Dr. Geneviève Bernard: Leukodystrophy Research Report

December 2021

the montreal children's hospital foundation

Leukodystrophies and the extraordinay impact of YOUR support

What are Leukodystrophies?

Dr. Bernard and her MyeliNeuroGene Lab team study leukodystrophies, a group of inherited (genetically determined) white matter disorders. White matter, or myelin, is the part of the brain that insulates and protects nerve fibers. Neurons signal to each other via these nerve fibers, which can be thought of as electrical wires, and myelin acts as the coating surrounding the wire. Myelin is critical for making sure the brain can send signals to different parts of the brain, or to muscles in the body like in the arms and legs. When this myelin is not present or is damaged, the brain can not send these signals as effectively. Leukodystrophies can be split into 2 groups - hypomyelinating (when myelin doesn't deposit normally during development) and non-hypomyelinating leukodystrophies (where myelination occurs normally in development, but the myelin then gets sick).

While Dr. Bernard's lab investigates both categories of leukodystrophies, **the main focus of the MyeliNeuroGene lab is hypomyelinating leukodystrophies**. There are many kinds of leukodystrophy caused by mutations in different genes and while each form is individually rare, collectively leukodystrophies are more common. **Recent estimates suggest leukodystrophies affect 1 in 4733 live births.** (Soderholm, et al 2020).

THANK YOU for your generous support of this cutting-edge research.

Many of the projects described in the following pages are still in need of funding. Your help makes this important work possible.

MyeliNeuroGene LAB

Dr. Geneviève Bernard

Dr. Geneviève Bernard is a pediatric neurologist and scientist at the Research Institute of the McGill University Health Centre.

10 years ago, Dr. Bernard established the MyeliNeuroGene lab research group and devoted herself and her team to the study of rare neurodegenerative disorders.

Within a short span of time, Dr. Bernard was **recognized internationally as one of the leading experts** on leukodystrophies, both in the clinic and the laboratory.

Since its inception in 2011, the MyeliNeuroGene lab has **pushed the rare childhood disease field forward and remains committed to unraveling the mysteries** behind myelin biology and disease processes.

Dr. Bernard has built a successful research program with a **multitude of international and national collaborations, more than 110 published manuscripts**, several consensus statements, book chapters and abstracts and has been invited as a keynote speaker at over 130 international, national and provincial conferences.

Recently, Dr. Bernard was **ranked 1st** for the Senior Clinical Research Scholar (2022-2025) salary award by the Fonds de Recherche du Québec en Santé (FRQS) and won a **prestigious project grant devoted to unsolved leukodystrophies in the esteemed Canadian Institutes of Health Research (CIHR), where she also ranked 1st of 63 grants.**

McGill University awarded Dr. Bernard the 2020 Maude Abbott Prize, a distinction reserved for **outstanding female faculty that have excelled and demonstrated great leadership in research** and the Royal College of Physicians and Surgeons named her the recipient of the 2019 Specialist of the Year Award – Regional “Prix d’Excellence”.

Supporting patients and their families have always been a priority for Dr. Bernard as exemplified by her high degree of involvement in various foundations, patient advocacy groups and international consortia, such as her role with the Pelizaeus-Merzbacher Disease Foundation, Yaya Foundation, Vanishing White Matter and Hypomyelination with Atrophy of the Basal Ganglia and Cerebellum Consortia and GLIA, to name a few. Most notably, **Dr. Bernard is the first woman, first Canadian and youngest individual to be selected as Chair of the Medical and Scientific Advisory Board of the United Leukodystrophy Foundation**, one of the largest leukodystrophy foundations in the world, founded in 1982.

Dr. Bernard's devotion to her patients: the gold standard

My life was turned upside down in November of 2017 when I was told my 4-year-old son, Thomas, had a rare genetic disease called adrenoleukodystrophy.

I was referred to Dr. Bernard at The Children's. Then came MRIs every 6 months to make sure the cerebral form didn't develop. In March of 2020, I got the fateful call from Dr. Bernard telling me the beast had awoken.

