Pacific Parkinson's
RESEARCH INSTITUTE

NeuroSeq Project Update

Partners in the Search for a Cure

The Pacific Parkinson's Research Institute (PPRI) partners with the UBC Faculty of Medicine to fund the strategic research priorities of the Pacific Parkinson's Research Centre (PPRC), a Canadian Centre for Excellence for the diagnosis and management of Parkinson's disease and related disorders. The strong partnership between the PPRI and PPRC mirrors the special bond between patients and clinician-scientists at PPRC—decisions on the best ways to improve the lives of people with Parkinson's disease in British Columbia are made locally and collaboratively.

For more information, please visit: www.pacificparkinsons.org

NeuroSeq: An Innovative Data-Sharing Platform

NeuroSeq is a web application that allows academic researchers all over the world to analyze their research data and share their findings at unprecedented speed. Discovering a precise genetic cause of Parkinson's disease is rare, and requires many years of effort to collect and integrate data from patients. NeuroSeq is a solution to this problem; it is accelerating our work in discovering the causes not only of Parkinson's, but also other related neurodegenerative disorders.

It's a vital tool that has a vast potential to enable us to create new treatments for specific groups of patients. For example, our team has had notable successes in this area including the discovery of mutations in alpha-synuclein—a protein present in the brain's neurons—that can lead to Parkinson's, and variations in the leucine-rich-repeat kinase 2 gene, which plays an integral part in turning on and off many cell activities and is connected to the onset of the disease.

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Expanding Scale, Deeper Collaboration

NeuroSeq allows researchers to access the genome sequencing results of more than 3,200 people from around the world, and as this number grows, so does its capacity to create virtual research communities that are making important discoveries in:

- New genes in early-onset Parkinson's disease (Straniero et al., 2017);
- Differential diagnoses, or possible causes, of parkinsonism-dementia (Lichtenstein et al., 2017; Appel-Cresswell et al., 2018);
- Epilepsy (Demos et al., 2019); and
- Pilot studies for rapid genetic sequencing of critically ill newborns (Guella et al., 2016; Elliott et al., 2019).

NeuroSeq is now at the heart of collaborations in more than 20 countries in North America, Europe, Australia, Africa and Asia, and the number of peer-review scientific publications it has supported is a testament to its success (see addendum).

In 2019, NeuroSeq was showcased at the Canadian College of Medical Genetics (CCMG) conference in Niagara Falls, and the American Society of Human Genetics (ASHG) annual meeting in Houston, USA. The CCMG meeting is a yearly gathering of clinical genetics professionals: the people who receive, analyze, interpret, and report on genetic testing across Canada.

NeuroSeq was featured as a clinician workshop where its speed, utility, ease of use and free access made a great impression. The experience at ASHG was similar; the meeting typically draws around 10,000 attendees from around the world, both researchers and clinicians who specialize in every aspect of genetics. NeuroSeq was presented as an academic solution to a common question posed in both clinical and research genetic labs: **"I have the data; now what?"**

Developing NeuroSeq

NeuroSeq is fast becoming an invaluable tool for clinicians and researchers, and work is underway to expand its capabilities, which includes:

- Adding new external data sources such as copy number changes (CNVs), where sections of the genome are repeated throughout its structure. This data can help researchers conclude whether or not having a CNV in a specific area may cause disease.
- Expanding the existing analytical toolset. Late-onset diseases like Parkinson's are extraordinarily complex, and with the new data will come analyses we couldn't previously consider, such as assessing the effect of mutations in more than one gene, and the role of rare variants that fall into the same gene, but at different positions.
- To develop 'clinical decision support' modules and help clinicians translate research into possible therapies and next steps.

To enable the NeuroSeq development and appropriately scale its innovation, we have recently partnered with the University of Florida (UF), the 8th largest academic research institution in terms of the National Institute of Health (NIH) funding in the United States.

The Department of Medicine and UF Health is to provide Institutional support for further software development, especially in 'clinical decision support' modules. Such an environment will expand upon the infrastructure and environment at UBC, improving robustness (given multiple developers and hosting sites) and performance at scale (given the opportunity for expanded research computing infrastructure). UBC's University-Industry Liaison Office (UILO) has agreed to provide a license to enable this enterprise and UF will further research and development of NeuroSeq as on-line software.

