Dr. Geneviève Bernard: Leukodystrophy Research Report

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

Leukodystrophies

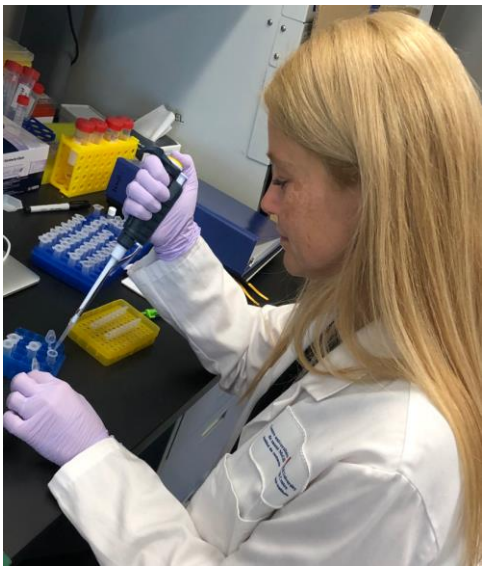
Dr. Geneviève Bernard and her team work on leukodystrophies, a group of *genetically determined* diseases that affect the white matter of the brain. The white matter of the brain is composed of fatty tissue (myelin) that envelopes nerve fibers (axons), which transmit messages from the brain to targeted body parts (i.e. arms and legs to move).

The axons are analogous to electrical wires, and the myelin to the insulation around the wires. When the myelin is not functional anymore, like in the case of leukodystrophies, information cannot be sent effectively from the source to the destination.

Leukodystrophies can be divided into two groups: hypomyelinating (which is a lack of myelin deposition in the brain; hypo = less than normal) and other disorders (sick myelin). While the lab investigates both groups of leukodystrophies, the focus of the group has been on hypomyelinating leukodystrophies.

Children with leukodystrophies are born healthy, however their genetic abnormalities lead to abnormal development or destruction of the myelin. This results in progressive disability and typically early death.

Dr. Bernard conducting research in the lab



Dr. Bernard (right), her student Mack (left) and her friend James (middle) running the Scotia Bank half-marathon to help raise funds for the MyeliNeuroGene Lab.

Dr. Geneviève Bernard

Dr. Geneviève Bernard is a pediatric neurologist & clinician-scientist at the McGill University Health Center Research Institute.

She started the MyeliNeuroGene lab in 2011 and in a short period has established herself as an international expert in hypomyelinating leukodystrophies in both clinical and research aspects.

She built a successful research program with numerous international and national collaborations, more than **100** published manuscripts, several consensus statements, book chapters and abstracts, and over **100** international, national and provincial conferences as an invited speaker.

She currently holds the **CIHR New Investigator Award 2017-2022**, received the **2019 Specialist of the Year Award – Regional "Prix d'Excellence"** from the Canadian Royal College of Physicians and Surgeons, and was awarded the **2020 Maude Abbott Prize** from McGill University which recognizes outstanding female faculty at an early career stage who have excelled and demonstrated great leadership in research. Additionally, she is **the *first woman, first Canadian and the youngest individua*l** to be selected as **Chair of the Medical and Scientific Advisory Board of the United Leukodystrophy Foundation**, one of the largest foundations of its kind in the world.

Dr. Bernard currently has a team of 5 graduate students, 2 medical students, 2 research assistants, and 2 research associates.

MyeliNeuroGene
LAB

Meet the MyeliNeuroGene Team!

Pouneh Amir-Yazdani

Sara Matovic

From left to right: Stephanie Perrier, Mackenzie Michell-Robinson, Luan Tran, Alexa Derksen, Lama Darbelli, Dr. Geneviève Bernard, Marie-Lou St-Jean, Alexandra Chapleau, Aaron Spahr.

The MyeliNeuroGene team is made up of exceptional students who have been the recipients of several prestigious scholarships.

- **Stephanie Perrier (PhD):** Fondation du Grand Défi Pierre Lavoie PhD Scholarship (2018-2020); FRQS Doctoral Training Scholarship (2018-2022).
- **Mackenzie Michell-Robinson (MD-PhD):** CIHR and Hilton J McKeown MD-PhD Training Award (2019-2023); Vanier Canada Graduate Scholarship (2020-2023)
- **Alexa Derksen (MSc):** Fondation du Grand Défi Pierre Lavoie MSc Scholarship (2018-2020); CIHR MSc Scholarship (2019-2020); Healthy Brain Healthy Lives Scholarship (2018-2019), Top-up award for outstanding student, Integrated Program in Neurosciences (2018-2019)
- **Alexandra Chapleau (MSc):** Healthy Brain Healthy Lives Scholarship (2019-2021); Fondation du Grand Défi Pierre Lavoie MSc Scholarship (2019-2020)
- **Aaron Spahr (MSc):** RI-MUHC Scholarship (2019-2020), Faculty of Medicine Studentship (2019-2020), Healthy Brain Healthy Lives Scholarship (2019-2020), Top-up Award for Outstanding Student, Integrated Program in Neurosciences (2018-2019).

