Institut de recherche
Centre universitaire de santé McGill
Research Institute
McGill University Health Centre

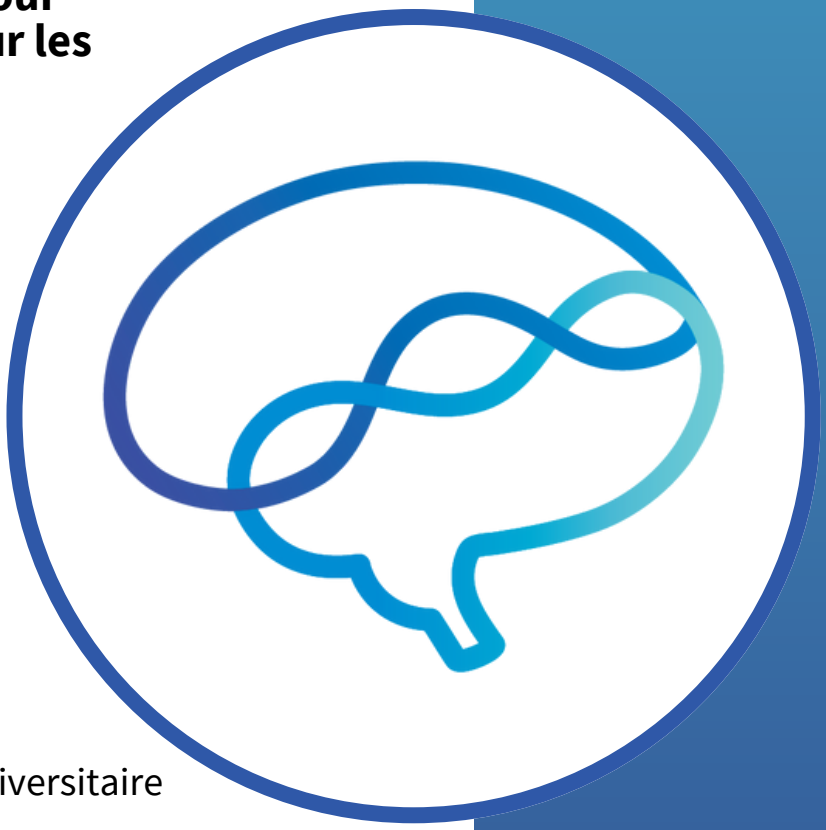
la fondation de l'hôpital de montréal pour enfants
the montreal children's hospital foundation

5 décembre 2025 | December 5 2025

CARELEUKO SYMPOSIUM 2025

L'Association canadienne pour l'excellence en recherche sur les leucodystrophies

Canadian Association for Research Excellence in Leukodystrophy



PROGRAMME

PROGRAM

Institut de recherche du Centre universitaire de santé McGill

Research Institute of the McGill University Health Centre

1001 Boulevard Décarie

Montréal, Québec, Canada

CARELeuko

CARELeuko SYMPOSIUM 2025

Symposium CARELeuko 2025

Association canadienne pour l'excellence en recherche sur la leucodystrophie

5 DÉCEMBRE 2025 | 7h30 à 21h30

Unir la communauté canadienne de la leucodystrophie : le mandat de CARELeuko pour favoriser la collaboration et accélérer la recherche et les soins

L'Association canadienne pour l'excellence en recherche sur les leucodystrophies (CARELeuko) a été fondée en 2024 par la directrice, Dre Geneviève Bernard, MD, MSc, FRCPc (Institut de recherche du Centre universitaire de santé McGill), et les codirecteurs, Dre Roberta La Piana, MD, PhD (Institut neurologique de Montréal) et Dr Thomas Durcan, PhD (Institut neurologique de Montréal) ainsi qu'une petite équipe de chercheurs à Montréal, Québec, Canada.

Financé par l'Institut de recherche du Centre universitaire de santé McGill (IR-CUSM), CARELeuko est né d'un constat partagé: malgré les progrès réalisés dans la compréhension et le traitement des leucodystrophies, le Canada manquait d'un cadre national coordonné pour relier les personnes et les institutions œuvrant dans ce domaine. Notre mission est de bâtir et de maintenir un réseau collaboratif et multidisciplinaire de recherche et de soins qui fait progresser la science et améliore les résultats cliniques pour tous les types de leucodystrophies.

Depuis son lancement, CARELeuko s'est engagé à identifier les lacunes en matière de soins et de recherche, à établir des partenariats avec des acteurs du secteur et des associations, et à favoriser des recherches collaboratives innovantes pour faire progresser le domaine. Notre premier symposium en 2024 a réuni plus de 50 intervenants du Canada et d'ailleurs, établissant ainsi une communauté nationale plus forte et plus soudée.

Pour l'avenir, CARELeuko s'engage à élargir son réseau, à développer des infrastructures nationales telles que des registres cliniques et des parcours de soins, et à veiller à ce que la voix des patients et des familles demeure au cœur de toutes nos actions. Ensemble, nous souhaitons créer un avenir où chaque personne atteinte d'une leucodystrophie au Canada recevra un diagnostic rapide, des soins complets et aura accès aux plus récentes avancées scientifiques.

Pour en savoir plus ou vous impliquer, veuillez visiter https://careleuko.org/fr ou nous contacter à careleuko@muhc.mcgill.ca .

FAITES UN DON POUR SUPPORTER CARELEUKO

Soutenu par la Fondation de l'Hôpital de Montréal pour enfants

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CARELeuko SYMPOSIUM 2025

2025 CARELeuko Symposium

Canadian Association for Research Excellence in Leukodystrophy

DECEMBER 5, 2025 | 07:30 AM - 9:30 PM

Uniting Canada's Leukodystrophy Community: The CARELeuko Mandate to Drive Collaboration and Accelerate Research and Care

The Canadian Association for Research Excellence in Leukodystrophy (CARELeuko) was founded in 2024 by Director, Dr. Geneviève Bernard, MD, MSc, FRCPc (McGill University Health Centre Research Institute), and co-directors, Drs. Roberta La Piana, MD, PhD (Montreal Neurological Institute) and Thomas Durcan, PhD (Montreal Neurological Institute), together with a small team of researchers in Montreal, Quebec, Canada.

Established with funding from the Research Institute of the McGill University Health Centre (RI-MUHC), CARELeuko was born out of a shared recognition that while progress is being made in understanding and treating leukodystrophies, Canada lacked a coordinated national framework to connect the individuals and institutions working in this space. Our mission is to build and sustain a collaborative, multidisciplinary research and care network that advances science and improves clinical outcomes across the spectrum of leukodystrophies.

Since its launch, CARELeuko has focused on identifying gaps in care and research, building partnerships with advocacy groups and industry stakeholders, and fostering new and innovative collaborative research to move the field forward. Our inaugural symposium in 2024 brought together over 50 stakeholders from across the country and beyond, laying the foundation for a stronger, more connected national community.

As we look ahead, CARELeuko is committed to expanding our network, developing national infrastructure such as clinical registries, and care pathways, and ensuring that the voices of patients and families remain central to everything we do. Together, we aim to create a future in which every individual affected by a leukodystrophy in Canada receives timely diagnosis, comprehensive care, and access to the latest scientific advances.

To learn more or get involved, please visit https://careleuko.org or reach out to us at careleuko@muhc.mcgill.ca.

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CARELeuko SYMPOSIUM 2025

Symposium CARELeuko 2025

Vendredi le 5 décembre | 7h30 à 17h30

7h30 à 8h30 — **Enregistrement et déjeuner**

8h30 à 8h40 — **Mot de bienvenue**
Dre Geneviève Bernard, MD, MSc, FRCPc (Centre universitaire de santé McGill)

8h40 à 9h05 — **Contexte clinique des Leukodystrophies au Canada**
Dre Sunita Venkateswaran, MD, FRCPc (London Health Sciences Centre)

1ière séance : Diagnostic précoce et précis

9h05 à 9h30 — **Séquençage du génome HiFi en longue lecture: défis, avantages et histoires de réussite chez des patients atteints de leucodystrophies**
Dre Isabelle Thiffault, PhD, FACMGG (Children's Mercy Kansas City)

9h30 à 9h55 — **Leucoencéphalopathies génétiques de l'adulte: apport du séquençage exomique/génomique et du phénotypage IRM inversé pour réduire les odyssées diagnostiques**
Justin Simo (Institut neurologique de Montréal)

9h55 à 10h20 — **Dépistage de l'adrénoleucodystrophie cérébrale infantile chez les nouveau-nés en Ontario: Résultats d'un projet pilote**
Dr Neal Sondheimer, MD, PhD (Children's Hospital of Eastern Ontario)

10h20 à 10h35 — **Pause-café**

2e séance : Recherche translationnelle en leukodystrophies

10h35 à 11h00 — **Des modèles aux thérapies : développement d'ASO pour la forme striatale de la leucodystrophie liée à POLR3**
Samuel Gauthier (Institut de recherche du Centre universitaire de santé McGill)

11h00 à 11h25 — **Que nous apprennent les oligodendrocytes dérivés de cellules souches iPSC?**
Dr Thomas Durcan, PhD (Institut neurologique de Montréal)

11h25 à 11h50 — **Développement de thérapies à base d'ARN pour l'ALSP**
Dre Jo Anne Stratton, PhD (Institut neurologique de Montréal)

11h50 à 12h15 — **Évaluation translationnelle de la thérapie génique AAV9 ciblant le système nerveux chez des souris âgées atteintes de MLD : efficacité et biodistribution interespèces**
Dre Stephanie Newman, PhD (London Health Sciences Centre)