We anticipate many hospitals and laboratories would also benefit, though they may be more comfortable in housing the data themselves due to the requirements of data privacy and protection. Through collaboration, we may ultimately develop an improved version of the software to license.

Thank You

The NeuroSeq team is deeply grateful for the PPRI's philanthropic support in supporting NeuroSeq's primary goal: to help the world's Parkinson's molecular research and neuroscience community to identify novel targets and catalyze their innovation in better models. It will aid the development of precision therapeutics to halt symptom progression. Although the vision cannot be achieved at UBC alone, our collaboration in this nascent enterprise is foundational to the effort.

Dan Evans, a bioscience IT specialist, and Omar Zabaneh, a web/database application programmer and analyst, are committed to remaining at the Djavad Mowafaghian Centre for Brain Health until at least 2021, as their enterprise in this web-based effort can be managed and integrated remotely. Given past productivity and future developments and potential partnerships, we very hope we can count on the continued support of the PPRI at UBC.

Matt Farrer, on behalf of the NeuroSeq team

Addendum: Past Publications Featuring NeuroSeq

Appel-Cresswell S, Guella I, Lehman A, Foti D, Farrer MJ. PSEN1 p.Met233Val in a Complex Neurodegenerative Movement and Neuropsychiatric Disorder. J Mov Disord. 2018 Jan;11(1):45-48. doi: 10.14802/jmd.17066. Epub 2018 Jan 11. PMID: 29316780

Demos M, Guella I, DeGuzman C, McKenzie MB, Buerki SE, Evans DM, Toyota EB, Boelman C, Huh LL, Datta A, Michoulas A, Selby K, Bjornson BH, Horvath G, Lopez-Rangel E, van Karnebeek CDM, Salvarinova R, Slade E, Eydoux P, Adam S, Van Allen MI, Nelson TN, Bolbocean C, Connolly MB, Farrer MJ. Diagnostic Yield and Treatment Impact of Targeted Exome Sequencing in Early-Onset Epilepsy. Front Neurol. 2019 May 21;10:434. doi: 10.3389/fneur.2019.00434. eCollection 2019. PMID: 31164858

Elliott AM, du Souich C, Lehman A, Guella I, Evans DM, Candido T, Tooman L, Armstrong L, Clarke L, Gibson W, Gill H, Lavoie PM, Lewis S, McKinnon ML, Nikkel SM, Patel M, Solimano A, Synnes A, Ting J, van Allen M, Christilaw J, Farrer MJ, Friedman JM, Osiovich H. RAPIDOMICS: rapid genomewide sequencing in a neonatal intensive care unit-successes and challenges. Eur J Pediatr. 2019 Aug; 178(8):1207-1218. doi: 10.1007/s00431-019-03399-4. Epub 2019 Jun 7. PMID: 31172278

Guella I, Huh L, McKenzie MB, Toyota EB, Bebin EM, Thompson ML, Cooper GM, Evans DM, Buerki SE, Adam S, Van Allen MI, Nelson TN, Connolly MB, Farrer MJ, Demos M. De novo FGF12 mutation in 2 patients with neonatal-onset epilepsy. Neurol Genet. 2016 Nov 10;2(6):e120. eCollection 2016 Dec.PMID: 27872899

Lichtenstein ML, Dwosh E, Roy Chowdhury A, Farrer MJ, McKenzie MB, Guella I, Evans DM, Nygaard HB, Shewchuk JR, Hayden S, Barton JJS, Feldman HH. Neurobehavioral characterization of adult-onset Alexander disease: A family study. Neurol Clin Pract. 2017 Oct;7(5):425-429. PMID:
29620072

Vollstedt EJ, Kasten M, Klein C; MJFF Global Genetic Parkinson's Disease Study Group. Using global team science to identify genetic parkinson's disease worldwide. Ann Neurol. 2019 Aug;86(2):153-157. doi: 10.1002/ana.25514. Epub 2019 Jun 26. No abstract available. PMID: 31155756