affect autophagy and how this may impact the function of affected and non-affected neurons.

### References:

- (1)Dooley, H.C., et al., WIPI2 links LC3 conjugation with PI3P, autophagosome formation, and pathogen clearance by recruiting Atg12-5-16L1. *Mol Cell*, 2014. 55(2): p. 238-52. 2.
- (2)Otomo, T., S. Chowdhury, and G.C. Lander, The rod-shaped ATG2A-WIPI4 complex tethers membranes in vitro. *Contact* (Thousand Oaks), 2018. 1.
- (3)Bakula, D., et al., WIPI3 and WIPI4  $\beta$ -propellers are scaffolds for LKB1-AMPK-TSC signaling circuits in the control of autophagy. *Nature Communications*, 2017. 8(1): p. 15637



# POSTER SESSIONS

EP21

## GENISTEIN AS AN AUTOPHAGY STIMULATION IN BETA-PROPELLER PROTEIN-ASSOCIATED NEURODEGENERATION (BPAN)

*<sup>1</sup>Zuzanna Cyske, <sup>1</sup>Lidia Gaffke, <sup>1</sup>Estera Rintz, <sup>1</sup>Karolina Pierzynowska, <sup>1</sup>Grzegorz Wegrzyn*

*<sup>1</sup>Department of Molecular Biology, University of Gdansk, Gdansk, Poland*

**Introduction:** Beta-propeller protein-associated neurodegeneration (BPAN) is one of the less common types of neurodegeneration. It is caused by a mutation in the WDR45 gene, which encodes a beta-propeller protein [1]. This protein is involved in many cellular processes, such as apoptosis, autophagy, regulation of transcription and transmission of intracellular signals [2,3]. The molecular mechanisms of BPAN are still not fully understood, which is why it is very difficult to develop an effective therapy for patients.

**Aim:** The aim of this study was to determine the efficiency of the autophagy process in a cellular model of beta-propeller protein-associated neurodegeneration (BPAN).

**Materials and Methods:** In this study, we used cell lines from patients suffering from BPAN and from healthy individuals (as controls). The cells were cultured under standard conditions (37 degrees Celsius, 5% CO<sub>2</sub>). The western-blotting method was used to determine the levels of selected proteins involved in the autophagy process. Fluorescence microscopy was used to assess abundance and location of selected proteins, like LAMP2, TFEB and BECLIN1.

**Findings:** Levels of autophagy marker proteins (LC3-II, p62) were determined in BPAN cells compared to control cells. Additionally, the levels and localization of proteins involved in the functioning and biogenesis of lysosomes were assessed. Obtained results indicated significant changes in levels of studied proteins, which suggests that the autophagy process may be impaired in the BPAN cellular model. The use of genistein (autophagy stimulator) resulted in the activation of the autophagy process suggesting that genistein-mediated autophagy stimulation might be considered a potential therapy for patients with BPAN.

**Conclusions:** Obtained results indicated that the autophagy process is disturbed in BPAN patients. These defects can be corrected by using autophagy stimulators, like genistein.

### References:

- (1) Saitsu, H., et al. (2013). Nature genetics, 45(4), 445–449e1. <https://doi.org/10.1038/ng.2562>
- (2) Zhu, Y., et al. (2024). Nature cell biology, 26(4), 542–551. <https://doi.org/10.1038/s41556-024-01373-3>
- (3) Tsukida, K., et al. (2022). Brain communications, 4(6), fcac304. <https://doi.org/10.1093/braincomms/fcac304>



[↑ Back to Scientific Program](#)

[↑ Back to Poster Session](#)

# POSTER SESSIONS

EP22

## ESTABLISHING OF DROSOPHILA MODEL FOR BPAN DISEASE

*<sup>1</sup>Celle Marion, <sup>1</sup>Aniorte Sahra, <sup>2</sup>Lesca Gaetan, <sup>1</sup>Walter Ludivine, <sup>1</sup>Mollereau Bertrand*

*<sup>1</sup>Laboratory of Biology and Modelling of The Cell – CNRS : UMR5239, INSERM U2110, Université De Lyon, ENS De Lyon, UMS344 Biosciences Lyon Gerland - France*

*<sup>2</sup>Department of Medical Genetics – University Hospital of Lyon – France*

**Introduction:** The Beta-Propeller protein Associated with Neurodegeneration (BPAN) is a rare genetic neurological disease characterized by iron accumulation in the brain of patients. BPAN is caused by mutations of the WDR45 gene, a known regulator of autophagy. WDR45 mutation led to a dysregulation of autophagy in several BPAN cellular and animal models. Moreover, iron metabolism and ER stress response are also dysregulated and the molecular events leading this dysregulation in WDR45 mutants are still largely unknown. To address this question, we establish a *Drosophila melanogaster* mutant for CG11975 (hereafter dWDR45), the *Drosophila* WDR45 homolog.

**Materials & methods:** We used CRISPR-CAS9 to establish a *Drosophila melanogaster* mutant for dWDR45. We perform lifespan analysis, SING assay and vortex-induced epilepsy-like phenotype to identify physiological disorder that mimic some hallmarks of BPAN. At cellular level we used western-blotting and immuno-fluorescence to highlight dysregulation of autophagy and ER stress. To investigate iron dysregulation in our model, we measure iron concentration through Ferrozine assay and visualize iron metabolism through feeding flies with iron diet and following of ferritin levels.