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CARELeuko SYMPOSIUM 2025

2025 CARELeuko Symposium

Friday, December 5 | 7:30 AM - 5:30 PM

7:30 – 8:30 AM **Registration and Breakfast**

8:30 – 8:40 AM **Welcome and Opening Remarks**
Dr. Geneviève Bernard, MD, MSc, FRCPc (McGill University Health Centre)

8:40 – 9:05 AM **Clinical Landscape of Leukodystrophies in Canada**
Dr. Sunita Venkateswaran, MD, FRCPc (London Health Sciences Centre)

Session I : Early and Accurate Diagnosis

9:05 – 9:30 AM **Long-read HiFi Genome Sequencing: Pitfalls, Benefits, and Success Stories of Leukodystrophy Patients**
Dr. Isabelle Thiffault, PhD, FACMGG (Children's Mercy Kansas City)

9:30 – 9:55 AM **Adult Genetic Leukoencephalopathies: The Roles of Whole Exome/Genome Sequencing and Reverse MRI Phenotyping in Reducing Diagnostic Odysseys**
Justin Simo (Montreal Neurological Institute)

9:55 – 10:20 AM **Screening for Childhood Cerebral Adrenoleukodystrophy in Ontario Newborns - Pilot**
Dr. Neal Sondheimer, MD, PhD (Children's Hospital of Eastern Ontario)

10:20 – 10:35 AM **Coffee Break**

Session 2 : Translational Research in Leukodystrophies

10:35 – 11:00 AM **From Models to Therapies: Advancing ASO Development for the Striatal Form of POLR3-Related Leukodystrophy**
Samuel Gauthier (McGill University Health Centre Research Institute)

11:00 – 11:25 AM **What can we learn from iPSC-derived Oligodendrocytes?**
Dr. Thomas Durcan, PhD (Montreal Neurological Institute)

11:25 – 11:50 AM **Development of RNA therapies for ALSP**
Dr. Jo Anne Stratton, PhD (Montreal Neurological Institute)

11:50 – 12:15 PM **Translational Evaluation of AAV9 Gene Therapy for Nervous System Targeting in Aged MLD Mice: Efficacy and Cross-Species Biodistribution**
Dr. Stephanie Newman, PhD (London Health Sciences Centre)

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12h15 à 13h45 **Dîner et séance de présentation d'affiches**
(Début de la présentation d'affiches à 12h45)

13h45 à 14h10 **Immunologie dans les leucodystrophies: un modèle de collaboration en science**
Dr Donald C. Vinh, MD, FRCPc, FACP (Centre universitaire de santé McGill)

3e séance : Recherche clinique et impact familial

14h10 à 14h35 **Prise en charge symptomatique des enfants atteints de leucodystrophies: l'impact de la collaboration sur la qualité de vie**
Dre Laurence Gauquelin, MD (CHU de Québec - Université Laval)

14h35 à 15h00 **Du diagnostic à l'espoir: le parcours d'une famille engagée dans le plaidoyer pour les leucodystrophies**
Riham Badawy (ALD Hope)

15h00 à 15h30 **Période de questions avec les représentants des patients**
Modératrices: Sabrina Alam, PhD and Ruwan Bedeir

15h30 à 15h45 **Pause-café**

4e séance : Collaboration transfrontalière

15h45 à 16h10 **Développer l'infrastructure de recherche et de soins sur la leucodystrophie**
Dre Adeline Vanderver, MD (Children's Hospital of Philadelphia)

16h10 à 16h35 **RareKids-CAN: un réseau canadien pour les essais cliniques et les traitements en maladies pédiatriques rares**
Dr Thierry Lacaze-Masmonteil, MD, PhD (RareKids-CAN)

16h35 à 17h00 **Programme d'éducation et de dépistage des porteurs de l'encéphalite crie et de la leucoencéphalopathie crie dans les communautés cries de la Baie-James (région de James Bay)**
Dre Anne-Marie Laberge, MD, PhD (CHU-Ste Justine) and Martine Roberge, RN (Conseil cri de la santé et des services sociaux de la Baie James)

17h00 à 17h10 **Perspective des familles autochtones**
Famille de la Nation crie

17h10 à 17h30 **Remarques finales**
Dre Roberta La Piana, MD, PhD (Institut neurologique de Montréal)

12:15 – 1:45 PM **Lunch and Poster Session**
(Poster session begins at 12:45 PM)

1:45 – 2:10 PM **Immunology in Leukodystrophies: A Model for Synergy in Science**
Dr. Donald C. Vinh, MD, FRCPc, FACP (McGill University Health Centre)

Session 3 : Clinical Research and Family Impact

2:10 – 2:35 PM **Symptomatic Care of Children with Leukodystrophies: How Collaboration Improves Quality of Life**
Dr. Laurence Gauquelin, MD (CHU de Québec - Université Laval)

2:35 – 3:00 PM **From Diagnosis to Hope: A Family's Journey Shaping Leukodystrophy Advocacy**
Riham Badawy (ALD Hope)

3:00 – 3:30 PM **Patient Representative Q&A**
Moderators: Sabrina Alam, PhD and Ruwan Bedeir

3:30 – 3:45 PM **Coffee Break**

Session 4 : Cross-National-Border Collaboration

3:45 – 4:10 PM **Developing Leukodystrophy Research and Care Infrastructure**
Dr. Adeline Vanderver, MD (Children's Hospital of Philadelphia)

4:10 – 4:35 PM **RareKids-CAN: A Canadian Pediatric Rare Disease Clinical Trial and Treatment Network**
Dr. Thierry Lacaze-Masmonteil, MD, PhD (RareKids-CAN)

4:35 – 5:00 PM **Cree Encephalitis and Cree Leukencephalopathy Education and Carrier Screening Program in Cree communities of James Bay**
Dr. Anne-Marie Laberge, MD, PhD (CHU-Ste Justine) and Martine Roberge, RN (Cree Board of Health and Social Services of James Bay)

5:00 – 5:10 PM **Indigenous Family Perspective**
Family from Cree Nation

5:10 – 5:30 PM **Closing Remarks**
Dr. Roberta La Piana, MD, PhD (Montreal Neurological Institute)

CONFÉRENCIERS | CONFÉRENCIÈRES | SPEAKERS

Dr. Geneviève Bernard
MD, MSc, FRCPC

La Dre Geneviève Bernard est neurologue pédiatrique et chercheuse principale à l'Hôpital de Montréal pour enfants, au Centre universitaire de santé McGill (CUSM) et à l'Institut de recherche du CUSM. Elle est professeure titulaire aux départements de neurologie et de neurochirurgie ainsi que de pédiatrie de l'Université McGill et membre associée du Département de génétique humaine. Elle est reconnue internationalement pour son approche « du chevet au laboratoire et retour au chevet ». Le programme de recherche de la Dre Bernard se concentre sur la recherche translationnelle dans le domaine des leucodystrophies, en particulier les troubles hypomyélinisants. Ses travaux portent sur la découverte de gènes, l'étude des mécanismes physiopathologiques, le développement de thérapies et les essais cliniques. Son équipe a identifié plusieurs gènes responsables de maladies, notamment ceux responsables de la leucodystrophie liée au gène POLR3, et a mené des études déterminantes caractérisant ses caractéristiques cliniques, radiologiques, génétiques et physiopathologiques.

Dr. Geneviève Bernard is a pediatric neurologist and senior scientist at the Montreal Children's Hospital, McGill University Health Centre (MUHC), and MUHC Research Institute. She is a Full Professor in the departments of Neurology and Neurosurgery and Pediatrics at McGill University and an associate member of the Department of Human Genetics. Internationally recognized for her bedside-to-bench-to-bedside approach, Dr. Bernard's research program focuses on translational research in leukodystrophies, particularly hypomyelinating disorders. Her work spans gene discovery, pathophysiological mechanisms, therapeutic development, and clinical trials. Her team has identified several disease-causing genes, including those responsible for POLR3-related leukodystrophy, and has led pivotal studies characterizing its clinical, radiological, genetic, and pathophysiological features.

Dr. Sunita Venkateswaran
MD, FRCPC

La Dre Sunita Venkateswaran est neurologue pédiatrique et professeure agrégée au département de pédiatrie de l'Université Western. Elle a rejoint la Division de neurologie et des sciences neurologiques cliniques de l'Hôpital pour enfants en 2022 et occupe le poste de chercheuse associée à l'Institut de recherche en santé infantile. La Dre Venkateswaran participe activement à plusieurs collaborations de recherche nationales et internationales axées sur les leucodystrophies, les troubles du mouvement, la sclérose en plaques pédiatrique et la neurodégénérescence avec accumulation de fer dans le cerveau (NBIA). Elle dirige des efforts de recherche internationaux sur la neurodégénérescence associée à l'hydroxylase des acides gras (FAHN/SPG35), une forme de NBIA et de leucodystrophie. Elle fournit également des soins à de jeunes adultes atteints de troubles de la substance blanche non diagnostiqués grâce à sa participation à l'initiative White Matter Rounds et à CARELeuko, deux réseaux canadiens.