Highlights of Current Research

The MyeliNeuroGene Lab continues to make important strides in its research endeavours. One major advancement is the development of the LORIS database to store the information of the MyeliNeuroGene biobank created in 2011, when the lab opened. The purpose of this database is to systematically record the data and samples collected and to be collected, which will help the team achieve its main goals:

- **To identify genes that cause leukodystrophies, genetically determined white matter disorders and other rare genetic diseases**
- **To understand the molecular processes leading to disease, and to develop treatments.**
- **To characterize the clinical evolution and natural progression of these diseases**
- **To understand the impact leukodystrophies have on patients and families**

So far, we have collected data from nearly **600 patients** and their families around the world, including biological samples, clinical and MRI data, as well as questionnaires.

Dr. Bernard has expertise in both clinic and research, has an ever-growing cohort of leukodystrophy patients and families, and has a thriving network of collaborators and supporters, all which make her uniquely positioned to continue to succeed in this research.

Presentations & Publications

Every year, Dr. Bernard participates in international, national and provincial conferences and meetings to continue to enrich her knowledge, educate her team as well as families. Her most recent highlight from June 2020 includes doing virtual presentations to families on “Pelizaeus-Merzbacher disease”, “4H leukodystrophy” and “Diagnosis Leukodystrophies” as part of the United Leukodystrophy Foundation Family Meeting.

Dr. Bernard presenting at the United Leukodystrophy Foundation Family Meeting

In addition to presentations, she has been very prolific in disseminating new scientific findings. Since January 2019, she has contributed to 26 publications that are currently submitted, in press, or published. For a full list of Dr. Bernard’s publications see: https://www.ncbi.nlm.nih.gov/myncbi/1vKxAlgE6PYQe/bibliography/public/

4H Leukodystrophy Research

In 2011, Dr. Bernard's team was the **first** to molecularly characterize 4H (hypomyelination, hypodontia, hypogonadotropic hypogonadism) leukodystrophy, otherwise known as POLR3-HLD. As such, the lab has been very motivated to continue to discover new aspects of this disease. Over the past year, the lab published several papers on expanding the phenotype of POLR3-HLD. Presented below are brief summaries of a few selected recent papers:

❖ Dystonia in RNA Polymeras III-Related Leukodystrophy

In 2019, Al Yazdani et al. examined the prevalence and severity of dystonia, a movement disorder caused by involuntary contraction of the muscles, in patients with POLR3-HLD (10 males:10 females). Among these 20 patients, they found:

- 19/20 patients presented dystonia.
- Only one patient had severe dystonia, whereas most of the other patients fell within the mild and mild to moderate range.
- When considering the dystonia distribution among body parts, the majority of patients had dystonia in many places, with the distal arms and legs being the most commonly affected, and the trunk the least frequently affected.

This clinical paper was important to show the prevalence of dystonia in these patients, which tends to be underdiagnosed.

Dr. Bernard with a patient who has POLR3-related leukodystrophy and his family.

❖ Clinical spectrum of POLR3-related leukodystrophy caused by biallelic *POLR1C* pathogenetic variants

In 2019, the MyeliNeuroGene lab, in collaboration with 25 sites worldwide, published a paper that was the first to describe the clinical spectrum of a POLR3-HLD caused by pathological genetic variants in the *POLR1C* gene (Gauquelin et al. 2019). This was the largest cohort of patients with POLR1C-related leukodystrophy ever reported with 23 patients.

- The initial symptoms for most patients was motor difficulties.
- All patients who lived beyond the neonatal period (22/23) showed cerebellar signs (ataxia, dysarthria, dysmetria, intention tremor, and nystagmus).
- Dystonia was noted in 7/22 patients.
- Cognitive impairment varied but was present in 15/22 patients.
- Seizures occurred in 5/22 patients.
- 5/22 patients presented with varying abnormal craniofacial development.
- Brain imaging showed that all patients had diffuse hypomyelination.

This study was the first to exemplify the variable clinical spectrum in *POLR1C*-related leukodystrophy.