**Results:** We have demonstrated that flies harboring dWDR45 mutation mimic some hallmarks of BPAN, such as lifespan decrease, locomotor disorders, epilepsy-like behaviors, autophagy, ER stress response dysregulations. Importantly, the *Drosophila* BPAN model shows iron accumulation in whole body and dysregulation of iron metabolism.

**Discussion:** The dWDR45 mutant flies exhibit both physiological and cellular defects that mimic those of BPAN. Thus, we have constructed a new model for studying the molecular basis of BPAN. In the long term, our study will contribute to a better understanding of BPAN and bring valuable knowledge to the development of therapeutic molecules.



[↑ Back to Scientific Program](#)

[↑ Back to Poster Session](#)

# POSTER SESSIONS

## PKAN / COPAN/NBIA SYSTEMIC GROUP B

EP23

### AUTOPHAGY AND NEURODEGENERATION: DISCOVERING CRITICAL INSIGHTS AND INNOVATIVE THERAPEUTIC STRATEGIES USING A NOVEL HUMAN NEURON MODEL OF BPAN

<sup>1</sup>Hetavi Zaverj, <sup>2</sup>Erin Kim, <sup>1</sup>Sarah Stumpf, <sup>2</sup>Sami Barmada, <sup>3</sup>Young-Ah Seo, <sup>3</sup>Louisa Aring, <sup>1</sup>Ted Dawson, <sup>1</sup>Valina Dawson, <sup>1</sup>Jason Chua

<sup>1</sup>Johns Hopkins Institute of Cell Engineering, Maryland, USA

<sup>2</sup>University of Michigan, Department of Neurology, Michigan, USA

<sup>3</sup>University of Michigan School of Public Health, Michigan, USA

BPAN ( $\beta$ -propeller protein-associated neurodegeneration) is the most common subtype of neurodegeneration with brain iron accumulation (NBIA), a group of neurological disorders which demonstrate excess iron deposition in the basal ganglia, progressive neurodegeneration, and impaired motor and cognitive function. Similar to other NBIAs, BPAN is associated with neurofibrillary tangle formation and axonal swelling, hinting at overlapping pathogenic sequelae despite genetic heterogeneity within the NBIA spectrum. BPAN is caused by mutations in the WDR45 gene, which encodes the autophagy effector protein, WIPI4. The role of autophagy in maintaining neuronal health is of increasing interest in the context of neurodegeneration, where accumulating evidence points to its dysfunction as a common pathogenic mechanism among many neurodegenerative diseases. To date, BPAN models in mice and cells have not fully recapitulated the complex phenotypes seen in patients, particularly the combination of neurodegeneration, iron accumulation, and autophagy impairment. To address this, we established a novel human neuron model for BPAN using patient-derived iPSCs carrying the WDR45 c.235G>A (p.Ala79Thr) mutation, and differentiated these cells into cortical neurons (iNeurons). Compare to WT cells, A79T iNeurons exhibited hallmark features of BPAN, including impaired autophagic flux and reduced viability. These defects could not be rescued by the pharmacologic inducer of autophagy, Torin1. Overexpression of WIPI4 is being explored to determine its effects on the survival of A79T neurons. Overall, our human iNeuron model serves as a powerful platform for probing the molecular basis of BPAN for understanding the essential mechanisms of neurodegeneration, with a special focus on identifying targetable mechanisms of innovative therapeutic strategies for this incurable and debilitating disorder. Through this work, we aim to elucidate new insights into how autophagy dysfunction drives neurodegeneration and open avenues for therapeutic intervention applicable to both BPAN other neurodegenerative diseases.



# POSTER SESSIONS

EP24

## BETA-PROPELLER PROTEIN ASSOCIATED NEURODEGENERATION (BPAN): ELECTROENCEPHALOGRAPHIC CHARACTERIZATION OF A COHORT OF 16 PATIENTS

<sup>1</sup>Alejandra Darling, <sup>2</sup>Itziar Alonso-Colmenero, <sup>2</sup>Amos ríos Calderón, <sup>3</sup>Heidy Baide Mairena, <sup>3</sup>Leticia Pías, <sup>3</sup>Rosana Mari Vico, <sup>3</sup>Alfonso De Oyarzabal, <sup>3</sup>Ángels García Cazorla, <sup>3</sup>Alejandra Darling

<sup>1</sup>Sant Joan De Déu Children's Hospital. Barcelona, Spain

<sup>2</sup>Neurophysiology Department, Neurology Department, Sant Joan De Déu Children's Hospital, Barcelona, Spain

<sup>3</sup>Metabolic Unit, Neurology Department, Sant Joan De Déu Children's Hospital. Barcelona, Spain

**Introduction:** BPAN is the most common neurodegenerative brain iron accumulation disorder (NBIA), with an estimated prevalence of 2 to 3 per million individuals. It is caused by de novo mutations in the WDR45 gene located at Xp11.23, which plays an important role in autophagy. It is characterized by global developmental delay with intellectual disability and epilepsy during childhood, followed by progressive neurological and cognitive impairment with dystonia and parkinsonism in adolescence or adulthood.

**Aim:** To describe the electroencephalographic findings of BPAN in a cohort of 16 patients.

**Material and Methods:** Patients with pathogenic variants in the WDR45 gene were included. A retrospective qualitative analysis of electroencephalographic recordings (EEGs) was performed during their follow-up.