Dr. Sunita Venkateswaran is a pediatric neurologist and associate professor in the Department of Paediatrics at Western University. She joined the Division of Neurology and Clinical Neurological Sciences at the Children's Hospital in 2022 and serves as an Associate Scientist at the Child Health Research Institute. Dr. Venkateswaran is actively involved in several national and international research collaborations focused on leukodystrophies, movement disorders, pediatric multiple sclerosis, and neurodegeneration with brain iron accumulation (NBIA). She leads international research efforts on fatty acid hydroxylase-associated neurodegeneration (FAHN/SPG35), a form of NBIA and leukodystrophy. She also provides care for young adult patients with undiagnosed white matter disorders through her involvement with the White Matter Rounds Initiative and CARELeuko, both Canadian-led networks.

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CONFÉRENCIERS | CONFÉRENCIÈRES | SPEAKERS

Dr. Isabelle Thiffault
PhD, FACMGG

Je suis directrice adjointe du laboratoire clinique et directrice de la génétique translationnelle au Genomic Medicine Center (GMC) du Children's Mercy Research Institute depuis 2014. En tant que directrice de la génétique translationnelle du GMC, j'ai eu l'occasion de contribuer à l'élaboration de notre programme, notamment des outils génomiques utilisés par notre équipe d'analyse. Ces outils ont facilité la mise en œuvre du séquençage du génome entier et de l'exome pour les tests cliniques et la recherche dans notre hôpital. J'ai codirigé l'analyse et l'interprétation des données de séquençage nouvelle génération (NGS). Ce travail a abouti à une preuve de concept historique : STATSeq, ou « génome rapide », un concept que de nombreux laboratoires ont ensuite commencé à imiter. Notre programme de recherche Genomic Answers for Kids (GA4K) est en train de transformer le domaine de la génomique pédiatrique grâce à ce qui est peut-être le système le plus avancé au monde pour le diagnostic des maladies rares. À la suite de notre initiative de recherche, nous avons achevé la validation clinique du séquençage du génome HiFi, et nous sommes le premier centre à le proposer comme test génomique clinique pour les patients gravement malades.

I serve as an Assistant Director of the Clinical laboratory and Director of Translational Genetics at Genomic Medicine Center (GMC) at Children's Mercy Research Institute since 2014. As the Director of Translational Genetics of the GMC, I had the opportunity to help shape the design of our program, including the genomic tools used by our analysis team. These tools facilitated the implementation of whole genome and exome sequencing for clinical and research testing in our hospital. The analysis and interpretation of the NGS data were co-led by me. This work led to a landmark proof-of-concept "STATSeq or rapid genome" a concept many labs have subsequently begun to emulate. Our Genomic Answers for Kids research program is changing the landscape of pediatric genomics through what may be the most advanced system for rare disease diagnosis in the world (GA4K). Following our research initiative, we completed the clinical validation of HiFi genome sequencing, and we are the first center offering it as clinical genomic testing for critically ill patients.

Justin Simo
Ph.D. Candidate

Justin Simo est doctorant dans le laboratoire du Dr Roberta La Piana à The Neuro (Institut et hôpital neurologiques de Montréal). En tant que neurogénéticien moléculaire en formation, Justin analyse les séquences génomiques de sujets adultes non diagnostiqués soupçonnés d'être atteints de leucoencéphalopathies génétiques avec un processus multiforme qui intègre les antécédents cliniques détaillés et les caractéristiques de l'IRM cérébrale de chaque sujet recruté. À ce titre, il a identifié plusieurs nouveaux diagnostics génétiques et ultra-rares qui ont grandement amélioré notre compréhension des mécanismes biologiques fondamentaux qui déterminent la santé de la substance blanche. Il étudie actuellement un sous-ensemble de ces diagnostics dans le cadre de son projet de doctorat, en s'appuyant sur une grande variété de techniques cellulaires et moléculaires.

Justin Simo is a Ph.D. candidate in the laboratory of Dr. Roberta La Piana at The Neuro (Montreal Neurological Institute-Hospital). As a molecular neurogeneticist in training, Justin analyzes the genome sequences of undiagnosed adult subjects with suspected genetic leukoencephalopathies, a multifaceted process that incorporates the detailed clinical history and brain MRI features of each recruited subject. In this capacity, he has identified multiple novel, ultra-rare genetic diagnoses that have serendipitously broadened our understanding of fundamental biological mechanisms influencing white matter health. He is currently investigating a subset of these as part of his doctoral project, leveraging a wide variety of cellular and molecular techniques.

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CONFÉRENCIERS | CONFÉRENCIÈRES | SPEAKERS

Dr. Neal Sondheimer
MD, PhD

Le Dr Sondheimer est généticien clinique et métabolique. Il a suivi une formation spécialisée à l'Hôpital pour enfants de Philadelphie. Il est professeur agrégé au département de pédiatrie de l'Université d'Ottawa et fait partie du personnel médical de l'Hôpital pour enfants de l'est de l'Ontario (CHEO). Sa recherche porte principalement sur les traitements des erreurs innées, le dépistage néonatal et l'impact des variants de séquence de l'ADN mitochondrial sur les maladies courantes et rares. Le Dr Sondheimer a rejoint la NSO en 2024 et en est le directeur médical.

Dr. Sondheimer is a clinical and metabolic geneticist. He completed his subspecialty training at The Children's Hospital of Philadelphia. He is an Associate Professor at the University of Ottawa in the Department of Paediatrics and is on the medical staff of The Children's Hospital of Eastern Ontario (CHEO). His research has focused on therapies for inborn errors, newborn screening, and the impact of mitochondrial DNA sequence variants on common and rare disease. Dr. Sondheimer joined NSO in 2024 and serves as its medical director

Samuel Gauthier
Ph.D. Candidate

Samuel Gauthier est doctorant en génétique humaine à l'Université McGill. Il a obtenu son diplôme de premier cycle en génétique moléculaire à l'Université de Rochester, où il a obtenu une mention d'excellence en recherche pour ses travaux sur le développement de cellules gliales hypoimmunogènes pour les études de transplantation, dans le laboratoire de Steven A. Goldman. S'appuyant sur son expérience, Samuel concentre ses études doctorales au sein du laboratoire de Geneviève Bernard sur les maladies liés à l'ARN polymérase III (POLR3-RD), un groupe de troubles neurologiques rares. Ses travaux portent sur la modélisation des maladies à l'aide de cellules souches pluripotentes induites dérivées de patients, le développement de stratégies thérapeutiques ciblées basées sur l'ARN et des études épidémiologiques visant à mieux définir la prévalence et le spectre clinique des POLR3-RD. Son objectif à long terme est de faire le lien entre les connaissances mécanistiques et le développement thérapeutique, afin de contribuer à une meilleure compréhension des leucodystrophies et de faire progresser les efforts vers des traitements efficaces.

Samuel Gauthier is a PhD Candidate in Human Genetics at McGill University. He completed is undergraduate degree in Molecular Genetics at the University of Rochester where he received Honors in Research for his work in Steven A. Goldman's lab on developing hypoimmunogenic glial cells for transplantation studies. Building on his background, his doctoral studies in Geneviève Bernard's lab focuses on RNA Polymerase III-related disorders (POLR3-RD), a group of rare neurological disorders. His work spans disease modeling using patient-derived induced pluripotent stem cells, the development of targeted RNA-based therapeutic strategies, and epidemiological studies to better define the prevalence and clinical spectrum of POLR3-RD. His long-term goal is to bridge mechanistic insights and therapeutic development, contributing to better understanding of leukodystrophies and advancing efforts towards effective treatments.

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CONFÉRENCIERS | CONFÉRENCIÈRES | SPEAKERS

Dr. Thomas Durcan

PhD

Le Dr Thomas M. Durcan est professeur agrégé à l'Institut neurologique de Montréal (The Neuro) et à l'Université McGill. Il est également directeur de l'Unité de découverte précoce de médicaments (EDDU) du Neuro, qui se consacre à l'utilisation de cellules souches pluripotentes induites humaines (iPSC) pour mener des projets de recherche fondamentale et translationnelle en partenariat avec le milieu universitaire et l'industrie. Fondé il y a moins de dix ans, son groupe a établi une cohorte de plus de 220 lignées iPSC, qui ont été intégrées à différents projets de recherche au sein de l'équipe et ont permis de générer un vaste éventail de sous-types neuronaux et gliaux, ainsi que des modèles d'organoïdes cérébraux 3D plus avancés. Lors de sa présentation, le Dr Durcan s'intéressera au développement et à la caractérisation des oligodendrocytes, ainsi qu'à la manière dont ces cellules peuvent être utilisées dans les travaux de découverte et de recherche translationnelle.

Dr. Thomas M. Durcan is an Associate Professor within the Montreal Neurological Institute (The Neuro) and McGill University. He is also Director of the Neuro's Early Drug Discovery Unit (EDDU), focused on the use of human induced pluripotent stem cells (iPSCs) for fundamental and translational discovery project through partnerships with academia and industry. Founded under a decade ago, the group has established a cohort of 220+ iPSCs that have been advanced into different projects within the group and used to generate a wide range of neuronal and glial subtypes, in addition to more advanced 3D brain organoid models. For the talk, Dr. Durcan will focus on the development and characterization of Oligodendrocytes and how they can be applied in discovery and translational work.

Dr. Jo Anne Stratton

PhD

La Dre Stratton est professeure adjointe à l'Université McGill et codirectrice du groupe de recherche sur les maladies neuroimmunologiques et la biologie des cellules gliales. Elle se spécialise dans les technologies biomédicales de pointe, notamment dans l'application des technologies omiques les plus avancées, les tests in vitro, la modélisation animale et l'analyse des cellules et tissus humains. Elle étudie de manière critique les cellules gliales à l'aide d'iPSC dans le contexte de maladies gliales définies, en se concentrant sur les affections monogéniques, pour lesquelles les patients présentant des variants génétiques ont déjà été identifiés et caractérisés. Son laboratoire génère des iPSC à partir de ces patients et utilisons ces modèles pour la recherche mécanistique et le développement de médicaments, en se concentrant sur l'essai de méthodes d'administration bien tolérées et permettant un chargement flexible, telles que les nanoparticules.