My world was turned upside down once again, but this time, with a whirlwind of information no parent wants to hear. **With great difficulty, I realized I might lose my little Thomas, then 6 years old.**

I had a choice: watch my son die a slow death or proceed with a bone marrow transplant. I had a remote consultation with Dr. Bernard and the transplant doctor to get as much information as possible about everything that would come next for Thomas, but also to understand what could go wrong. Those were very difficult months for my family.

I wouldn't wish the experience on any parent, but luck and the tireless work of the many specialists at the Children's allowed my son to survive each step and beat the disease.

I owe my son's life to Dr. Bernard's work ethic and determination. I now call her the "goddess of leukodystrophy." This extraordinary woman has devoted her career to helping patients with the disease, while helping their parents cope the best they can with this sword of Damocles and all the potential symptoms the disease brings. On top of that, her entire research team is dedicated to leukodystrophies, as she believes it's essential to go beyond just prevention and treatment. She has my eternal gratitude for everything she did for him. **From the bottom of my heart, I hope research will find a way to stop us from losing more kids to the disease. Research is the only way to understand and fight the enemy that is adrenoleukodystrophy.**

-Valérie, Thomas' mom

Current Research Highlights

➢ Dr. Bernard is leading clinical trials for leukodystrophies!

Since our last update, our team has continued to work closely with industry to evaluate the safety and efficacy of emerging interventional treatments for leukodystrophies. We are currently working with Ionis Pharmaceuticals on a clinical trial (ION373) for Alexander disease. **Our site has recruited the first patient worldwide**, recruited two other patients, with the possibility of more to come. We are also working closely with Passage Bio on two gene therapy trials for leukodystrophies. These studies are in the start-up phase right now and will likely be recruiting patients in early 2022. This work would not be possible without collaboration from our clinical and administrative friends at the Centre for Innovative Medicine, as well as The Children's Cardiology and Hemodynamics team, and Anaesthesia and Surgery teams, to name only a few!

➢ Developing and improving the MyeliNeuroGene LORIS database to study rare diseases

In the last MUHC report, we mentioned the development of this database to facilitate collaborations on rare diseases research. Since this update, a paper was published in 2021 on the creation and customization of this database and its use in systematically recording samples and data!

See more in the highlights of recent research publications on page **12**.

➢ Characterizing the clinical progression and evolution of POLR3-related leukodystrophy

Natural history studies are crucial to characterize the natural progression and evolution of a disease. It helps clinicians and scientists create specific markers of disease progression. Having a well delineated clinical course is imperative when designing a clinical care plan and can aid in preparing patients and their families for the future. **Importantly, these studies lay the foundation for future clinical trials as they provide a method to measure whether clinical outcomes in patients have improved**, allowing for a more robust evaluation of the proposed therapy. Dr. Bernard and the clinical team have started and contributed to natural history studies for several leukodystrophies, including for POLR3-related leukodystrophy.

➢ Pathophysiology

Dr. Bernard's team works to better understand the molecular processes leading to leukodystrophies, with a focus on POLR3-related leukodystrophy.

This is a crucial aspect of research as better understanding disease pathogenesis is critical to one day be able to develop therapies for it!

Current Research Highlights - continued

➢ Genetic identification of new genes causing white matter diseases

One of the main focuses of the MyeliNeuroGene lab is identifying new causative genes of leukodystrophies and related disorders. Many individuals remain undiagnosed for years, which has implications in providing the most appropriate care plan, as well as the unique difficulties for patients and their loved ones. Identifying the cause her patients' white matter disorders is a primary focus for Dr. Bernard. This year, Dr. Bernard's lab published a paper identifying *LSM7* as a potential new gene for leukodystrophy, as well as, in close collaboration with Care-4-Rare (Dr. Kym Boycott), *ABHD16A* as a cause for a novel disorder with spastic paraparesis and leukoencephalopathy.

Dr. Bernard has extensive expertise in clinic and research which has allowed her to build a comprehensive research program on leukodystrophies.