**Results:** Within the series of 16 patients, 13 were girls and 3 were boys. A total of 20 recordings obtained between 1 and 17 years of age were included. Sleep phase recordings were obtained in 14/16. A total of 15/16 of the recordings showed a basal brain activity in wakefulness that was poorly organized according to their age. On the 14 of the tracings in which sleep recording was obtained, there was a lack of a well-organized physiological graphoelements. Beta rhythms of variable amplitude according to age and diffuse distribution in both wakefulness and sleep were identified in 90% of the recordings. Intercritical epileptiform findings (present in all but one register) showed: 1- bilateral and/or generalized epileptiform discharges (70%); 2- focal epileptiform activity (15%) and; 3- multifocal epileptiform activity (10%). The distribution of these alterations was predominantly in anterior and/or posterior areas. In 2 patients, with a severe neurological phenotype, findings of status epilepticus were identified during sleep. Critical episodes were recorded in only one patient, in the form of epileptic spasms followed by generalized non-motor seizures, absence type, associated. One patient had "atypical" EEG findings, with dominant posterior rhythm and sleep structuring appropriate for the patient's age at the time of recording and absence of diffusely distributed fast rhythms.

**Conclusions:** In this cohort of BPAN patients, in a large proportion, EEG findings showed a combination with: poorly organized brain activity, absence of adequate NREM sleep phase structuring, fast rhythms of diffuse distribution and bilateral and/or generalized intercritical disturbances from early ages. The finding of status epilepticus during sleep, in patients with similar features, is remarkable and useful for the clinical setting, with treatment consequences. We postulate the EEG as a potential biomarker for BPAN patients.



[↑ Back to Scientific Program](#)

# POSTER SESSIONS

[↑ Back to Poster Session](#)

EP25

## ALTERED AUTOPHAGY INVOLVED IN NEURODEVELOPMENT AND NEURODEGENERATION: STUDY OF A COHORT OF PATIENTS WITH BPAN (BETA-PROPELLER PROTEIN-ASSOCIATED NEURODEGENERATION), NEW INSIGHTS AND PHENOTYPES

*<sup>1</sup>Alejandra Darling, <sup>2</sup>Alejandra Darling, <sup>2</sup>Heidy Baide, <sup>3</sup>Luca soliani, <sup>2</sup>Yaiza Díaz Osorio, <sup>2</sup>Leticia Pías Peleteiro, <sup>4</sup>Marta Pereira Silva Soares, <sup>5</sup>Otilia Martínez-Mugica, <sup>6</sup>Alberto García Oguiza, <sup>5</sup>Itxaso Martí, <sup>7</sup>Ana Camacho Salas, <sup>2</sup>Mar O Callaghan, <sup>2</sup>Rosana Mari Vico, <sup>2</sup>Alfonso De Oyarzabal Sanz, <sup>2</sup>Ángels García-Cazorla*

<sup>1</sup>Sant Joan De Déu Children's Hospital. Barcelona, Spain

<sup>2</sup>Neurology Department, Sant Joan De Déu Children's Hospital. Barcelona, Spain

<sup>3</sup>Istituto Delle Scienze Neurologiche, Bologna, Italy

<sup>4</sup>Hospital Universotaria Santa María. Lisbon, Portugal

<sup>5</sup>Hospital Universitario Donostia. San Sebastián, Spain

<sup>6</sup>Hospital Universitario De Álava - Txagorritxu. Vitoria-Gasteiz, Spain

<sup>7</sup>Hospital Universitario 12 De Octubre. Madrid, Spain

**Background:** Autophagy is a key pathway with a critical role in the protein homeostasis and maintenance. Different studies give evidence of the importance of autophagy in neurodegeneration mechanisms. Several monogenic defects related to autophagy have emerged, including the WDR45 gene, associated with the  $\beta$ -propeller protein-associated neurodegeneration (BPAN). Our aim is to describe the clinical and biochemical profile, including the demonstration of the autophagic flux defect in BPAN patients.

**Methods:** Observational and clinical study in a cohort of pediatric BPAN patients. Clinical evaluation, biochemical, radiological, neurophysiological and genetic data were assessed. Autophagic markers in fibroblasts were investigated using western blot and immunofluorescence techniques.

**Results:** A total of 26 BPAN patients were assessed by the group in 2 sites, 4/26 males, ages ranging from 0.5-18 years. The main symptom at onset was global neurodevelopmental delay, associated with febrile seizures (n=4), language regression (n=2) and severe hypotonia (n=2). The age at onset was before 15 months in all cases. The evolution was variable, including different degrees of developmental delay/intellectual disability (23), epilepsy (21), different patterns of motor and movement disorders including early parkinsonian signs (17), sleep disorders (14) and behavioural issues (12). A systematic assessment of the dysmorphology were assessed, showing recognizable particular features. Elevated liver transaminases were present in 14 cases. Brain MRI showed T2/SWI hypointense signal in globus pallidus and sustancia nigra in 23/26 cases. The cohort showed novel pathogenic variants (15/26), most of them de novo in the WDR45 gene, with the exception of one whose mother showed mosaicism for the WDR45 variant. CSF studies were performed, showing alterations in the neurotransmitters profile in 4 patients. NfL (Neurofilament Light chain) levels were explored in plasma and CSF in 15 individuals, showing a significative correlation with the neurological phenotype. Fibroblasts studies showed alterations in markers compatible with a defect in the autophagic flux (LC3BI/II ratio, LAMP1 and p62).