Dr. Stratton is an Assistant Professor at McGill University and Co-Director of the Neuroimmunological Diseases & Glia Biology Research Group. She specializes in advanced biomedical technologies, including in the application of the most advanced omics technologies, in vitro assays, animal modeling, and human cell/tissue analysis. Critically, we study glia using iPSCs in the context of defined glial-related diseases, with a focus on monogenic conditions, where patients with genetic variants are already identified and characterized. We generate iPSCs from these patients and use these models for mechanistic research and drug development with a focus on testing delivery methods that are well tolerated with flexible cargo loading, such as nanoparticles.

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Dr. Stephanie Newman
PhD

La Dre Stephanie Newman est professeure adjointe au département de pathologie et de médecine de laboratoire de l'Université Western et scientifique de laboratoire clinique au London Health Sciences Centre. Elle a obtenu son doctorat à l'Université d'Oxford et se spécialise dans la génétique biochimique, l'enzymologie lysosomale et les maladies lysosomales rares. Le travail clinique du Dr Newman se concentre sur les tests diagnostiques et l'interprétation des troubles du stockage lysosomal, tandis que ses recherches, soutenues par la Fondation pour la recherche Bethany's Hope, visent à développer des traitements de thérapie génique pour la leucodystrophie métachromatique, une maladie neurodégénérative rare de l'enfance. Ses contributions scientifiques comprennent des études sur la fonction lysosomale, la maladie de Niemann-Pick et des approches thérapeutiques innovantes. Passionnée par le rapprochement entre la recherche et la pratique clinique, le Dr Newman s'engage à faire progresser le diagnostic et les thérapies des maladies rares grâce à la collaboration et à l'innovation.

Dr. Stephanie Newman is an Assistant Professor in the Department of Pathology and Laboratory Medicine at Western University and a Clinical Laboratory Scientist at London Health Sciences Centre. She earned her PhD from the University of Oxford and specializes in biochemical genetics, lysosomal enzymology, and rare lysosomal storage disorders. Dr. Newman's clinical work focuses on diagnostic testing and interpretation for lysosomal storage disorders, while her research, supported by Bethany's Hope Research Foundation, aims to develop gene therapy treatments for metachromatic leukodystrophy, a rare childhood neurodegenerative disease. Her scholarly contributions include studies on lysosomal function, Niemann-Pick disease, and innovative therapeutic approaches. Passionate about bridging research and clinical practice, Dr. Newman is committed to advancing diagnostics and therapies for rare disorders through collaboration and innovation.

Dr. Donald C. Vinh
MD, FRCPC, FACP

Le Dr Vinh est spécialiste des maladies infectieuses et microbiologiste médical au Centre universitaire de santé McGill, où il occupe le poste de chef de section du programme Maladies infectieuses – Hématologie/Oncologie/Transplantation. Il est également clinicien-chercheur principal financé par la province à l'Institut de recherche du Centre universitaire de santé McGill, où il dirige un programme de recherche translationnelle sur la susceptibilité génétique humaine aux infections. Ses travaux ont permis de définir de nouvelles erreurs innées de l'immunité et des troubles médiés par des auto-anticorps qui sous-tendent la vulnérabilité aux maladies mycobactériennes, virales et fongiques. Il a notamment apporté des contributions fondamentales à la compréhension du déficit en GATA2, du déficit en CARD9, du déficit en ICOSL, des déterminants génétiques et auto-anticorps de la gravité de la COVID-19 et des causes génétiques des troubles lymphoprolifératifs associés à l'EBV. Il est membre de la Société d'immunologie clinique et de la Société américaine des maladies infectieuses, et membre élu de la Société Henry Kunkel. Ses recherches font le lien entre les soins cliniques et les découvertes moléculaires afin d'améliorer les résultats pour les patients immunodéprimés.

Dr. Vinh is an Infectious Disease specialist and Medical Microbiologist at the McGill University Health Centre, where he serves as Section Chief of the Infectious Diseases–Hematology/Oncology/Transplant program. He is also a provincially funded Senior Clinician-Scientist at the Research Institute of the McGill University Health Centre, leading a translational research program on human genetic susceptibility to infection. His work has defined novel inborn errors of immunity and autoantibody-mediated disorders underlying vulnerability to mycobacterial, viral, and fungal diseases. This includes seminal contributions to the understanding of GATA2 deficiency, CARD9 deficiency, ICOSL deficiency, genetic and autoantibody determinants of COVID-19 severity, and genetic causes of EBV-associated lymphoproliferative disorders. He is a Fellow of the Clinical Immunology Society and the Infectious Diseases Society of America, and an elected member of the Henry Kunkel Society. His research bridges clinical care and molecular discovery to improve outcomes for immunocompromised patients.

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Dr. Laurence Gauquelin

MD, FRCPC

La Dre Laurence Gauquelin est une neurologue pédiatrique qui travaille actuellement au CHU de Québec – Université Laval, à Québec. Elle a terminé sa résidence à l'Université McGill en 2018, puis a poursuivi une formation clinique et de recherche en génomique avancée dans le domaine des maladies pédiatriques rares à l'Hôpital pour enfants malades, affilié à l'Université de Toronto. La Dre Gauquelin participe régulièrement aux soins cliniques d'enfants atteints de troubles neurogénétiques rares. Elle s'intéresse particulièrement aux troubles génétiques du mouvement et aux maladies neurodégénératives. Elle participe à la prise en charge collaborative d'enfants atteints de leucodystrophies et de leurs familles, en collaboration avec d'autres professionnels de la santé et chercheurs.

Dr. Laurence Gauquelin is a paediatric neurologist currently working at the CHU de Québec – Université Laval, in Québec. She completed residency training at McGill University in 2018, then pursued a clinical and research fellowship in advanced genomics in paediatric rare disease at The Hospital for Sick Children, affiliated with the University of Toronto. Dr. Gauquelin is regularly involved in the clinical care of children with rare neurogenetic disorders. Her specific interests focus on genetic movement disorders and neurodegenerative diseases. She participates in collaborative care of children with leukodystrophies and their families together with other health-care providers and researchers.

Riham Badawy

(ALD Hope)

Riham Badawy est cofondatrice et PDG d'ALD Hope, un organisme canadien à but non lucratif qui se consacre à la sensibilisation, au soutien des familles et à la promotion de la recherche sur l'adrénoleucodystrophie (ALD) et sur l'insuffisance surrénale. Elle a transformé le parcours de sa famille en une mission visant à autonomiser les autres par l'éducation, la défense des droits et le soutien communautaire. Sous sa direction, ALD Hope a lancé des campagnes de sensibilisation, développé des ressources éducatives et favorisé la collaboration internationale avec des organisations spécialisées dans les maladies rares. Elle est membre active de l'Organisation canadienne des maladies rares (CORD), de la Société canadienne d'Addison, d'ALD Connect, de l'ALD Alliance, de Rare Diseases International et d'autres réseaux internationaux, où elle s'efforce de faire entendre la voix des patients dans la recherche et les politiques. Passionnée par le rapprochement entre les familles, les chercheurs et les prestataires de soins de santé, Riham s'engage à faire en sorte que les perspectives des patients guident l'innovation et les soins. Son travail reflète sa conviction profonde que, malgré la rareté de l'ALD, la collaboration et l'espoir sont de puissants moteurs de changement.

Riham Badawy is the Co-Founder and CEO of ALD Hope, a Canadian nonprofit organization dedicated to raising awareness, supporting families, and advancing research for adrenoleukodystrophy (ALD) and adrenal insufficiency. She transformed her family's journey into a mission to empower others through education, advocacy, and community support. Under her leadership, ALD Hope has launched awareness campaigns, developed educational resources, and advanced international collaboration with rare disease organizations. She is an active member of the Canadian Organization for Rare Disorders (CORD), the Canadian Addison Society, ALD Connect, ALD Alliance, Rare Diseases International and other international networks, where she works to amplify the patient voice in research and policy. Passionate about bridging the gap between families, researchers, and healthcare providers, Riham is committed to ensuring patient perspectives guide innovation and care. Her work reflects a core belief that while ALD is rare, collaboration and hope are powerful forces for change.

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Dr. Adeline Vanderver

MD

La Dre Adeline Vanderver, M.D., est professeure de neurologie à la division de neurologie de l'hôpital pour enfants de Philadelphie (CHOP), au département de neurologie de la Perelman School of Medicine de l'Université de Pennsylvanie et titulaire de la chaire Jacob A. Kamens en troubles neurologiques et neurothérapie translationnelle. Elle est également directrice du programme du Centre d'excellence en leucodystrophie du CHOP. Sous la direction de la Dre Vanderver, l'équipe multidisciplinaire du Centre de leucodystrophie se concentre sur la création de nouvelles normes de soins pour les enfants atteints de leucodystrophies en faisant progresser la découverte des gènes responsables de la leucodystrophie, en créant de nouvelles thérapies et en soutenant et défendant les patients et leurs familles. Conjointement à ce programme clinique solide, les projets de recherche préclinique et clinique de la Dre Vanderver visent à découvrir des thérapies moléculaires ciblant la génétique des sous-types de leucodystrophie. Outre ses activités cliniques et de recherche, la Dre Vanderver dirige la Global Leukodystrophy Initiative, un consortium financé par les NIH qui regroupe des parents, des cliniciens et des chercheurs, afin de sensibiliser le public à ces maladies, de préparer des essais cliniques et d'étudier l'histoire naturelle des leucodystrophies.