❖ Expanding the phenotypic and molecular spectrum of RNA polymerase III-related leuko«dystrophy

In June 2020, Perrier et al. published a paper describing 6 cases of POLR3-HLD that presented with a very severe form of the disease. These patients show a dramatic clinical presentation with:

- Severe developmental delay and motor regression in infancy.
- Prominent feeding and breathing difficulties – all eventually required a feeding tube.
- Interestingly, the myelination of the brain was very distinct such that there was more myelin than the typical POLR3-HLD phenotype, with progressive basal ganglia involvement. This leads us to believe that this extreme variant of POLR3-HLD affects the brain in a very specific way.

These findings illustrate an expanded phenotypic spectrum of POLR3-HLD in patients with a specific combination of variants in *POLR3A*, which contributes to the severity of the disease.

New Gene

Dr. Bernard collaborates with labs around the world to continue to discover new genes and genetic variants for this group of diseases.

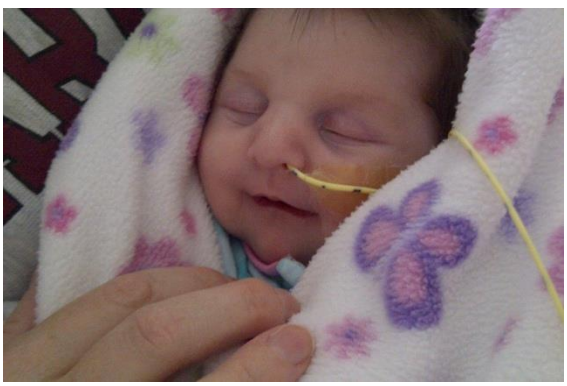
One of the main goals of the MyeliNeuroGene Lab is to identify genes that cause leukodystrophies and related disorders. Most recently, Dr. Bernard's team helped discover that mutations in *VARS1* gene caused a neurodevelopmental and neurodegenerative disease. This finding was published in *Nature Communications* in 2019.

Biallelic mutations in valyl-tRNA synthetase gene *VARS* are associated with a progressive neurodevelopmental epileptic encephalopathy

In 2019, the MyeliNeuroGene lab, in collaboration with researchers from the University of California, San Diego, was the first to associate a gene, *VARS1*, with a specific neurological disorder that causes progressive neurodevelopmental epileptic encephalopathy with abnormal development of myelin in some patients. The *VARS1* gene encodes a protein, valyl-tRNA synthetase, which is important for forming proteins.

- These gene mutations were identified in 7 patients from 5 unrelated families.
- The severity of the neurodevelopmental delay, epileptic encephalopathy and microencephaly varied between patients.
- Over time, patients showed progressive brain atrophy and white matter volume loss.

The discovery of this gene is the first step to finding a potential treatment for this disease.



Photograph of Mathilde, the child admitted to the Children's that contributed to the identification of the gene responsible for this rare neurological disorder.

(https://www.lapresse.ca/sciences/decouvertes/201902/24/01-5215939-un-bebe-atteint-dune-maladie-rare-fait-avancer-la-science.php)

Freshly Accepted and Published

The MyeliNeuroGene Lab recently produced two manuscripts.

The first paper, now accepted, is an international cross-sectional study that evaluated the endocrine and growth abnormalities in 150 POLR3-HLD patients. The results from this study showed that the most common endocrine abnormalities were delayed puberty and short stature. Also, abnormal thyroid function was reported. This was the first study to systematically analyze endocrine abnormalities in a large cohort of patients affected by POLR3-HLD

Beyond the molecular and clinical research that focuses on the cause and presentation of leukodystrophy, the MyeliNeuroGene lab also looks at the impact of leukodystrophy on the patients and their families.

The second paper, now published, is a manuscript entitled “Stress in parents of children with genetically determined leukoencephalopathies”, which demonstrated that:

- Behavioural difficulties and decreased or impaired gross motor functions are two main factors associated with increased stress in mothers.
- A small but significant proportion of parents had clinically significant stress: in the 65th percentile as compared to the 50th percentile. These parents would benefit from professional interventions.

Overall, these findings have implications for the mental health of these parents, of course, but also for the care of their children.

Dr. Bernard with her patient during a physical examination at the Leukodystrophy clinic, Montreal Children’s Hospital.

Looking Ahead

Dr. Bernard's research program is centered around understanding the clinical, radiological, genetic, molecular and pathophysiological bases of leukodystrophy.

Over the past years, she has established herself as an international expert in leukodystrophies and often has patients referred to her from around the world for clinical assessments and to participate in her research program.