**Conclusion:** We describe a cohort of BPAN patients, with a homogeneous and systematic assessment. A recognizable and particular phenotype is described in a subset of patients, including neurological, dysmorphic, biochemical, neuroimaging, and electrophysiological patterns. A potential biomarker is described, that showed an association with the neurological severity in this cohort. The cellular studies contribute to understand the pathomechanism that will allow the development of new therapeutical approaches.





[↑ Back to Scientific Program](#)

[↑ Back to Poster Session](#)

# POSTER SESSIONS

MPAN / KRS  
GROUP A

EP26

## MODELING C19ORF12 DEFICIENCY IN ZEBRAFISH

*<sup>1</sup>Barbara Gnutti, <sup>2</sup>Barbara Buffoli, <sup>1</sup>Daniela Zizioli, <sup>1</sup>Giuseppe Borsani, <sup>1</sup>Dario Finazzi*

*<sup>1</sup>University of Brescia, Department of Molecular and Translational Medicine, Brescia, Italy*

*<sup>2</sup>University of Brescia, Department of Clinical and Experimental Sciences, Brescia, Italy*

WITHDRAWN



# POSTER SESSIONS

EP27

## EARLY-ONSET DEMENTIA IN A CASE OF LATE-ONSET MPAN

<sup>1</sup>[Hatice Yuksel](#), <sup>1</sup>[Cemre Guclu Ozbeycan](#), <sup>1</sup>[Kymbat Asekova](#), <sup>1</sup>[Fadime Erdogan Kucukdagli](#), <sup>2</sup>[Zuhal Yapici](#)

<sup>1</sup>*Ankara Bilkent City Hospital Department of Neurology, Türkiye*

<sup>2</sup>*Istanbul University, Istanbul Faculty of Medicine Department of Child Neurology, Türkiye*

**Introduction:** Mitochondrial membrane protein-associated neurodegeneration (MPAN) is the third most common subtype of neurodegeneration with brain iron accumulation, primarily caused by mutations in the C19orf12 gene and typically inherited in an autosomal recessive manner. Disorders, neuropsychiatric issues, optic atrophy, and axonal motor neuropathy. In contrast, the late-onset form of MPAN may predominantly feature neuropsychiatric disorders, including psychosis and dementia. This report describes a case of late-onset MPAN with early-onset dementia symptoms, emphasizing the necessity of considering MPAN in the differential diagnosis when dementia presents at an early stage of life.

**Case:** A 39-year-old male patient was referred to our outpatient clinic with complaints of memory, attention, speech, and gait problems. The patient's neurological symptoms began at age 29 with tremors initially affecting his right hand and subsequently both hands. At age 32, he developed difficulty with walking. By age 38, he sought evaluation at a neurology clinic due to additional speech difficulties and mild memory issues, but no definitive diagnosis was made. In the year preceding his admission to our clinic, his memory and concentration problems worsened significantly, impairing his job performance. Upon presentation to our neurology outpatient clinic in 2023, the patient, a primary school graduate and right-hand dominant furniture tailor, was hospitalized for further evaluation. His medical history was notable only for a left hip fracture sustained in a traffic accident. He was the third child of consanguineous parents, with a 42-year-old brother experiencing gait difficulties but undiagnosed, and a 55-year-old uncle with undetermined dementia. Neurological examination revealed disorientation to time and place, bilateral temporal disc pallor, slow saccades, and prominent bilateral resting and postural tremor, predominantly on the right side. Additionally, rigidity, bradykinesia, and brisk deep tendon reflexes in the upper extremities were observed. The patient scored 14/30 on the Mini-Mental State Examination and exhibited numerous errors on the clock drawing test. Brain magnetic resonance imaging (MRI) with T2-weighted sequences showed marked hypointensity indicative of abnormal iron deposition in the basal ganglia, particularly in the bilateral putamen, substantia nigra, and globus pallidus. Electromyography, electroencephalography, somatosensory evoked potentials, routine cerebrospinal fluid analysis, and detailed cardiac evaluations were unremarkable. Visual evoked potentials from the right eye were abnormal. Given the patient's family history, neurological findings, and MRI results, a genetic disorder associated with brain iron accumulation was prioritized in the differential diagnosis. Genetic analysis identified homozygous NM\_031448.6c.-2C>T (IVS1-2C>T) mutations in the C19orf12 gene, confirming the diagnosis of MPAN. Consequently, the patient was granted disability retirement.

**Conclusion:** We present a case of MPAN diagnosed after the onset of cognitive decline that significantly impacted daily life, despite the initial symptoms emerging 10 years prior. In instances of early-onset dementia, MPAN should be considered as a potential, albeit rare, etiology, particularly when accompanied by extrapyramidal symptoms and a relevant family history. Although a cure for MPAN remains unavailable, early diagnosis is crucial for facilitating genetic counseling and planning for future management.