Dr. Bernard has built a large cohort of patients and families affected with leukodystrophies and a vast network of collaborators, putting her in an ideal position to continue to succeed in this research.

Thank you for helping make this happen!

Dr. Bernard's Team

Dr. Bernard's team is amazing, and she reminds them regularly how lucky she is to work which such incredible professionals and scientists. This year, she wanted them to introduce themselves to you – so you can really know who *YOU* are supporting!

Luan Tran, MSc – Clinical Research Assistant

"I'm on Dr. Bernard's clinical research staff. I've worked closely with her and her patients for the past 8+ years. I also serve as the main liaison between the research team and our clinical colleagues, international collaborators, and industry partners. I'm very fortunate to be able to work in an environment that allows me to have a very diverse and rich day-to-day and advocate for patients who are often underrepresented."

Xiaoru Chen, PhD, postdoc – Laboratory Research Associate

"I am Xiaoru Chen, PhD in Pharmacology, working as a Research Associate in Dr. Bernard's lab. I joined this position in October 2020. I am working on developing mouse models to investigate the pathogenesis of leukodystrophy and to evaluate potential therapeutic strategies for the treatment of leukodystrophy. I am passionate about fundamental research in Dr. Bernard's lab and I hope my work could contribute to the further understanding of these rare genetic diseases and to the development of therapies."

Simon Fournier, MSc – Clinical Research Assistant

"I am a clinical research assistant in Dr. Geneviève Bernard's laboratory. I work on several aspects of our clinical research program (recruitment of participants, data and samples collection, budgeting, administration, mentoring of students). I am also involved in different clinical trials, and I analyze patients' DNA to find the cause of their medical condition. I joined the team in late 2020 and I instantly felt the need to help these brave children as much as I can! They are a great example of resilience."

MyeliNeuroGene LAB

Dr. Bernard's Team - continued

Alexa Derksen, MSc – Master's Student, Research Assistant

"I was a Master's student from 2018-2020 in Dr. Bernard's lab working on a project studying *LSM7,* a gene which we demonstrated may be associated with an ultra-rare neurological disease. After my Master's, I worked as a research assistant in the lab managing our next generation sequencing platform. Throughout my time in Dr. Bernard's lab, I was able to publish several papers, two of which were from my Master's work. I was also awarded the prestigious Canadian Institutes of Health Research Graduate Scholarship. My time in Dr. Bernard's lab has inspired me and has led me to where I am today, a first year MD/PhD student at the University of Ottawa where I hope to have a positive impact on the lives of patients and their families."

Stefanie Perrier, HBSc – PhD student

"I am a PhD candidate in Dr. Bernard's lab studying the disease mechanisms underlying POLR3-related leukodystrophy, and a specific severe form of the disease. I also study groups of patients with white matter abnormalities but without a genetic diagnosis to try to identify new disease-causing genes. I am involved in both wet lab and clinical research and enjoy learning about the disease on different levels. On the clinical research end, we recently published a large cohort study on the endocrinology of 150 patients with POLR3-related leukodystrophy in the *Journal of Clinical Endocrinology and Metabolism*, which demonstrated that abnormalities are common, and exemplified the importance of future large cohort studies to study specific disease features. I have been a member of Dr. Bernard's MyeliNeuroGene lab since 2016 and have thoroughly enjoyed the opportunity to work with so many motivated individuals. Ultimately, I am inspired by the strength of our patients and their families and believe in the importance of developing treatment options to help those affected by these diseases. I am the recipient of the prestigious FRQS Doctoral Training Scholarship (2018-2022)."

