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McGill

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New "atlas" of genetic influences on osteoporosis

A ground-breaking new study has succeeded in compiling an atlas of genetic factors associated with estimated bone mineral density (BMD), one of the most clinically relevant factors in diagnosing osteoporosis. The paper, published in *Nature Genetics*, identifies 518 genome-wide loci, of which 301 are newly discovered, that explain 20% of the genetic variance associated with osteoporosis. Having identified so many genetic factors offers great promise for the development of novel targeted therapeutics to treat the disease and reduce the risk of fracture.

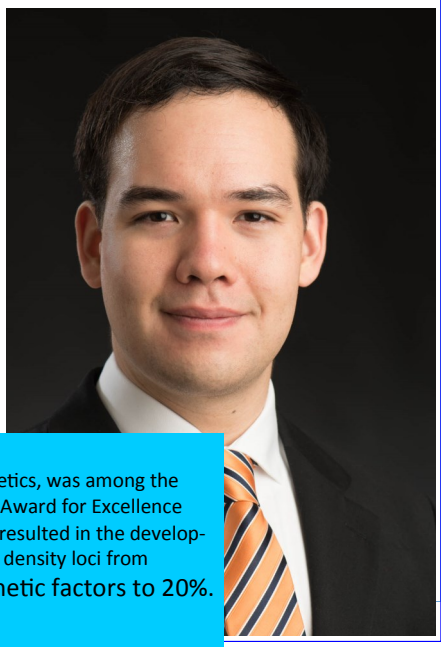
"Our findings represent significant progress in highlighting drug development opportunities," explains **Dr. Brent Richards**, the lead investigator, a geneticist at the LDI who treats patients with osteoporosis in his practice at the JGH. "This set of genetic changes that influence BMD provides drug targets that are likely to be helpful for osteoporotic fracture prevention."

Osteoporosis is a very common age-related condition characterized by the progressive reduction of bone strength, which results in a high risk of fracture. Especially among older patients, fractures can have severe consequences, including the risk of mortality. Among all sufferers, fractures pose major burdens of hospitalization and extended rehabilitation. As the population ages, the urgency of improving preventive measures becomes all the more intense.

"We currently have few treatment options," said Dr. Richards, "and many patients who are at high risk of fractures do not take current medications because of fear of side effects. Notwithstanding that it is always better to prevent than to treat. We can prescribe injectables that build bone, but they are prohibitively expensive. We have medications that prevent loss of bone, but they must be taken on a strict schedule. As a result, the number of people who should be treated, but are not, is high. Therefore, we believe that we will have greater success in getting patients to follow a treatment regimen when it can be simplified."

This was the largest study ever undertaken of the genetic determinants of osteoporosis, assessing more than 426,000 individuals in the UK Biobank. After analyzing the data, the researchers further refined their findings to isolate a set of genes that are very strongly enriched for known drug targets. This smaller set of target genes will allow drug developers to narrow their search for a solution to the clinical problem of preventing fractures in those people who are predisposed to osteoporotic fractures. Animal models have already proven the validity of some of these genes.

"Although we found many genetic factors associated with BMD, the kind of precision medicine that genetics offers should allow us to hone in on those factors that can have the greatest effect on improving bone density and lessening the risk of fracture," said Dr. John Morris, also from the LDI and McGill University, the first author on the study.



John Morris, who recently completed his PhD studies in McGill's Department of Human Genetics, was among the finalists for the 2018 American Society of Human Genetics (ASHG) Charles J. Epstein Trainee Award for Excellence in Human Genetics Research. The award was conferred on the strength of the research that resulted in the development of a genetic "atlas" of osteoporosis, increasing the number of associated bone mineral density loci from previous studies two-and-a-half fold and increasing the variance explained by genetic factors to 20%.

10th Annual LDI Scientific Retreat

Thursday May 2, 2019 8:30—17:30

Gelber Conference Centre
5151 Côte Ste Catherine (2 Cummings Square)

Keynote Speakers:

Dr. Brian J, Druker
Professor of Medicine, Division of Hematology / Medical Oncology, School of Medicine
Associate Dean, Oncology
Oregon Health & Science University
Director, OHSU Knight Cancer Institute School of Medicine
JELD-WEN Chair of Leukemia Research

Dr. Druker's research focuses on activated tyrosine kinases with an emphasis on signal transduction and cellular transformation and the application of this knowledge to cancer therapies. The BCR-ABL oncogene is his lab's primary model system because of its central role in the pathogenesis of a human disease, chronic myeloid leukemia (CML).

Dr. Nada Jabado
Professor, Department of Pediatrics
Associate Member, Department of Medicine, Division of Experimental Medicine, McGill University

Dr. Jabado has embarked on elucidating genetic signatures of pediatric astrocytomas and examining how they compare to adults. These are deadly brain tumours that originate in the brain and include glioblastomas (GBM, the highest grade of astrocytomas), which are one of the deadliest cancers in humans.