# POSTER SESSIONS

EP28

## AUTOPHAGY DISTURBATION IN FIBROBLASTS DERIVED FROM PATIENTS SUFFERING FROM MITOCHONDRIAL MEMBRANE PROTEIN-ASSOCIATED NEURODEGENERATION (MPAN), A TYPE OF NEURODEGENERATION WITH BRAIN IRON ACCUMULATION (NBIA)

*<sup>1</sup>Grzegorz Wegrzyn, <sup>1</sup>Lidia Gaffke, <sup>1</sup>Karolina Pierzynowska, <sup>1</sup>Zuzanna Cyske, <sup>1</sup>Estera Rintz, <sup>1</sup>Aneta Szulc, <sup>1</sup>Karolina Wisniewska, <sup>1</sup>Magdalena Zabinska*

*<sup>1</sup>University of Gdansk, Gdansk, Poland*

**Introduction:** Neurodegeneration with brain iron accumulation (NBIA) is a group of inherited diseases, characterized with neurodegeneration accompanied with accumulation of iron in the brain. There are several types of NBIA, distinguished on the basis of mutations on different genes, causing specific biochemical effects and symptoms. One of NBIA types is mitochondrial membrane protein-associated neurodegeneration (MPAN), caused by mutations in the C19orf12 gene. Despite the identification of the mutations, molecular mechanisms of MPAN is still incompletely understood, with scarce knowledge on molecular processes which can be disturbed in cells of patients.

**Aim:** The aim of this work was to assess the effectiveness of autophagy in fibroblasts derived from patients suffering from mitochondrial membrane protein-associated neurodegeneration (MPAN), a type of neurodegeneration with brain iron accumulation (NBIA).

**Materials and Methods:** Eight lines of fibroblasts derived from patients with MPAN were used in this study, along with control fibroblasts. Cells were cultured under standard laboratory conditions. Fluorescent microscopy was used to assess abundance of tested proteins in cells, using specific antibodies and immunofluorescence. Western-blotting was employed to determine levels of specific proteins in cells.

**Findings:** Levels of autophagy markers, LC3-II and p62 proteins, were assessed in MPAN and control fibroblasts. Moreover, abundance of proteins involved in lysosomal biogenesis and functions, TFEB, LAMP2, and BECLIN1, were assessed. The results indicated that levels of the investigated proteins were slightly, but statistically significantly modulated in MPAN fibroblasts, suggesting impairment of the autophagy process in these cells. Treatment with genistein, an autophagy stimulator, resulted in activation of the autophagy process.

**Conclusions:** The autophagy process is likely impaired in cells of MPAN patients. This deficit can be corrected by the use of autophagy stimulators, like genistein.



# POSTER SESSIONS

EP29

## MITOCHONDRIAL MEMBRANE-PROTEIN ASSOCIATED NEURODEGENERATION (MPAN) PRESENTING WITH PARKINSONISM FINDINGS: CASE REPORT

*<sup>1</sup>İrem Aydın, <sup>1</sup>Mehmet Güney Şenol*

*<sup>1</sup>Sultan Abdülhamid Han Educational and Research Hospital, İstanbul, Türkiye*

**Aim:** In this article, we aimed to bring MPAN syndrome to mind among the preliminary diagnoses in a case that presented with Parkinsonism findings, urinary incontinence, dysarthria and cognitive impairment.

**Materials and Methods:** Our article is compiled on a single case; The pathological signs and symptoms of MPAN syndrome are shown with detailed anamnesis, neurological examination, related blood and urine tests, neuroimaging, electroencephalography, electromyography, neuropsychological evaluation, necessary specialist opinions and genetic examination.

**Findings:** When the anamnesis was deepened, it was understood that the young patient, who applied to our polyclinic with dysarthria, urinary incontinence and slow walking, had behavioral disorders and muscle stiffness in addition to his complaints. When the patient's family history was questioned, consanguinity was found between the parents. Difficulty in performing repetitive movements, tremor, rigidity, and inability of the upper extremities to participate in the associated movement during walking were among the notable findings in the neurological examination. Upon observation of suspicious accumulations in the basal ganglia in the patient's cranial MRI images, necessary blood and urine tests were requested to check for diseases associated with accumulation, but no significant pathological results were obtained. In the neuropsychological evaluation of the patient, who was thought to be cognitively affected, a secondary type of impairment in memory was noticed in the process of learning and retrieving verbal material and difficulty in maintaining attention. In the psychiatric evaluation of the patient, a decrease in speech rate and amount, social participation and affect was noticed. In the patient's genetic test results, a homozygous, pathogenic change in the C19orf12 gene was detected in exome sequencing analysis. Pathogenic changes in this gene caused the disease "Neurodegeneration 4 with brain iron accumulation" and explained the clinical findings of the patient. It was understood that the detected change was also present in other members of the family as heterozygous and that the parents were carriers. In the light of the results obtained, the patient was diagnosed with mitochondrial membrane protein associated neurodegeneration (MPAN), which results with iron accumulation in the basal ganglia, and the patient was started on symptomatic treatment with Rasagiline, Piribedil, Sertraline and Coenzyme Q10.

**Conclusion:** Although MPAN (Mitochondrial membrane protein-associated neurodegeneration) is rare, it is a genetic disease that should be kept in mind, especially in young patients presenting with Parkinsonism findings, gait disorders, urinary incontinence and dysarthria. The most common symptom is gait disturbance in MPAN. Tremor, rigidity, Parkinsonian gait and dysarthria are common findings in neurological examination. For diagnosis an appearance that may be due to hypointense trace element accumulation at all levels at the level of the basal ganglia on cranial MR imaging will be helpful. In genetic examination of patients, a homozygous, pathogenic change in the C19orf12 gene will be detected in the exome sequencing analysis. This pathogenic change is responsible for the accumulation of iron at basal ganglia and all other features of the disease.

### Reference:

(1)Gregory A, Klopstock T, Kmiec T, et al. Mitochondrial Membrane Protein-Associated Neurodegeneration. 2014 Feb 27 [Updated 2021 Mar 4]. In: Adam MP, Feldman J, Mirzaa GM, et al.