Mack Michell-Robinson, MSc – MD-PhD student

"I have worked in Dr. Bernard's laboratory since January 2019. I am a MD-PhD student developing a mouse model of POLR3-related Hypomyelinating Leukodystrophy. This is a devastating disease manifesting primarily in young children who currently do not have any treatment options that could improve the course of the disease. Our goal is to use mouse models of the disease to test and develop therapeutics which we hope will eventually make an impact on patients' quality of life. Ideally, by improving disease outcomes and reducing the burden faced by patients. Prior to my enrolment in the MD-PhD program, I completed my MSc. in neuroscience at McGill as well as working as an Associate Scientist at Biogen. When I am not working in the lab, I manage the McGill Journal of Medicine as Co-Editor-in-Chief and am an executive member of the MD-PhD Student Council at McGill. I am passionate about science and hope to use my background in translational research to explore the potential of gene therapy for diseases of the brain. I am the recipient of two very prestigious scholarships: the CIHR and Hilton J McKeown MD-PhD Training Award (2019-2023) and the Vanier Canada Graduate Scholarship (2020-2023)".

Dr. Bernard's Team - continued

Alexandra Chapleau, BSc – PhD student

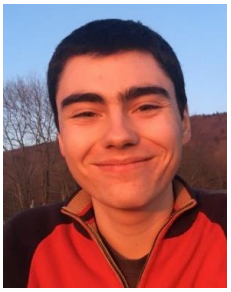
"I am a PhD student in Dr. Bernard's lab. I work on the iPSC (induced pluripotent stem cell) team with a specific focus on creating a cellular disease model of *EPRS1*-related leukodystrophy. I first joined the lab as a summer researcher in 2018 and quickly caught the research bug, subsequently returning in a full capacity in 2019 after completing my undergraduate degree. One of my favourite aspects of Dr. Bernard's lab is the strong emphasis on connecting basic science research to the clinic and improving the patients' and families' experience. I am beyond ecstatic to continue my research on rare diseases with Dr. Bernard and I look forward to what the next few years will bring! I have received scholarships from Healthy Brains, Healthy Lives (2019-2021), and La Fondation du Grand Défi Pierre Lavoie (2019-2022)".

Julia Macintosh, BSc – MSc student

"I am a 2nd year master's student in Dr. Bernard's MyeliNeuroGene lab, having started in September 2020. As part of the wet lab team, my research focuses on a specific subset of cells in the brain, oligodendrocytes, and working to elucidate their involvement in the inherited white matter disorder POLR3-related leukodystrophy. Working in the research field of rare, pediatric neurodegeneration under Dr. Bernard's supervision has been an incredible experience so far and I especially enjoy the way basic science research and clinical research work merge in the lab! I feel incredibly passionate about the research I work on and I am looking forward to the rest of my degree. I was awarded the following: Faculty of Medicine Internal Studentship, Healthy Brains, Healthy Lives Master's Fellowship (2021-2022) and Integrated Program in Neuroscience Recruitment Award (2020-2021)."

Helia Toutounchi, BSc – MSc student

"I am a master student in Dr. Bernard's lab. I am a part of the clinical team in the lab. My project is a natural history study on 4H leukodystrophy. Working with the members of the lab is always enjoyable and it's amazing to be surrounded by people that are so motivated to help children affected by these diseases. Being a part of the clinical team, I am fortunate enough to meet the patients, which really puts everything in perspective. I adore meeting the kids and playing with them and I hope that our work in the lab can help these families."



Olivier Pouliot, DEC – MD student

"I am a Medical Student and I've been working in Dr. Bernard's lab since the summer of 2021. I work on different clinical projects, including on data entry for the 4H natural history project. I am really interested in neurology, genetics and new perspectives of treatment, so working in Dr. Bernard's lab gives me a really nice perspective on these topics!"

Dr. Bernard's Team - continued

Neeti Jain, BSc – MSc student

"Hi! I started in the MyeliNeuroGene Lab in September 2021 as a Master's student. I am part of the lab team where I work with iPSCs to develop a cellular model for studying POLR3A leukodystrophy. I became interested in wet lab research during my undergrad and soon found my passion in studying neurodegenerative diseases. I love working in the Bernard Lab due to the emphasis placed on "bench to bedside" research and I'm looking forward to my time here!"