Dr. Adeline Vanderver, M.D. is a Professor of Neurology in the Division of Neurology at the Children's Hospital of Philadelphia (CHOP), the Department of Neurology at the Perelman School of Medicine, University of Pennsylvania and the Jacob A. Kamens Endowed Chair in Neurologic Disorders and Translational Neurotherapeutics. She is also Program Director of the Leukodystrophy Center of Excellence at CHOP. Under Dr. Vanderver's leadership, the multidisciplinary Leukodystrophy Center team is focused on creating new standards of care for children with leukodystrophies by advancing leukodystrophy gene discovery, creating new therapies, and supporting and advocating for patients and their families. In parallel with this strong clinical program, Dr. Vanderver's preclinical and clinical research projects will aim to discover molecular therapeutics that target the genetics of leukodystrophy subtypes. In addition to her clinical and research efforts, Dr. Vanderver leads the Global Leukodystrophy Initiative, an NIH funded consortium that includes parents, clinicians and researchers, to raise disease awareness, create clinical trial readiness, and explore natural history of the leukodystrophies.

Dr. Thierry Lacaze-Masmonteil

MD, PhD

Le Dr Thierry Lacaze est chercheur principal désigné du réseau RareKids-CAN : Réseau d'essais cliniques et de traitement des maladies rares pédiatriques, et directeur scientifique du Réseau de recherche sur la mère, l'enfant et le jeune depuis 2018. Le Dr Lacaze est néonatologiste de formation et professeur clinique de pédiatrie à l'Université de Calgary.

Dr. Thierry Lacaze is the RareKids-CAN: Pediatric Rare Disease Clinical Trials and Treatment Network Nominated Principal Investigator and the Scientific Director of the Maternal Infant Child and Youth Research Network since 2018. Dr. Lacaze is a neonatologist by training and Clinical Professor of Pediatrics at the University of Calgary.

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Dr. Anne-Marie Laberge
MD, PhD

La Dre Laberge est généticienne médicale et cheffe de la division de génétique médicale au CHU Sainte-Justine, ainsi que professeure au département de pédiatrie et au département de médecine sociale et préventive de l'École de santé publique de l'Université de Montréal. Elle a obtenu son doctorat en médecine et effectué sa résidence en génétique médicale à l'Université de Montréal. Elle a ensuite obtenu une maîtrise en santé publique avec une spécialisation en génétique, sur les facteurs prédictifs du succès des programmes de dépistage des porteurs, et un doctorat en génétique avec une spécialisation en santé publique, sur l'utilité clinique des tests génétiques et le rôle des lignes directrices dans la définition des normes de soins, tous deux à l'Université de Washington. La Dre Laberge est actuellement présidente du Comité consultatif québécois sur le dépistage néonatal, du Groupe de travail sur les découvertes fortuites du Réseau de diagnostic moléculaire du Québec et du tout nouveau Comité central d'éthique québécois sur la procréation médicalement assistée. Ses recherches actuelles portent notamment sur l'évaluation des programmes de dépistage des porteurs au Québec et sur l'utilité clinique et le point de vue des patients/parents et des cliniciens concernant le séquençage de l'exome et du génome en pédiatrie.

Dr. Laberge is a Medical Geneticist and Head of the Division of Medical Genetics at CHU Ste-Justine, and Professor in the Department of Pediatrics and in the Department of Social and Preventive Medicine at the School of Public Health at the University of Montreal. She completed her MD and her residency in Medical Genetics at Université de Montréal. She then completed an MPH in Public Health Genetics, on the factors predicting the success of carrier screening programs, and a PhD in Public Health Genetics, on the clinical utility of genetic tests and the role of guidelines in defining standard of care, both at the University of Washington. Dr Laberge is currently Chair of the Quebec Advisory Committee on Newborn Screening, of the Quebec Molecular Diagnosis Network Incidental Findings Working Group and of the newly formed Quebec Central Ethics Committee on Medically Assisted Reproduction. Her current research includes an assessment of carrier screening programs in Quebec and evaluations of the clinical utility and patient/parent and clinician perspectives of exome and genome sequencing in pediatric care.

Martine Roberge
RN

Martine Roberge est infirmière-conseillère pour le Programme d'éducation et de dépistage des porteurs de la leucoencéphalopathie crie (CLE) et de l'encéphalite crie (CE).

Martine Roberge is a nurse counsellor for the Cree Leucoencephalopathy (CLE) and Cree Encephalitis (CE) Education and Carrier Screening Program

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Dr. Roberta La Piana
MD, PhD

La Dre La Piana a obtenu son doctorat en médecine à l'Université de Pavie, en Italie, où elle s'est spécialisée en neurologie et en psychiatrie pédiatriques. Elle a complété un doctorat en neurosciences à l'Université McGill. Après avoir travaillé pendant plus de 10 ans sur les leucodystrophies pédiatriques, la Dre La Piana s'est intéressée aux maladies génétiques de la substance blanche chez l'adulte et a développé un profil interdisciplinaire combinant son expertise en imagerie et en génétique avec sa formation clinique. Ses travaux ont conduit à la découverte de phénotypes en expansion de plusieurs leucodystrophies de l'adulte et à l'identification de nouvelles variantes responsables de maladies. Parmi les nombreuses leucodystrophies apparaissant à l'âge adulte, son équipe s'est particulièrement intéressée aux troubles liés au CSF1R. En collaboration avec d'autres laboratoires du Neuro, le laboratoire de la Dre La Piana a mis au point un nouveau protocole permettant de différencier les microglies issues d'iPSC dérivées de patients présentant une mutation du CSF1R. En 2013, elle a lancé les White Matter Rounds. Ces réunions interdisciplinaires mensuelles, qui avaient pour but de discuter des manifestations atypiques des maladies de la substance blanche, ont évolué pour devenir un réseau international regroupant des chercheurs et des cliniciens de plus de 15 centres à travers le monde.

Dr. La Piana earned her MD at University of Pavia, Italy, where she then specialized in Pediatric Neurology and Psychiatry. She completed her PhD in Neuroscience at McGill University. After working on pediatric leukodystrophies for more than 10 years, Dr. La Piana became interested in adult-onset genetic white matter diseases and developed an interdisciplinary profile which combines expertise in imaging and genetics with her clinical training. This work has led to the discovery of expanding phenotypes of several adult leukodystrophies and the identification of novel disease-causing variants. Among the many adult-onset leukodystrophies, her team developed a specific interest in CSF1R-related disorder. In collaboration with other labs at the Neuro, Dr. La Piana's lab developed a novel protocol to differentiate microglia from CSF1R-mutated patient-derived iPSCs. In 2013 she launched the White Matter Rounds. These interdisciplinary monthly meetings aimed to discuss atypical white matter disease presentations have evolved into an international Network including researchers and clinicians from more than 15 centers around the world.

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Report of Ethnic and Geographic Origins in Scientific Papers on Mitochondrial Leukoencephalopathies mimicking multiple sclerosis: A Literature Review

Lanyun Wu, BSc Student1, Rachel Levin, MD Student1, Hanifa Hasan, Master Student1, Roberta La Piana, PI2,1

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Background: The mention of a patient's ancestry is crucial in general and in leukodystrophies specifically, since it provides researchers with genetic variation indications and helps future researchers to compare between different population groups. This is especially relevant in Canada, where distinct populations such as French Canadians and Indigenous communities have unique genetic architectures. For instance, some leukodystrophies have specific phenocopies in Canadian Indigenous populations and others have founder effects in the French Canadian population. However, key terminologies such as "race", "ethnicity" and "ancestry" lack a consensus definition in scientific research. Race is widely acknowledged to be a social rather than a biological construct. Ethnicity is a construct that encompasses common cultural characteristics; it may also reflect common ancestry or geographic origin. Ancestry can be defined geographically, genealogically, or genetically. The interchangeable use of these terms can result in misclassification of research participants and mislead genetic association. **Aim**: As part of a larger literature review study on mitochondrial leukoencephalopathies mimicking multiple sclerosis (MS), our project aimed to assess the rate to which ethnicity and ancestry are reported in scientific papers on these rare disorders. **Methods**: We performed a literature review by screening a total of 182 articles in MEDLINE, Scopus, ProQuest and Web of Science under the supervision of McGill Librarians. 44 articles were excluded since they were qualitative reviews. Any mention of ethnic, ancestry, and publication years was recorded; mention of race was excluded because it did not provide genetic insights into patients' backgrounds. Statistical analysis indicates a linear increase in reporting ethnic origin over time. **Results**: Of the 138 included articles on Mitochondrial Leukoencephalopathies mimicking MS, 61 articles (44%) contained mention of ethnic or ancestral origin. 77 articles (56%) did not mention any type of origin. Statistic analysis indicated that ancestry reporting is on the rise in recent years. **Discussion**: The growing inclusion of ancestry information in studies of mitochondrial leukoencephalopathies mimicking MS reflects increasing awareness of its importance for genetic interpretation. Standardized reporting is relevant in the field of leukodystrophies, where certain populations — including French Canadian founder populations and Indigenous communities in Canada — exhibit distinct genetic profiles.