[↑ Back to Scientific Program](#)

[↑ Back to Poster Session](#)

# POSTER SESSIONS

MPAN / KRS  
GROUP B

EP30

## MITOCHONDRIAL MEMBRANE PROTEIN-ASSOCIATED NEURODEGENERATION PRESENTING WITH PARKINSONISM: A CASE REPORT

<sup>1</sup>*Miray Erdem*, <sup>2</sup>*Mehmet Balal*, <sup>3</sup>*Zuhal Yapıcı*, <sup>2</sup>*Meltem Demirkıran*

<sup>1</sup>*Adana City Training and Research Hospital, Department of Neurology, Adana, Türkiye*

<sup>2</sup>*Cukurova University Faculty of Medicine, Department of Neurology, Adana, Türkiye*

<sup>3</sup>*Istanbul Faculty of Medicine, Department of Child Neurology, Istanbul, Türkiye*

**Introduction:** Mitochondrial membrane protein-associated neurodegeneration (MPAN) is an inherited disorder caused by a mutation in the C19orf12 gene and characterized by a variety of neurological and psychiatric symptoms involving the basal ganglia. MPAN is typically characterized by progressive dystonia-parkinsonism in childhood or adolescence, optic atrophy, axonal motor neuronopathy and iron accumulation in the globus pallidus-substantia nigra on imaging. We would like to present a case of MPAN, which is the third most common subtype of neurodegenerative disease with brain iron deposition (NBIA).

**Case:** A 22-year-old woman, born to consanguineous healthy parents with no known health issues and a normal birth and developmental history, was admitted to our clinic in June 2023 with a one-year history of left hand tremor and slowing of movements. A neurological examination revealed the presence of bilateral moderate postural tremor in the upper left hand, as well as bilateral moderate bradykinesia and moderate rigidity in the upper left hand. Pramipexole was initiated prior to the diagnosis of Parkinson's disease. Magnetic resonance imaging (MRI) of the brain revealed the presence of mineral deposits in the basal ganglia, while serum copper and ceruloplasmin levels were within the normal range. The levels of ferritin and transferrin saturation were within the normal limits, whereas serum iron levels were found to be low. A peripheral smear examination revealed a prevalence of 5-10% acanthocytes. The results of the echocardiography and abdominal ultrasonography were within the normal range. An ophthalmological examination was conducted, and no pathological findings were identified. In November 2023, levodopa was introduced to the treatment regimen with a gradual dose increase due to the emergence of new symptoms, including urinary incontinence, loss of appetite, loss of balance, neuropsychiatric symptoms, and deterioration in cognition. MRI demonstrated the presence of symmetrical T2/Flair hypointensities in the bilateral basal ganglia, accompanied by a faint hyperintensity along the medial medullary lamina, indicative of MPAN. The PANK2 mutation was found to be absent. The introduction of quetiapine and sertraline was indicated due to the onset of neuropsychiatric symptoms. The frequency of hallucinations decreased, oral intake improved and the severity of the patient's symptoms exhibited a regression to a certain extent. The patient was referred to an external facility for further examination. A brain PET/CT scan showed evidence of diffuse hypometabolism in the bilateral parietal superior and inferior gyri, precuneus and posterior cingulate gyri, with a particularly pronounced presentation on the right side. A genetic examination revealed a homozygous mutation in the C19orf12 gene, which lead to a diagnosis of MPAN. The case continues to progress clinically, with the patient undergoing psychiatric and supportive treatment in addition to dopaminergic therapy.

**Conclusions:** A variety of mutations in the MPAN gene may result in the manifestation of different phenotypes. MPAN should be considered in the differential diagnosis of patients presenting with early-onset parkinsonism accompanied by psychiatric symptoms, rapid disease progression and iron accumulation in the basal ganglia on MRI



[↑ Back to Scientific Program](#)

[↑ Back to Poster Session](#)

# POSTER SESSIONS

EP31

## CLINICAL PROFILE OF KUFOR-RAKEB SYNDROME AND EVALUATION OF QUANTITATIVE SENSITIVITY ANALYSIS

<sup>1</sup>*İbrahim Kamacı*, <sup>2</sup>*Gullu Tarhan*, <sup>3</sup>*Nazlı Basak*, <sup>4</sup>*Murat Gultekin*, <sup>5</sup>*Petr Dusek*, <sup>6</sup>*Gencer Genc*, <sup>7</sup>*Bulent Elibol*, <sup>1</sup>*Zuhal Yapici*

<sup>1</sup>*Istanbul University, Istanbul Medical Faculty, Department of Neurology, Istanbul, Türkiye*

<sup>2</sup>*Department of Neurology, Bitlis State Hospital, Bitlis, Türkiye*

<sup>3</sup>*Neurodegeneration Research Laboratory, Suna and Inan Kirac Foundation, KUTTAM, School of Medicine, Koc University, Istanbul, Türkiye*

<sup>4</sup>*Department of Neurology, Faculty of Medicine, Kayseri University, Kayseri, Türkiye*

<sup>5</sup>*Department of Neurology and Center of Clinical Neuroscience, First Faculty of Medicine, Charles University and General University Hospital and Department of Radiology, First Faculty of Medicine, Charles University and General University Hospital, Praha*

<sup>6</sup>*Department of Neurology, Sisli Etfal Training and Research Hospital, University of Health Sciences, Istanbul, Türkiye*

<sup>7</sup>*Department of Neurology, Faculty of Medicine, Hacettepe University, Ankara, Türkiye*

**Introduction:** Kufor-Rakeb Syndrome (KRS) is a rare neurodegenerative disorder resulting from mutations in the ATP13A2 gene, which encodes the lysosomal type 5P ATPase. It is characterized by extrapyramidal signs, supranuclear gaze palsy, neuropsychiatric symptoms, cognitive deterioration, facial-myoclonic jerks, and pyramidal signs. There are also cases of KRS that present with long-term cognitive decline, pyramidal symptoms, or motor neuron signs.