Laura Lentini, BSc – MSc student

"Hello! I am a first-year Master's student on the clinical team. After completing my undergraduate degree in Honours Behavioral Neuroscience, I joined the lab in the summer of 2021 as a research summer student. After being awarded the Integrated Program in Neuroscience Recruitment Award (2021-2022), I joined the MyeliNeuroGene lab as Master's student, and am currently working on studying stress and quality of life of parents with children with 4H Leukodystrophy. Being a part of the MyeliNeuroGene lab with Dr. Bernard and her team has allowed me to combine my love for neuroscience and my passion for working with children and their families, which will all be beneficial for my future career goals!"

Amytice Mirchi, MD - Resident (PGY-3) in Pediatric Neurology

"I am a 3rd year Pediatric Neurology resident at the Montreal Children's Hospital. In the past, I have examined quality of life in patients with genetically determined leukoencephalopathies. I am currently working on assessing bone health in a cohort of patients with neurodegenerative diseases and taking part in other clinical research projects in the laboratory. Working in Dr. Bernard's laboratory performing clinical research has allowed me to meet patients and families that she cares for, inspiring me with their courage and their resilience. Furthermore, I have had the opportunity to witness the start of clinical trials for some of these neurodegenerative conditions, bringing the hope for future treatments for these disorders."

Aline Laurendeau, DEC – MD student

"I am a third-year medical student working with the clinical team since the summer 2021. My project focuses on delineating the psychomotor developmental trajectory of children affected by POLR3-related of 4H leukodystrophy, an essential milestone toward understanding the disease natural history study, which is, in turn a crucial step toward designing clinical trials to improve patients' outcomes. Working alongside Dr. Bernard has been inspiring as I am considering a career in pediatric neurology."

Dr. Bernard's Team - continued

Pouneh Amir-Yazdani, DEC – MD student

"I am medical student at University Laval and a research student in Dr. Bernard's lab since the summer of 2019. I worked on two qualitative research projects in the last years. The first one seeks to understand the experience of parents with the healthcare system and the second project aims to characterize parents' experience with telemedicine during the pandemic. I have always been passionate about positively influencing the health and quality of life of children and their families, and doing research in Dr. Bernard's lab allowed me to reach out to those families and identify modifiable factors that could improve their lives in the future."

Marie-Lou St-Jean, BSc – MD student

"I started working in Dr. Bernard's lab during the summer of 2019 as an undergraduate student after the second year of my bachelor's degree in neuroscience. I was very interested in the ongoing clinical research, and I participated in many related projects. I enjoyed my experience so much that I spent a second summer in the lab before starting medical school in 2020. Then, I worked with P. Amir-Yazdani on our own project: a qualitative study exploring the experience of parents of children followed in Dr. Bernard's clinic within the healthcare system. We are now in the process of publishing two papers related to this project. Working in Dr. Bernard's lab has given me the opportunity to be amazed by how strong and invested these families are, and I am very pleased to bring my own contribution for improving their quality of life with clinical research."

Ying Chen, DEC – MD student

"I am Ying, a first-year medical student at McGill. I was a summer student at the MyeliNeuroGene lab during the summer 2021, as part of McGill's Research Bursary Program. My project involved analysis of Exome Sequencing analysis to identify potential disease-causing variants in patients with leukodystrophies. I am very grateful to Dr. Bernard and the MyeliNeuroGene team for welcoming and mentoring me, and for this introduction to the fascinating subject of genetics."

Anne Michèle Laperrière – High School Student

"My name is Anne Michèle, and I am a high school student. I worked for Dr. Bernard's lab from June to August 2021, doing data entry and helping with other clinical research tasks. I learned so much working in the MyeliNeuroGene lab and I hope to follow in Dr. Bernard's footsteps and pursue a career in medicine someday."

On behalf of Luna, who suffers from a form of Leukodystrophy, and her mom Jennifer, thank you for supporting Dr. Bernard's research!
Jennifer credits Dr. Bernard with helping Luna celebrate her 5th birthday.