Estimating the Prevalence of POLR3-Related Disorders Through Integrated Genomic Approaches

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RNA Polymerase III-related disorders (POLR3-RDs) are a heterogeneous group of disease forms caused by biallelic pathogenic variants in genes encoding subunits of RNA Polymerase III. Despite a growing patient cohort and comprehensive genotype-phenotype analyses, population-level prevalence estimates remain limited and often confounded by overlapping phenotypes and variant misclassification. This project aims to generate refined, genotype-informed prevalence estimates ofPOLR3-RDs using integrated genomic approaches. By combining data from the largest curated clinical cohort with allele frequencies from gnomAD and CARTaGENE, we implemented an adapted Hardy-Weinberg model incorporating both homozygous and compound heterozygous genotypes. Variant classification followed ACMG/AMP guidelines with automated and manual curation, allowing for comparison of phenotype-restricted and phenotype-agnostic prevalence across populations. Preliminary results indicate a global prevalence of approximately 1-2 per 100,000, with enrichment in non-Finnish European groups, and a founder effect in the French-Canadian population. Our data reveal distinct population-specific variant distributions and highlight potential underdiagnosed cohorts, particularly within *POLR1C*- and *POLR3A*-associated disease. This work provides the first comprehensive prevalence model for POLR3-RDs, establishing a foundation for clinical trial readiness, improved diagnostic interpretation, and future epidemiological studies across rare diseases.

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Prevalence of clinically relevant variants in clinical next-generation sequencing panels of patients with suspected genetic leukoencephalopathies initially assessed for multiple sclerosis

Cérine Hamaidi1, Mayra Aldecoa, clinical fellow1,2,3, Pablo Iruzubieta, clinical fellow3, Bernard Brais, Director of the Rare Neurological Diseases Group, Montreal Neurological Institute3,1, Roberta La Piana, PI, Department of Neurology and Neurosurgery1,3

1 McGill University,2 MUHC,3 The Neuro(Montreal Neurological Institute)

Background: Individuals affected by rare neurological disorders often face long delays before getting a final diagnosis, and many of them remain without a diagnosis despite extensive clinical investigations. Subjects with adult genetic leukoencephalopathies have to face unique challenges in their diagnostic process, and this is partly due to these disorders frequently mimicking acquired demyelinating disorders, particularly the multiple sclerosis (MS) spectrum. **Aims and Methods**: This study aims to determine the frequency and characteristics of clinically relevant genetic variants identified through clinical next-generation sequencing (NGS) genetic tests in a cohort of adult patients initially assessed in MS clinics, for which genetic leukoencephalopathies were also considered. We included patients 1) who were initially assessed by MS specialists and then referred to the leuko clinics to exclude a genetic leukoencephalopathy, and 2) who underwent at least one NGS panel for genetic leukoencephalopathies. We developed a customized database to compile data from the clinical charts of included patients assessed at the Montreal Neurological Institute. The collected data included demographic, clinical, and genetic information. We then determined whether variants identified through NGS panels had clinical relevance compatible with the phenotype presented by each patient, particularly in those with initially suspected MS. **Results**: A total of 34 patients were included in the study (male-to-female ratio of 1:7; mean age 52). For these patients, a total of 45 NGS tests were available and reviewed. Clinically relevant variants were documented in 25/45 tests (56%), with the majority located in genes associated to brain development and myelination. Notably, half of the recurring variants were associated with mitochondrial leukoencephalopathies, including POLG, MT-CYB, and MT-ATP6. Regarding the compatibility with patients' phenotypes, 10 variants were interpreted as compatible, 12 were deemed incompatible and 3 had undetermined compatibility. **Conclusions**: Our study documented that clinically relevant variants are frequently documented in patients initially assessed in the MS clinics for which a genetic leukoencephalopathy is also considered. The high prevalence of variants in mitochondrially associated genes is particularly interesting for the shared pathophysiology between some hereditary inflammatory white matter diseases and MS.

Literature review of Tandem Repeats Associated Leukoencephalopathy

Abbe Lai1, Roberta LaPiana1

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Genetic leukoencephalopathies (GLEs) are a group of disorders characterized by white matter (WM) abnormalities. These abnormalities, often bilateral, symmetric, and either multifocal or confluent, typically appear as T2 hyperintense signals on brain MRI. Most known GLEs are caused by single nucleotide variants or copy number changes, and the diagnostic yield of next-generation sequencing (NGS) is estimated at 30-60%. Could the unsolved cases be due to tandem repeat expansions, undetectable by traditional sequencing methods? To investigate, a comprehensive literature review was conducted to determine the total number of repeat expansion disorders, and the presence of MRI abnormalities were assessed for each gene-disease pair. A PubMed search was performed with filters: "repeat expansion," "tandem repeat," "expansion syndrome," "expansion disorder," "expansion disease," while excluding "tumor" articles. The PubMed search yielded 50 publications, from which I generated a comprehensive list of 65 expansion disorders. The review of the gene-based literature found that 13 of 66 disorders have been associated with T2 WM abnormalities, ATN1, ATXN1, CNBP, DMPK, FGF14, FMR1, PHOX2B, NOTCH2NLC, NUTM2B-AS1/LOC642361, RFC1, SAMD12, TBP, and VWA1. The clinical phenotypes and patterns of WM involvement in these expansion disorders vary. The WM lesions can be focal (SAMD12), bilateral asymmetric (PHOX2B), or bilateral diffuse (NOTCH2NLC). Additionally, WM involvement in these repeat expansion disorders is often accompanied by abnormalities in other CNS structures, such as cerebellar atrophy (FGF14), cortical atrophy (ATN1), or abnormal T2 signal in the basal ganglia (TBP). Our results indicate that incorporating repeat expansions analysis could be beneficial for individuals presenting with leukoencephalopathy. Moreover, traditional NGS-based technologies may have limitations in detecting expansions in these genes, highlighting the need for more comprehensive genetic evaluation in these individuals.

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Characterization of the Dental Abnormalities in POLR3-related Leukodystrophy

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Background RNA polymerase III-related hypomyelinating leukodystrophy (POLR3-HLD) is a rare, genetically-determined neurodegenerative disorder affecting the white matter of the central nervous system. It is caused by biallelic pathogenic variants in genes encoding subunits of RNA polymerase III (Pol III), namely POLR3A, POLR3B, POLR1C, POLR3K, and POLR3D. POLR3-HLD is known colloquially as 4H leukodystrophy due to its hallmark clinical features (hypomyelination, hypodontia, and hypogonadotropic hypogonadism). Despite hypodontia being a core feature of POLR3-HLD, dental abnormalities remain underexplored in the literature. In-depth characterization of these abnormalities may improve recognition of this disorder and guide clinical management. Furthermore, identifying patterns of dental involvement in POLR3-HLD may offer insight into other rare diseases where dentition is similarly affected, contributing to more comprehensive and multidisciplinary care approaches. We therefore sought to explore and characterize the dental abnormalities observed in patients with POLR3-HLD. **Methods** We are conducting a retrospective clinical chart review of 187 genetically confirmed research patients with POLR3-HLD, using data stored in the MyeliNeuroGene Biobank and OACIS. All available medical and dental records, and panorex images are being reviewed by the research team. Collected clinical information includes the presence and timing (deciduous vs. permanent) of hypodontia, oligodontia, delayed dentition, abnormal eruption patterns, tooth shape and position, caries susceptibility, and other relevant features are being recorded. Additionally, relevant neurological (e.g., delayed development, ataxia, dysarthria, dysphagia, movement disorders, etc.) and non-neurological (e.g., endocrine, visual/ocular, craniofacial, and musculoskeletal) features are being recorded to explore possible associations with these dental abnormalities. **Results** Preliminary findings highlight the heterogeneity of dental abnormalities between patients. In addition to hypodontia, we observed frequent reports of delayed eruption, abnormal tooth shape and positioning, microdontia, and enamel discoloration. Both deciduous and permanent dentition were affected, including cases of congenital absence and significant delays. Dental anomalies were often identified in early childhood but varied considerably across individuals. **Conclusion** Our findings reinforce dental anomalies as a significant clinical component of POLR3-HLD and underscore the need for early dental screening in these patients. This work contributes to the clinical phenotyping of POLR3-HLD and highlights the importance of integrating dental assessment into the multidisciplinary management of leukodystrophies.

Modeling 4H Leukodystrophy Pathogenesis Through Conditional Polr1c Exon 3-4 Deletion in Pdgfrα⁺ Cells in mice Reveals Dual Pol I/III Impairment

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Background: POLR3-related leukodystrophy (4H leukodystrophy) is characterized by hypomyelination, hypodontia, and hypogonadotropic hypogonadism, and is caused by biallelic pathogenic variants in Pol III subunit genes. Variants in POLR1C, encoding a shared Pol I/III subunit, can cause either Treacher Collins syndrome (TCS) or hypomyelination, suggesting phenotype-specific dysfunction of Pol I or Pol III, respectively. While hypomyelination-associated variants mainly impair Pol III assembly, some 4H patients present with both hypomyelination and craniofacial features reminiscent from TCS. To dissect these contributions, we generated a conditional Polr1c exon 3-4 deletion model targeting Pdgfrα+ oligodendrocyte lineage cells. **Methods**: Polr1c loxP/loxP mice were crossed with Pdgfra-CreERT2 mice, and tamoxifen was administered at P2-P5 to induce OPC-specific recombination. Phenotypes were evaluated using histology, biochemistry, RNA-seq, behavioral testing, and imaging. **Results**: Polr1c exon 3-4 deletion caused reduced Polr1c protein level and disrupted Pol III assembly. qPCR revealed reduced Pol I- and Pol III-dependent transcripts, confirming dual polymerase dysfunction. Mutants exhibited early cortical OPC loss, impaired OPC differentiation, severe hypomyelination, craniofacial abnormalities, neurological deficits, and reduced survival. Transcriptomic analysis showed marked p53 activation and neuroinflammatory pathways. p53 deletion rescued OPC loss but failed to restore myelination, indicating p53-dependent OPC survival defects and p53-independent myelination deficits. **Conclusions**: This OPC-targeted Polr1c exon 3-4 deletion model recapitulates key features of 4H leukodystrophy and demonstrates that dual Pol I/III dysfunction contributes to pathology beyond Pol III-specific defects. The findings identify p53-mediated OPC depletion and Pol III translation defects as central mechanisms, revealing new therapeutic targets for POLR1C-related leukodystrophy.