**Method:** Our study included a cohort of 15 genetically confirmed patients with KRS who were followed at the Neurology Department of Istanbul University and the Turkish NBIA Study Group between 2005 and 2024. The clinical, demographic, and electrophysiological characteristics of the patients were evaluated in detail according to the study protocol. SWI, T1, and MPRAGE images obtained from 11 patients using a Philips Achieva 3.0 Tesla MRI scanner were analyzed with the Quantitative Susceptibility Mapping (QSM) technique and compared with healthy controls.

**Results:** The study involved 15 patients from 9 families, 6 of whom were female. The median age was  $36.40 \pm 12.05$  years (range: 16-58 years), and the median age at onset was  $24.21 \pm 13.38$  years (range: 5-43 years). Symptoms began in the first decade for one patient and in the second decade for 6 patients. The most common initial symptoms were slow walking and frequent falls, while other early symptoms included tremors, leg stiffness, cramps, forgetfulness, loss of fine motor skills, and memory impairment. Cognitive impairment was present in all patients, with 9 patients having a mean verbal IQ of  $69.22 \pm 15.75$  (range: 50-93). All but one patient, who was followed for 13 years, exhibited only pyramidal findings. Seven patients had significant proximal muscle weakness in the lower extremities. Extrapyramidal findings were noted in all patients except one. Minimyoclonus around the mouth and face, an important symptom, was observed in 3 patients. Supranuclear gaze palsy was detected in 6 patients. Among the 12 patients who underwent conduction and needle electromyography, 3 had normal results, while the others demonstrated axonal polyneuropathy, widespread chronic myogenic involvement without denervation, and multisegmental anterior root/horn involvement. Correlation analyses revealed a positive correlation between Hoehn-Yahr scores and putamen QSM values. There was also a statistically significant difference in QSM values between patients with and without spasticity ( $p \leq 0.05$ ). Additionally, QSM values in the substantia nigra were found to be significantly higher in the patient group compared to the control group ( $p \leq 0.05$ ). Furthermore, a reduction in putamen volume was observed in the patient group relative to the control group.

**Discussion/Conclusion:** This study represents the largest single-center cohort reported to date for Kufor-Rakeb Syndrome (KRS) and is also the largest single-center study focusing on KRS using QSM and volumetric analysis. We believe these findings will provide valuable insights into the pathophysiology of this ultra-rare disease. The QSM data revealed significantly higher iron accumulation in MR imaging than in healthy controls, addressing the concern that some KRS patients may not exhibit detectable iron accumulation. Additionally, the potential use of QSM data in future therapeutic trials, both pre- and post-treatment, offers exciting possibilities for monitoring treatment efficacy.

[↑ Back to Scientific Program](#)[↑ Back to Poster Session](#)

# POSTER SESSIONS

EP32

## A CASE OF NBIA WITH IRON ACCUMULATION NOT DETECTED BY CONVENTIONAL GENETIC TESTING

<sup>1</sup>*Malika Egemberdiyeva, <sup>1</sup>Tuğba Eyigürbüz, <sup>1</sup>Sebatije Erdoğan, <sup>1</sup>Nilüfer Kale*

<sup>1</sup>*Health Sciences University Bağcılar Training and Research Hospital, Neurology, Türkiye*

**Introduction:** Neurodegeneration with brain iron accumulation (NBIA) is a heterogeneous group of neurodegenerative disorders characterized by progressive motor dysfunction and significant iron accumulation in the basal ganglia, detectable on radiologic imaging. Various NBIA phenotypes, including PKAN, PLAN, MPAN, and BPAN, influence the clinical presentation and progression of the disease. The genetic and clinical characteristics of each phenotype are crucial in guiding the management of these conditions. We report a case of suspected NBIA in a patient, despite no variants being identified in known genetic loci associated with NBIA.

**Case Presentation:** A 38-year-old woman presented with complaints of incomplete speech, nasal speech, slurred speech, and difficulty walking. Her speech disorder had first appeared in the fifth month of her pregnancy at age 33 and had progressively worsened since. Neurological examination revealed dysarthria, lingual dystonia, hyperreflexia, lower extremity spasticity, and an ataxic gait. Bilateral bradykinesia and rigidity were observed, with a predominance on the left side. A detailed family history revealed similar progressive speech and gait disturbances in her two aunts and her mother, all of whom had symptom onset around the same age. Brain MRI showed symmetrical bilateral hypointensity in the globus pallidus and substantia nigra on T2- and SWI-weighted images. Clinical exome sequencing (CES) did not detect any pathogenic variants in known NBIA-related genes, prompting the decision to perform whole exome sequencing (WES). The patient was started on anticholinergic therapy, and botulinum toxin A injections were considered for symptomatic management.

**Conclusion:** Genetic testing plays a pivotal role in the diagnosis and management of NBIA. Early intervention can significantly improve patients' quality of life. Greater awareness of NBIA syndromes can enhance our understanding of their pathophysiology and facilitate the development of targeted therapeutic strategies.