See a clip of her story here:
(starts at 1:13) https://montreal.ctvnews.ca/annual-radiothon-raises-funds-for-montreal-children-s-hospital-1.5563184

Selected Presentations

Every year, Dr. Bernard is invited to present at international, national and provincial conferences to share her clinical and research expertise with fellow scientists and clinicians and to educate families.

This year, these conferences included:

A talk on **POLR3-related (4H) leukodystrophy** at Fundacíon Lautaro Te Necesita, a leukodystrophy non-profit based in Argentina in October

A talk on **4H** at the United Leukodystrophy Foundation Virtual Family Conference in June 2021

In late 2020, Dr. Bernard also participated in **the first Leukodystrophy 4H Collaboration Network meeting**, hosted by the Yaya Foundation for 4H leukodystrophy, where she presented on both "Natural History & Existing Understanding of 4H" and "Developing Mice Models of POLR3-related (4H) Leukodystrophy".

Highlights of Recent Research Publications

Dr. Bernard has been prolific in disseminating her scientific findings this year! Presented below are brief summaries from selected papers recently published. For a more comprehensive list, see:
https://www.ncbi.nlm.nih.gov/myncbi/1vKxAlgE6PYQe/bibliography/public/

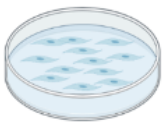
1. A novel candidate gene possibly associated with an ultra rare leukodystrophy

HGG Advances **REPORT**

Variants in *LSM7* impair LSM complexes assembly, neurodevelopment in zebrafish and may be associated with an ultra-rare neurological disease

A recent paper published by Derksen et al. in Dr. Bernard's lab identified the gene ***LSM7*** as a potential candidate gene for an **ultra-rare form of leukodystrophy**.

The LSM7 protein works in a complex to regulate RNA, the template for instructing the body on how to make proteins. This paper described 2 unrelated individuals with variants in the *LSM7* gene, one who had a clinical diagnosis of leukodystrophy and one who died *in utero*. Prior to this paper, *LSM7* had never been implicated in a disease. It will be important to identify more patients with variants in this gene before we can for sure say that it is disease-causing. We hope that this publication will lead to clinicians and researchers to contact us or publish more patients.



Through studying cells from the affected individual, they found reduced function of the LSM complex compared to unaffected individuals. As the LSM complex is crucial for making proteins, it suggests these individuals are likely to have difficulty making proteins.

The authors of this paper also modeled the disease using the zebrafish animal model to show the mutation affected brain development by impairing the survival of oligodendrocytes, the myelin-producing cells of the brain.

While various genes have been found to cause leukodystrophy, as many as 20-30% of individuals with a clinical diagnosis of leukodystrophy remain without a molecular diagnosis, meaning a causative gene has not been identified. Identifying new genes that cause leukodystrophy and related disorders has been one of the main focuses of Dr. Bernard's lab. By uncovering new mutations that cause leukodystrophy, we also build a deeper understanding of this group of disorders – the first step in developing novel treatment strategies!

Recent Research Publications - continued

2. Creation of a rare disease database

The LORIS MyeliNeuroGene rare disease database for natural history studies and clinical trial readiness

Orphanet Journal of Rare Diseases

There is an increasing need for clinicians to have an easily accessible database to store electronic patient records. LORIS is an open-source program with the ability to store a variety of metrics such as genetic data, medical history, medical imaging and motor and cognitive assessments.

LORIS will help facilitate collaborations with rare disease scientists and medical experts around the world! A large barrier to orphan disease research is the small sample of patients, which can make it more difficult to draw conclusions. There is a pressing requirement for natural history studies in rare diseases to develop a representative timeline of disease progression in patients. Without an accurate depiction of the clinical course, there is no method to measure beneficial outcomes in patients, an important aspect of clinical trial preparedness. LORIS provides a platform to measure various biomarkers and disease milestones which paves the road for investigating new treatments and therapies.