Her unceasing goal is to provide families with answers regarding the diagnoses and progression of their child's white matter disease, improve their clinical care and search for cures for these devastating diseases.

Dr. Bernard and her team are excited to announce a few innovative projects that will begin in the near future. Stay tuned on their Facebook group **facebook.com/myelineurogene** and twitter: @**myelineurogene** for updates.

1. Clinical Trial for Children with Late Infantile Metachromatic Leukodystrophy by Shire/Takeda:

Children with Metachromatic Leukodystrophy lack a certain enzyme "arylsulfatase A". This clinical trial is testing the delivery of a drug that has the same function of arylsulfatase A to see if it will improve the condition and outcome of children with this disease.

2. Gangliosidosis (GM1) Natural History Study, a study lead by University of Pennsylvania:

GM1 gangliosidosis is a rare disease caused by the accumulation of lipids, called gangliosides. Abnormal lipid accumulation happens because the function of a certain enzyme called GM1 is reduced or absent. Currently, this disease is not yet well characterized; therefore, this study aims to collect various sources of medical data and biological samples in infantile and juvenile populations to help us better understand the disease.

3. COVID-19 Stress in Caregivers of a Child with Leukodystrophy:

The outbreak of COVID-19 has created unprecedented challenges to healthcare systems globally and is heavily impacting both physical and mental health in communities. Specifically, for children with a leukodystrophy and their caregivers, the COVID-19 pandemic impacted the child's regular health care and has increased the responsibility of the caregivers. The goal of this project is to characterize the stress experienced by our patients and their caregivers during the COVID-19 pandemic using questionnaires.

Press & Media

April 2020

Interview at "Tout un Matin" on the reality of being a physician and the mother of an immunocompromised child during the COVID-19 Pandemic http://www.radio-canada.ca/util/postier/suggerer-go.asp?nID=4497746

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

March 2020

Royal College of Physicians and surgeons: Women's Day
https://www.facebook.com/TheRoyalCollege/posts/2915076065211033
https://www.facebook.com/TheRoyalCollege/posts/2915062961879010

September 2019

Royal College of Physicians and Surgeons of Canada's Prix d'Excellence: Specialist of the Year award for Region 4

- *Med e-News:* https://publications.mcgill.ca/medenews/2019/09/24/pediatric-neurologist-dedicates-her-career-to-leukodystrophies/
- *Royal College newsroom:* https://newsroom.royalcollege.ca/pediatric -neurologist-dedicates-her-career-to-leukodystrophies/
- *MUHC:* https://muhc.ca/news-and-patient-stories/news/dr-genevieve-bernard-years-recipient-prix-dexcellence-specialist-year

March 2019

Manuscript on *VARS1* (Nature Communications) The McGill Tribune:
http://www.mcgilltribune.com/sci-tech/vars-gene-a-new-link-to-a-harrowing-group-of-brain-diseases-250319/

February 2019

Huffington post: https://quebec.huffingtonpost.ca/2019/02/24/bebe-atteint-maladie-rare-fait-avancer-science_a_23676840/

The Gazette: https://montrealgazette.com/news/mcgill-team-part-of-international-group-of-scientists-that-identify-rare-pediatric-brain-disorder

MUHC: https://muhc.ca/newsroom/news/international-team-scientists-detect-cause-rare-pediatric-brain-disorder

For more information on Dr. Bernard's work: MyeliNeuroGene.com, facebook.com/MyeliNeuroGene, and twitter: @MyeliNeuroGene

We are grateful for the community of families, foundations and donors that have united to help fight leukodystrophies. Thank you!

Estate of Daphne Dale Townsend

Foundation of Stars

Fondation du Grand Défi Pierre Lavoie

Fondation Le Tout pour Loo

Leuco-Action

Association Lueur d'espoir pour Ayden

The Mel Hoppenheim Family Foundation

Fondation Les amis d'Elliot

Fondation Leuco dystrophies

Tallman Family

Rachel et Eric Schonbachler

PMD Foundation

Nakashima-Altman Family Endowment Fund

Moss family

Bethany's Hope Foundation

Rare Disease Foundation and the BC Children's Hospital Foundation

Wakefield Canada

Chapleau Family

Emmanuel Ferreira and Christina Andrade

Helem Family

Désirée le Papillon

Oshika Family

Stanhope Family

The successes of Dr. Bernard's lab are attributed to the growing support of families and foundations, which have allowed her to achieve her goals, to work with renowned scientists and recruit exceptional students.

Her ambitious research program is built on highly productive research efforts and a large network of collaborators, like you.

THANK YOU!

heal

love

bond

For more information, please contact

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