

Effects of genetic variants on the transcriptome of the cellular and molecular architecture of the human brain

DESIRED PROFILES ☐ Internship (CEGEP / undergrad) ☐ M.Sc. ☒ Ph.D. ☒ Postdoc

RESEARCH TEAM

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RESEARCH INTERESTS

Our laboratory investigates how rare genomic variants shape cognition, behaviour, and risk for neurodevelopmental and psychiatric conditions such as autism spectrum disorder, intellectual disability, and schizophrenia. These variants are now returned routinely to patients in the pediatric genetics clinic, yet how they affect the human brain development remains almost entirely uncharacterized.

We work at the interface of human genetics, functional genomics, and neuroscience, using large-scale, quantitative approaches: whole-genome sequencing in cohorts of hundreds of thousands of individuals (SPARK, UK Biobank, All of Us, PGC-CNV), deep phenotyping of cognition and behaviour, brain MRI, electronic health records, and, increasingly, direct molecular measurement in human brain tissue. Over the past two years the lab has assembled two resources that are central to this project: a harmonized collection of ~4,000 post-mortem human cortical samples pairing whole-genome sequencing with bulk and single-nucleus transcriptomes, and the "Molecular Architecture of the Developing Brain" (MADB) fetal brain bank at CHU Sainte-Justine, the only biobank of its kind covering mid- to late gestation with paired MRI, genomics, transcriptomics, and chromatin accessibility in the same specimens.

The lab is embedded in the Azrieli Research Centre of CHU Sainte-Justine, with access to the UniC high-performance computing platform, the IMAGINE neuroimaging platform, and a large network of national and international collaborators (UCSF, Oxford, UCSD, UCLA, SickKids, IIT Madras).

DESCRIPTION OF THE RESEARCH PROJECT

Genetic testing in the clinic identifies an increasing number of rare gene-disrupting variants that contribute to neurodevelopmental and psychiatric disorders. It is reasonable to posit that these variants act by perturbing the molecular program of the developing and mature brain, but the

consequences of genetic liability on the transcriptome, epigenome, and cytoarchitecture of human brain tissue remain essentially unknown. Post-mortem studies have described transcriptomic signatures of the disorders themselves, but it is unclear whether these profiles reflect the end state of illness or the effect of the variants that confer risk — and almost nothing is known about the developing brain, the very period during which these conditions take root.

This project will characterize, at the tissue and single-cell level, how naturally occurring gene-disrupting variants perturb the human brain transcriptome and epigenome, and whether these effects reflect mechanisms of disease. The central hypothesis is that variants increasing liability for neurodevelopmental and psychiatric conditions produce convergent, quantifiable transcriptomic and epigenetic signatures in human brain tissue that partly overlap with disorder-associated dysregulation, but differ fundamentally between the mature and the developing brain.

The work is made feasible by two purpose-built resources: (i) an aggregated, harmonized dataset of ~4,000 human cortical samples pairing whole-genome sequencing with brain transcriptomes (bulk and single-nucleus RNA-seq) across GTEx, CommonMind, HBCC, psychAD, ROSMAP and NABEC, in which all classes of rare gene-disrupting variants have been uniformly called; and (ii) the prospective MADB fetal brain bank (2nd and 3rd trimester), collecting typically and atypically developing brains carrying neurodevelopmental variants, with paired high-resolution post-mortem MRI, fresh-frozen tissue, transcriptomics, and ATAC-seq.

The successful candidate will join a multidisciplinary team spanning clinical and human genetics, functional genomics, single-cell and epigenomics, developmental neurobiology, and neuroimaging, and will work on one of the projects below.

The team is recruiting for three distinct sub-projects. Candidates are invited to specify their preference for one or the other of these sub-projects in their cover letter.

Sub-project 1: Effect of gene-disrupting variants and neurodevelopmental disorders on the cellular and molecular architecture of the human brain.