3. Exploring therapeutic approaches in POLR3-related leukodystrophy

POLR3-Related Leukodystrophy: Exploring Potential Therapeutic Approaches

frontiers in Cellular Neuroscience

The ultimate goal of human health research is to help develop therapeutic interventions to improve patients' lives. This past year, Dr. Bernard and two of her students published an important review paper on all potential future therapies for POLR3-related leukodystrophy.

This paper pushes the field forward by discussing each therapeutic option in detail, including both potential benefits and limitations. Specifically, this review delves into specific therapies that have shown potential in other leukodystrophies and highlights the most important and suitable ones for POLR3-related leukodystrophy. Without a solid base of knowledge delineating all therapeutic avenues, it can be difficult to determine the best path forward.

Recent Research Publications - continued

4. Characterizing the endocrine and growth abnormalities in POLR3-related leukodystrophy

Clinical Research Article

Endocrine and Growth Abnormalities in 4H Leukodystrophy Caused by Variants in *POLR3A*, *POLR3B*, and *POLR1C*

ENDOCRINE SOCIETY

Recently, Pelletier et al. published a report on the endocrine and growth abnormalities associated with POLR3-related leukodystrophy. While the disease is known to manifest with neurological features, patients also present with endocrine manifestations.

In this paper, Dr. Bernard's team, together with numerous international collaborators, looked at a large cohort of 150 patients to investigate the common endocrine features associated with the disease. Specifically, the authors discovered that: (1) Endocrine impairment is a common feature; (2) Many patients experience absent/delayed/arrested puberty and pathology suggests the issue arises with malfunctioning of the pituitary gland; (3) Short stature is seen in more than half of the patients.

It is essential to gain a complete understanding of the clinical phenotype associated with POLR3-related leukodystrophy to provide proper treatment for individuals affected. **This study is the first to thoroughly examine the spectrum of endocrine abnormalities associated with POLR3-related leukodystrophy.**

5. A new gene found to cause hereditary spastic paraplegia

ABHD16A deficiency causes a complicated form of hereditary spastic paraplegia associated with intellectual disability and cerebral anomalies

A newly published study for which Dr. Bernard was a co-lead author, together with Dr. Kym Boycott (Care-4-Rare) identified a new causative gene, *ABHD16A* in hereditary spastic paraplegia, a progressive disorder that affects walking (gait disorder).

While *ABHD16A* had never been associated with a disease before, here they identify 11 individuals (from 6 families) where mutations in this gene leading to a deficiency of this lipid signalling molecule and which cause a progressive neurological condition. In particular, these individuals were found to have: (1) Developmental delays/intellectual disability, (2) Leukoencephalopathy, (3) Spasticity that affects the legs, and to a lesser extent the arms

This is the first case of disease from mutations and reduced function of *ABHD16A* and identifies a new gene as causative for hereditary spastic paraplegia.

Looking Ahead

The MyeliNeuroGene lab is passionate about shedding light on the clinical, radiological, genetic, molecular and pathophysiological bases of leukodystrophies.

Dr. Bernard remains committed to pushing the leukodystrophy field forward and providing support and answers to families about their child's white matter disease, improvements in clinical care and searching for future therapeutics.

Thank you for your invaluable support in achieving these goals!

Despite all the significant accomplishments Dr. Bernard and her team were able to achieve in this past year, many more exciting innovative projects are on the horizon.

A) First large-scale clinical study of bone health in *POLR3*-related leukodystrophy patients:

Children with POLR3-related leukodystrophy are known to present with significant growth impairments and bone abnormalities. However, no studies to date have exclusively analyzed bone health in patients with 4H. This project aims to characterize how 4H may manifest in the skeletal system and provide clinical guidance to improve bone health in these patients.

B) Genotype-phenotype studies of ultra-rare leukodystrophies:

Correlating the clinical presentation (the phenotype) of patients to their specific genetic mutation (the genotype) is an important step in discovering common disease manifestations. They are of particular importance for rare diseases which are usually associated with a large clinical spectrum and a low population prevalence, making diagnosis and supportive care more difficult. Discovering the range of symptoms associated with a rare disease, as well as potential clinical predictions based on the genotype, can help guide future diagnoses and standard of care.