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Quality of Life and Stress in Families Affected by a Leukodystrophy: A Longitudinal Study

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Introduction: Leukodystrophies are rare inherited disorders affecting the brain's white matter. They are often progressive, leading to increasing disability and often premature death. The psychosocial impact of these disorders on families remains poorly understood and no studies have examined these impacts longitudinally. This project aims to prospectively investigate parental stress and quality of life (QOL) in families affected by leukodystrophies. We hypothesize that parental stress and QOL will correlate with clinical features, life stressors, and functional scales over time. Furthermore, we expect mothers to report higher stress and lower QOL scores than fathers and parental stress to vary by leukodystrophy subtype, with rapidly progressive diseases associated with higher stress levels. **Methods**: Parents of children diagnosed with leukodystrophies were recruited between 2014 and 2025. Parents completed the PedsQL™ Family Impact Module (FIM), the PedsQL™ Generic Core Scales Parent Proxy Report, the Parenting Stress Index (PSI) or the Stress Index for Parents of Adolescents (SIPA), and a demographic questionnaire. Clinical data, including the presence of eight clinical features and five functional scales were also assessed. Questionnaires and clinical assessments were administered every six months to one year. Three timepoints per participant were used for analysis. Non-parametric tests were used to analyze changes over time, group differences, and comparisons to norms. Analyses were conducted with SPSS. **Preliminary results**: 65 parents of 49 children completed three questionnaires over the study period. No significant percentile changes were observed over time for the FIM (n = 62) or PedsQL scores (n = 26). Mothers and fathers showed similar FIM scores. The PSI revealed parental stress levels were significantly above average (Median = 69.0; W = 301, p = 0.001, r = 0.63) but did not vary significantly across timepoints (n = 26). **Conclusions**: Preliminary analysis indicates that family impact and parental stress levels remain stable over time, with parents experiencing consistently elevated stress compared to normative levels. Ongoing analyses will assess how stress and QOL evolve with clinical progression and leukodystrophy subtype.

Pre-clinical evaluation of the efficacy of Riluzole for the treatment of RNA-polymerase III-related leukodystrophy in a Polr3b exon 10 deletion mouse model

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Leukodystrophies are inherited disorders characterized by central nervous system white matter abnormalities. RNA polymerase III-related hypomyelinating leukodystrophy (POLR3-HLD) is caused by biallelic pathogenic variants in genes encoding subunits of RNA Polymerase III (Pol III), including *POLR3A*, *POLR3B*, *POLR1C*, *POLR3D*, and *POLR3K*. These mutations impair Pol III assembly, stability, and transcriptional function, disrupting the synthesis of small non-coding RNAs essential for cellular homeostasis. The *Polr3bΔ10* conditional mouse model, in which exon 10 deletion is induced in oligodendrocyte precursor cells (OPCs), recapitulates key POLR3-HLD features, including hypomyelination, reduced body size, craniofacial abnormalities, and premature death. Riluzole, an FDA-approved neuroprotective drug, partially promotes Pol III complex assembly and induces heat shock responses. This study evaluated Riluzole's efficacy in treating Pol III defects and ameliorating disease phenotypes. *In vitro*, *Polr3bΔ10* impaired OPC proliferation and oligodendrocyte (OL) maturation, with partial transcriptional recovery and modest increases in proliferation and MBP expression following Riluzole treatment. *In vivo*, Riluzole did not improve survival, weight gain, or myelination at any dose, and high doses caused toxicity-induced mortalities. These results indicate that while Riluzole exerts beneficial effects at a cellular level, its therapeutic effects do not fully translate *in vivo*, highlighting the need for refined treatments and complementary therapeutics.

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RARE.Qc: Building a Collaborative Rare Disease Research Ecosystem in Quebec

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RARE.Qc is a pan-provincial FRQ thematic research network uniting over 300 clinicians, researchers, and patient partners dedicated to improving the diagnosis, understanding, and treatment of rare diseases in Quebec. Its mission is to strengthen research efforts across institutions by fostering collaboration, integrating data and leveraging provincial expertise to accelerate rare disease research. Led by a director and 3 co-directors who are leading rare disease researchers representing diverse expertise and institutions, RARE.Qc has established a governance structure of seven executive and advisory committees guided by the principles of open science, sustainable health, and EDI (equity, diversity, and inclusion) to align priorities with community needs. Patients and caregivers actively participate, contributing to decision-making and to the development of the network's knowledge mobilization framework. RARE.Qc's activities are organized around three research pillars. Pillar 1 (Database and biobanking) focuses on creating a provincial database of longitudinal clinical and genetic data of rare disease patients hosted on the Centre québécois de données génomiques (CQDG) platform. This database will integrate data from healthcare and research sources, enabling researchers to explore and request specific datasets to advance their research. RARE.Qc is currently defining the database's framework and governance. Pillar 1 also includes the development of a provincial biospecimen directory consolidating information about samples from biobanks and research laboratories, and the implementation of a patient online portal for recruitment and consent. Pillar 2 (Physiopathology and therapy development) strengthens collaboration and capacity-building by creating a centralized directory of Quebec rare disease researchers, a catalog of available research resources, promoting open science practices such as the sharing of samples, protocols, and reagents, and fostering collaboration and training opportunities for researchers and students. Pillar3 (Patient-centered clinical research) focuses on harmonizing and streamlining clinical research processes, developing a centralized database of standard operating procedures (SOPs), and supporting regulatory and health resource evaluations. These efforts aim to position Quebec as a hub for rare disease clinical research and facilitate translation of discoveries into therapies. Through these three pillars, RARE.Qc provides a comprehensive framework combining infrastructure, collaboration, and clinical support to accelerate rare disease research and improve patient outcomes across Quebec.

Cree leukoencephalopathy (CLE) and Cree encephalitis (CE) Screening Program A Community-Driven Public Health Initiative

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CLE and CE are two rare, severe, hereditary diseases that typically manifest within the first months of life. These autosomal recessive conditions are currently incurable and often result in early childhood death. Based on 2013 data, approximately 1in 11 individuals are carriers of CLE, and 1 in 17 are carriers of CE. This initiative aims to present an innovative, community-led public health prevention program. It brings together community members, schools, clinics, and public health professionals to co-design and implement a population-based carrier screening strategy. Since 2006, the program has offered targeted screening, not universal testing, focusing on informed participation. The program was developed through a three-stage approach: **Community Mobilization**: Initiated by parents and families who had lost children to CLE and CE, leading to the creation of the Eeyou Awaash Foundation in 1999. **Public Health Engagement**: In 2002, the Cree Board of Health and Social Services of James Bay (CBHSSJB) regional Public Health Department proposed a screening initiative, which was officially launched in 2006. **Collaborative Implementation**: Today, the program is a partnership between local communities (schools and clinics), the Eeyou Awaash Foundation, and the Public Health Department, with support from the provincial genetic laboratory at Le Centre hospitalier universitaire Sainte-Justine. Managed by the CBHSSJB, the program spans all nine communities of the Cree Nation of Eeyou Istchee. To date: Over **3,800 individuals** have been screened through schools and clinics since 2006. Annual awareness and screening campaigns are conducted in all nine community Secondary schools. Clinical staff—including nurses, Primary Care Community Representatives (PCCRs), and midwives—receive regular training and presentations. Each year, more than **200 community members** (individuals, couples, and families) receive personalized support. This public health screening initiative exemplifies how health departments can build on community strengths, knowledge, and structures. Developed from the ground up, the program is rooted in cultural safety and respect. Ongoing education and tailored materials for both professionals and community members continue to enhance the quality and accessibility of screening services.