**FIRST CLOSE LOOK AT PROTEASOME IN NEURODEGENERATION WITH BRAIN IRON ACCUMULATION PATIENTS**

<sup>1</sup>*Lidia Gaffke, <sup>1</sup>Estera Rintz, <sup>1</sup>Zuzanna Cyske*

<sup>1</sup>*Department of Molecular Biology, University of Gdansk, Gdansk, Poland*

**Introduction:** Genetic diseases represent some of the greatest challenges of modern medicine. It appears that even among monogenic diseases, the exact mechanisms of pathogenesis of these conditions remain unclear. This poses a major obstacle to predicting disease progression in patients, on the one hand, and to finding targets for therapies under development, on the other [1]. Neurodegeneration with brain iron accumulation (NBIA) is a heterogeneous group of inherited neurodegenerative diseases. Iron accumulates in brain structures, usually in the globus pallidus, black matter, reticular part, and striatum. Symptoms include various movement disorders, neuropsychiatric disorders, and cognitive impairment [2]. Apart from iron accumulation and already detected gene mutations that determine the type of disorder, the pathomechanism of these diseases is still unknown.

**Aim:** The purpose was to determine whether patients with beta-propeller protein-associated neurodegeneration (BPAN), pantothenic kinase-associated neurodegeneration (PKAN) and mitochondrial membrane protein-associated neurodegeneration (MPAN) show abnormalities in one of the degradation pathways - the ubiquitin-proteasome system.

**Materials and methods:** The study was conducted on fibroblasts taken from patients with different variants of NBIA and corresponding healthy controls. Cells were cultured under standard conditions. Several assays were performed, including evaluating proteasome activities (Trypsin-; Chymotrypsin-; Caspase-like), examining the levels of its individual subunits ( $\alpha$  and  $\beta$  and their core, respectively) and total ubiquitin protein levels in patients. In addition, changes in ubiquitination levels of individual proteins (49 simultaneously) and differences in cytokine levels (105 simultaneously) were assessed.

**Findings:** In this report, a comprehensive analysis of the ubiquitin-proteasome system in various NBIA patients was conducted for the first time. Changes in activity and abnormal levels of numerous proteins were indicated. Similarities and differences were also pointed out by using Venn diagram analysis. The results clearly show that MPAN is least different from the control in case of proteasome activities and changes in cytokine level.

**Conclusions:** Emerging evidence suggests that dysregulation of the ubiquitin-proteasome system and impaired proteostasis may be central to the pathophysiology of NBIA. Continued research into the mechanisms linking iron metabolism, mitochondrial function, and protein quality control in these disorders will be critical for developing targeted therapies. Moreover, exploring the links between proteasome dysfunction and the clinical manifestations of NBIA holds promise for identifying biomarkers that could facilitate early diagnosis and prognostication.

**Reference:**

(1) Spaul, Robert V V et al. "Towards Precision Therapies for Inherited Disorders of Neurodegeneration with Brain Iron Accumulation." Tremor and other hyperkinetic movements (New York, N.Y.) vol. 11 51. 24 Nov. 2021, doi:10.5334/tohm.661.

(2) Dusek, Petr, and Susanne A Schneider. "Neurodegeneration with brain iron accumulation." Current opinion in neurology vol. 25,4 (2012): 499-506. doi:10.1097/WCO.0b013e3283550cac.



# International Congress of Parkinson's Disease and Movement Disorders®

Honolulu, Hawaii, USA - October 5-9, 2025



International Parkinson and  
Movement Disorder Society



[mdscongress.org](https://mdscongress.org)



# Join the International Parkinson and Movement Disorder Society

 [www.movementdisorders.org](http://www.movementdisorders.org) 

## Membership Benefits:

- Education and resources
- Member directory
- Special Interest Groups
- Global networking
- Reduced registration fees
- Quarterly newsletter
- Peer-reviewed journals



# No-Fee Membership

MDS offers no-cost membership for eligible individuals from **100+ lower-income countries**, students, juniors, and retirees.

## Member benefits include:

- 2 peer-reviewed journals
- Video library of 2,000 patient cases
- eLearning resources
- Access to 50+ active groups
- COA / rating scale training



International Parkinson and  
Movement Disorder Society

Apply now:

[movementdisorders.org/membership](https://movementdisorders.org/membership)



# 9<sup>th</sup> INTERNATIONAL SYMPOSIUM ON NBIA

October 17-19, 2024

Istanbul University, Central Campus  
BEYAZIT - ISTANBUL



## Gold Level



International Parkinson and  
Movement Disorder Society

Boston  
Scientific

bridgebio

ÇİĞDEM DİLEK & MURAT DİLEK

## Silver Level

Gen

INTERGEN



## Bronze Level

ABBVIE  
ABDI İBRAHİM  
ARIS  
BIOGEN



OSMAN FUAT NEVİR & ERCAN ÇAĞMAN  
İLKO  
LIFE MED  
NUTRICIA  
TURKISH NEUROLOGICAL SOCIETY



SANOVEL  
SAPIENS  
TURKISH PARKINSON DISEASE  
ASSOCIATION  
UCB

ORGANISATION SECRETARIAT

**burkon**  
TOURISM & CONGRESS

444 9 443  
onur.oral@burkon.com



Contact Person: Prof. Dr. Zuhal YAPICI