Dr. Bernard wearing her essential PPE to see patients in the clinic.

Follow the MyeliNeuroGene lab Facebook group (facebook.com/myelineurogene) and twitter (@myelineurogene) for updates.

Press & Media

- **(September 2021) The Yaya Foundation for 4H Leukodystrophy Research Grant**

https://rimuhc.ca/-/new-4h-leukodystrophy-study-to-be-led-by-ri-muhc-researcher

https://healthenews.mcgill.ca/new-4h-leukodystrophy-study-to-be-led-by-ri-muhc-researcher/

- **(August 2020) Antisense Oligonucleotides Restore Function in Mouse Model of Pelizaeus-Merzbacher Disease, by Eve Bender, Neurology Today (invited commentary)**

https://journals.lww.com/neurotodayonline/Fulltext/2020/08200/Antisense_Oligonucleotides_Restore_Function_in.9.aspx

- **(July 2020) Dr. Bernard - Winner of the Maude Abbott Prize for 2020**

-McGill University News and Events 2020/08/07:

https://www.mcgill.ca/channels/channels/news/dr-genevieve-bernard-awarded-2020-maude-abbott-prize-323525

-Med e-News – 2020/07/30:

https://publications.mcgill.ca/medenews/2020/07/30/2020-maude-abbott-haile-t-debas-and-rosemary-wedderburn-brown-prize-winners-announced/

- **(April 2020) Montreal Children's Hospital Foundation interview on covid-19**

https://fondationduchildren.com/en/heroes/life-during-the-covid-19-crisis-a-chat-with-dr-bernard

- **(April 2020) Royal College of Physicians and Surgeons: Women's Day**

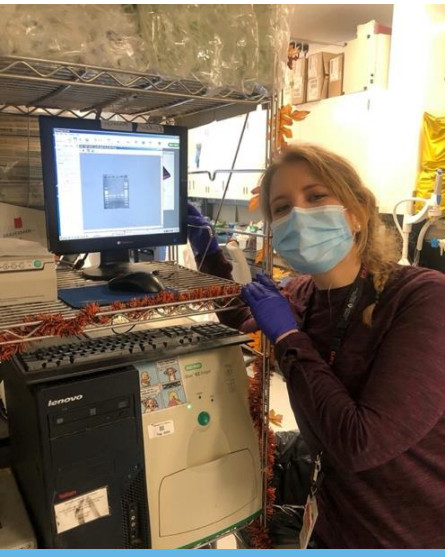
https://www.facebook.com/TheRoyalCollege/posts/2915062961879010

https://www.facebook.com/TheRoyalCollege/posts/2915076065211033

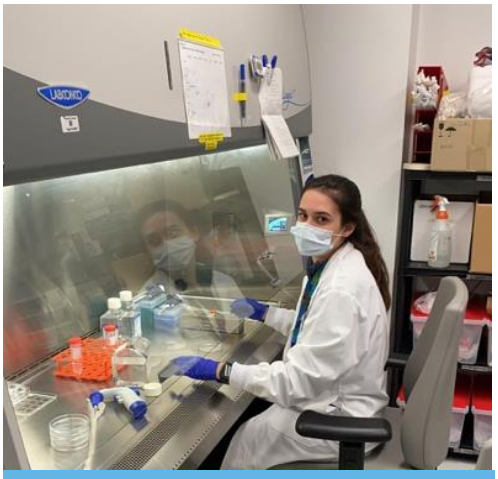
Alex and Stefanie enjoying a Lick Leukodystrophy brain lollipop from the ULF.

Alex Chapleau celebrating Easter in the lab.

The lab displaying their Halloween spirit! The lab won 2nd place in the Halloween window decorating competition!



Stefanie Perrier proudly displaying a successful gel.



Julia Macintosh setting up her experiments in the tissue culture hood.

Thomas, one of Dr. Bernard's patients

To all of Dr. Bernard's donors, supporters and collaborators:
THANK YOU!

For more information, please contact
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