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Transcriptomic and behavioral signatures of RARS1 truncation in HLD9

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Mutations in arginyl-tRNA synthetase (RARS1) cause a hypomyelinating leukodystrophy characterized by early-onset neurological dysfunction. Clinically, this includes motor and language delays, microcephaly, seizures, spasticity, and intellectual disability. RARS1 is one of the 20 cytosolic aminoacyl-tRNA synthetases responsible for charging tRNAs with their cognate amino acids. The most prevalent disease-associated mutation produces an N-terminally truncated form of RARS1 that retains aminoacylation activity, leaving the molecular basis of the disorder unresolved. To explore the molecular and cellular implications of RARS1-associated neurodevelopmental disease, we developed an in vivo model of RARS1 truncation. Prior transcriptomic analysis of HEK cells expressing truncated RARS1 revealed dysregulation of gene networks critical for neural development, which suggests that RARS1 is a key player in neurodevelopment. Based on these insights, we selectively disrupted full-length RARS1 expression in the forebrain of mice, resulting in brain atrophy and reduced body weight. These mice exhibit striking behavioral phenotypes, including impaired coordination, deficits in balance, and increased anxiety-like behavior, suggesting a profound impact on neural function. These phenotypes were robust across both male and female animals, indicating sex-independent behavioral outcomes resulting from RARS1 loss in the forebrain. The observed phenotypes closely mirror clinical manifestations in RARS1 patients, such as ataxia and motor delay. To understand the molecular basis of these behavioral deficits, we performed RNA-sequencing on brain tissue, which revealed significant downregulation of genes involved in oligodendrocyte differentiation and axon ensheathment. These transcriptomic changes point to potential disruptions in myelination and neural connectivity as contributors to the observed behavioral impairments. This model not only captures key clinical features of RARS1-related disease but also implicates oligodendrocyte dysfunction and white matter abnormalities in the pathology. Altogether, this work lays the foundation for a better understanding of the molecular and cellular causes of RARS1-related brain disorder and provides a model for the exploration of therapeutic interventions.

Validating an MRI-based Diagnostic Flowchart for Adult-onset Leukodystrophies

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BACKGROUND: Leukodystrophies (LDs) are genetically determined white matter diseases with variable involvements of any white matter component. While they are commonly considered typical of the pediatric population, many may only present later in life with radiological phenotypes difficult to discern from within the broad LD category, as well as from acquired demyelinating disorders. As treatment strategies and prognoses differ widely, early recognition is essential for appropriate care and genetic counselling. Therefore, we intend to develop and validate a diagnostic flowchart for adult-onset LDs based on key imaging features to narrow down the differential diagnosis and reduce diagnostic delays. **METHODS**: A scoping review was conducted to identify key MRI features of adult-onset LDs. Disorders were first categorized by T1- and T2-weighted signal behaviour to distinguish hypomyelinating, demyelinating, cavitary, and vascular forms. The flowchart incorporates lesion distribution (confluent vs multifocal), fibre involvement (periventricular, subcortical, U-fibres), regional predominance (e.g., frontal, parietal, posterior fossa), and involvement of key structures (e.g., corpus callosum, basal ganglia). Ancillary imaging (DWI, MR spectroscopy, CT) are also integrated. Validation was conducted using MRI data from genetically confirmed LD cases, with assessments by one neuroradiology fellow and two neurology fellows, for diagnostic accuracy, utility, and confidence enhancement. **RESULTS**: We present a stepwise diagnostic framework optimized for neuroradiology workflows, integrating characteristic imaging patterns and basic clinical context to streamline interpretation. The flowchart assists in differentiating the various forms of genetic white matter diseases and provides guidance on when to pursue additional testing modalities. Clinical history, particularly psychiatric or cognitive symptoms, contextualizes atypical imaging features. The tool facilitates early, pattern-based suspicion of LDs, leading to targeted genetic confirmation. Utilization of this flowchart led to a significant improvement in the diagnostic accuracy of adult-onset LDs, as well as a significant increase in diagnostic confidence. **CONCLUSION**: As novel adult-onset leukodystrophies continue to emerge, structured diagnostic tools are critical for timely recognition. This MRI-based flowchart provides neuroradiologists with a practical, imaging-driven framework to efficiently narrow the differential and determine the most appropriate follow-up investigations. Future directions include expanding clinical validation and quantifying diagnostic impact across different experience levels.

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Unraveling the Transcriptomic Heterogeneity of Human Oligodendrocyte Progenitor Lineages In Vitro

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Generating oligodendrocytes (OLs), the central nervous system's myelinating cells, from human induced pluripotent stem cells (iPSCs) is frequently hampered by cellular heterogeneity, often resulting from the spontaneous co-generation of astrocytes from shared progenitors. To address this challenge, we utilized single-cell RNA sequencing (scRNAseq) and pseudotime analysis to characterize the heterogeneity and developmental dynamics within human iPSC-derived glial progenitor cultures. Starting from a glial-restricted progenitor (GRP) cluster, we identified three transcriptionally distinct developmental trajectories. Lineage 1 progressed toward an astrocyte fate, while Lineage 3 delineated the pre-oligodendrocyte branch that leads to mature OLs. In contrast, Lineage 2 represented a transcriptionally stable, resting oligodendrocyte progenitor (OPC) branch, reminiscent of homeostatic OPCs observed in the postnatal rodent brain. Differential gene expression analysis at the lineage bifurcation point revealed distinct molecular programs driving these fates. The OL-committed branch (Lineage 3) was enriched for SGCD, RNF144A, DNM3, and PKP4, genes associated with cytoskeletal dynamics and differentiation signaling. Conversely, the resting OPC branch (Lineage 2) displayed elevated RMST, CCSSER1, DLX6-AS1, and GAD2 expression, indicating roles in transcriptional regulation and maintenance of progenitor quiescence. The persistence of this transcriptionally quiescent OPC lineage highlights an intrinsic mechanism generating progenitor heterogeneity within human glial differentiation. Elucidating how these regulatory genes maintain the resting state or promote OL differentiation will enhance understanding of OPC lineage diversification. These insights may inform strategies to harness human OPC plasticity for remyelination therapies and improve modeling of developmental and degenerative white matter disorders in human systems.

Does substrate stickiness stretch sheaths: Tuning myelin membrane extension and wrapping with adhesive polymers

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During myelin wrapping, oligodendrocyte (OL) processes undergo complex adhesive interactions with axons. Studies investigating myelin-related adhesion molecules have yielded conflicting results, prompting a need for experimentally accessible systems to model how adherence influences OL - axon contact, process extension, and wrapping to form myelin. Here, we employed different ratios of synthetic adhesive and non-adhesive polymers, poly-D-lysine (PDL), polyethylene glycol (PEG), and dendritic polyglycerol amine (dPGA), to tune the adhesiveness of tissue culture substrates. Surface energies of glass coated with these different polymers were measured via water contact angle and zeta potential electrophoresis, and growth of HEK293T cells and primary rodent OLs quantified on each. In conventional 2D cultures, increasing substrate adhesiveness promoted the outgrowth of MBP positive processes. To model myelin wrapping, we used electrospun fibers coated with different ratios of adhesive and non-adhesive polymers. In these 3D cultures, fibers coated with non-adhesive PEG exhibited fewer wrapped segments, indicating that adhesion is required for an OL to initiate wrapping. Increasing fiber adhesivity was correlated with more wrapped segments elaborated per OL. In contrast, the length of wrapped segments peaked with moderate adhesion, balancing adequate adhesion without restricting wrapping. Investigating dPGA, an adhesive polymer with particularly high surface energy, we found that it significantly increased the length of wrapped segments, but reduced the number of wrapped segments per cell, consistent with individual OLs elaborating a discrete amount of myelin. Together, our results indicate that adhesion is required for OL process outgrowth and to initiate wrapping, but that excessive adhesion inhibits the elongation of a wrapped segment, revealing an adhesive "Goldilocks zone" for optimal myelination. These findings improve our understanding of how axo-glial interactions shape myelin sheaths and support the design of improved in vitro myelination assays to screen for novel therapeutics, potentially positioning the axonal surface as a target to promote myelination.

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Modeling EPRS1-Related Hypomyelinating Leukodystrophy Reveals Oligodendrocyte Defects and Integrated Stress Response Activation

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EPRS1-related leukodystrophy is an ultra-rare hypomyelinating disorder caused by hypomorphic mutations in the proline domain of the bifunctional aminoacyl-tRNA synthetase, EPRS1. While prior studies have begun to uncover molecular mechanisms involved in this disease, the specific cellular dysfunction underlying hypomyelination remains unclear. To address this, we generated induced pluripotent stem cells (iPSCs) from two individuals with genetically confirmed EPRS1-related leukodystrophy and differentiated them into the myelin-producing cells of the CNS, the oligodendrocytes. Lineage analysis revealed modest abnormalities at the oligodendrocyte progenitor cell (OPC) stage, which became more pronounced upon maturation, characterized by an accumulation of immature oligodendrocytes and increased susceptibility to cell death. Interestingly, progressive activation of the integrated stress response (ISR) was noted upon commitment to the oligodendrocyte lineage in patient-derived cultures. Proline supplementation during differentiation partially ameliorated oligodendrocyte deficits, including reduction of ISR-related gene expression. Together, these findings identify stage-specific oligodendrocyte vulnerability and ISR dysregulation as central features of EPRS1-HLD and supports amino acid supplementation as a potential adjunctive therapeutic strategy.

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Cet événement témoigne de la force des partenariats entre les milieux de la recherche, de la clinique, de l'industrie et de la défense des droits. Nous sommes profondément reconnaissants de leur engagement commun à faire progresser les soins, la collaboration et l'innovation pour les personnes et les familles touchées par les leucodystrophies partout au Canada.

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This event is a reflection of the power of partnership across the research, clinical, industry, and advocacy communities. We are deeply grateful for their shared commitment to advancing care, collaboration, and innovation for individuals and families affected by leukodystrophies across Canada.

We would like to extend our sincere thanks to the Montreal Children's Hospital Foundation for their generous support and partnership in co-organizing the 2025 CARELeuko Symposium. Their commitment to advancing pediatric research and care has been instrumental in bringing this event to life.

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Nous remercions chaleureusement l'équipe organisatrice, les conférenciers, les partenaires de défense des droits des patients et les bénévoles pour leur précieuse contribution. Cet événement n'aurait pas été possible sans votre dévouement, votre expertise et vos efforts collectifs.

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