Most gene-disrupting CNVs and single-nucleotide variants conferring risk for neurodevelopmental and psychiatric disorders are ultra-rare ($<1/10,000$) and distributed across many genes, so they cannot be studied one locus at a time even in large datasets. This project aims at quantifying the transcriptome-wide effect of each variant class in the human cortex.

Analyses will be conducted at the bulk and single-nuclei resolution across ~3,000-samples.

Signatures measured in adolescent and adult brain tissue may partly reflect years of plasticity and secondary remodeling rather than the primary developmental insult. The same approach will therefore be conducted in primary tissue from the developing brain.

We will relate those variant-driven signatures to the dysregulation associated with psychiatric autism and schizophrenia. The candidate will reprocess all available independent datasets through a single harmonized pipeline to deliver the first meta-analysis of case-control brain transcriptomic data in autism, then test the degree of convergence between the disease signature and the variant-driven signatures.

Project 2: Somatic mosaicism in the developing human brain

Germline exome and whole-genome yields a diagnosis in ~30–40% patients with a brain malformation, and brain anomalies such as ventriculomegaly, agenesis of the corpus callosum and cortical malformations affect 1–3% of newborns. A compelling explanation for that diagnostic gap is postzygotic somatic mosaicism: mutations arising after fertilization, present in only a subset of cells, absent from blood and invisible to standard clinical sequencing. Proof of concept exists (somatic PI3K–AKT–mTOR variants in hemimegalencephaly and FCD) but it comes almost entirely from postnatal surgical specimens in drug-resistant epilepsy. The somatic mutational landscape of the developing brain is uncharacterized, and there is no normative reference against which pathogenic variants can be judged.

This sub-project will perform high-depth whole-genome sequencing on developing primary brain tissue with several anomalies such as ventriculomegaly and cortical malformations, as well as structurally normal controls. The candidate will build the first atlas of somatic variant allele fractions, mutational signatures and regional distribution in the developing human brain; identify genes and pathways recurrently disrupted beyond PI3K–mTOR.

Project 3: MRI structural brain alterations across genetic risk for neurodevelopmental disorders.

Our understanding of the effects on brain structure, of genetic variants associated with neurodevelopmental disorders is derived from a very small number of genetic variants. In a collaborative project, we will use electronic health records from both the SickKids and the Sainte Justine Hospital to investigate structural brain MRIs across hundreds of different genetic variants linked to neurodevelopmental and psychiatric disorders.

The project will require processing complex dataset including several tens of thousands of MRI.

STUDY PROGRAMS

Individuals who have completed or are about to complete training in the following areas are invited to apply:

- Human genetics, medical genetics or genomics; bioinformatics or computational biology; biomedical sciences; neuroscience; statistical genetics, biostatistics or statistics; computer science, data science or machine learning; molecular biology with a strong quantitative component. Physicians (M.D.) with research training in genetics or neuroscience are also encouraged to apply.

REQUIRED EXPERTISE AND SKILLS

Depending on the project, the candidate should have skills in some of the following areas:

- Strong programming skills in R and/or Python, and comfort working on a high-performance computing cluster.
- Experience analyzing transcriptomic data: single-nuclei RNA-seq (e.g. Seurat, Scanpy, limma-voom, DESeq2, pseudo-bulk differential expression, cell-type annotation).

- Familiarity with human genomic data and variant calling from whole-genome or whole-exome sequencing (CNVs, SNVs, indels).
- Solid grounding in applied statistics.
- Reproducible workflow practices.
- Neuroimaging analysis.

FUNDING

The positions are fully funded.

KEYWORDS

brain transcriptomics; single-nucleus RNA-seq; copy-number variants; rare variants; whole-genome sequencing; autism; schizophrenia; neurodevelopmental disorders; functional genomics; epigenomics; ATAC-seq; fetal brain development; neuroimaging genomics; bioinformatics; statistical genetics.

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