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Deadline for Abstract Submission: April 2
Deadline to Register: April 16

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CIHR Project Grant Recipients

Eight principal investigators from the LDI were awarded project grants from the Canadian Institutes of Health Research:

- **Dr. Sonia del Rincon** received $761,175 over five years for "Inhibiting the MNK1/2-eIF4E axis, to favor anti-tumor immunity in melanoma."
- **Dr. Arezu Jahani-Asl** received $753,525 over five years for "OSMR Regulation of Glioblastoma Pathogenesis."
- **Dr. Stephanie Lehoux** received $688,500 over five years for "eIF4E-dependent translation in atherosclerosis."
- **Dr. Andrew Mouland** received $1,013,625 over five years for "HIV-1's hold on host cell vesicular trafficking and metabolism and the impact on pathogenesis, latency and treatment."
- **Dr. Brent Richards** received $983,026 over three years for "Genetically Identified and Validated Biomarkers for Osteoporosis."
- **Dr. Uri Saragovi** received $1,361,700 over four years for "Elucidating the paradox of TrkC receptor isoforms causing either neuronal survival or degeneration: target validation and therapeutic rationale using isoform-selective pharmacological and biological tools."
- **Dr. Brett Thombs** received $348,074 over three years for "The Scleroderma Support group Leader EDucation (SPIN-SSLED) Program: a randomized controlled trial."
- **Dr. Mark Trifiro** received $772,650 over five years for "Using a novel androgen receptor knock-in mouse model to investigate defects in circadian rhythm linked to the development Metabolic Syndrome.

Sonia del Rincon (right) was one of only four new investigators to receive a CIHR Institute Community Support—Early Career Award in Cancer Research . The award is given to new investigators with the highest ranked applications in the Project Grant competition.

Developmental abnormalities in the brain offers clue to schizophrenia

Close examination of the hippocampus in human and mouse brains revealed that the dentate gyrus is noticeably underdeveloped in individuals with schizophrenia, providing the first clear anatomical signature for this condition. **Dr. Hyman Schipper** proposes that the retention of immature properties in this region of the brain into adulthood could be responsible for the disease, which doesn't usually present in males until they are in their twenties, and ifemales in their twenties or thirties. The findings were published in *The Neuroscientist*.

"This abnormality may account for many cardinal symptoms of schizophrenia," Dr. Schipper said, "because the dentate gyrus is associated with the brain's capacity to separate and process sensory stimulation and to distinguish the real from the delusional."

Molecular and electrophysiological abnormalities in the dentate gyrus had already been identified in schizophrenic patients, but no one had previously described a specific anatomical anomaly.

"Because the dentate gyrus is anatomically normal until adolescence in schizophrenia and animal models of the disease, it appears as though developmental arrest within this brain structure manifesting soon after adolescence may be responsible for the emergence of psychotic symptoms," he elaborates.

There is currently no validated biomarker for diagnosing schizophrenia. It is possible that a high resolution MRI would allow for diagnosis based upon the architecture of the dentate gyrus. This promises to be more efficient and accurate than a clinical (psychiatric) evaluation of an individual in the midst of psychosis, which is the current practice.

Drug therapies shown to be effective in preventing maturational arrest of the dentate gyrus in animal models could be tested in humans at-risk for schizophrenia, offering an unprecedented opportunity to possibly influence the pathogenesis of the disease and not merely its symptoms.

Ayda Tavitian, a PhD candidate in Dr. Schipper's lab who first recognized the immature hippocampal morphology, won the IPN Star award from McGill's Integrated Program in Neuroscience for her work on this paper.

14th Annual Psychiatry Research Day

Building Better Bridges: Assessment and Treatment of Immigrant Mental Health Problems

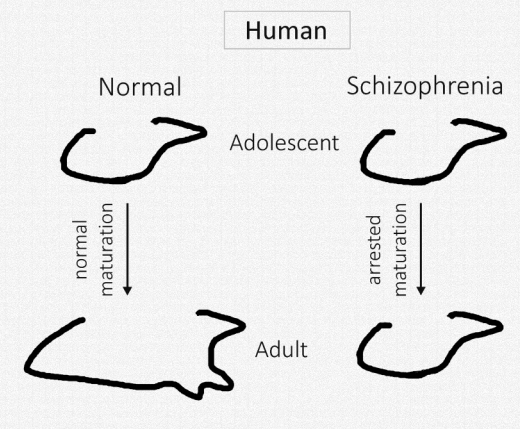
Friday, March 29, 2019, 8:30 AM and 12:30 PM
ICFP Amphitheatre
4333 chemin de la Côte Ste-Catherine

Click here to register

Featuring:
Dr. Cecile Rousseau—*From being at risk to being a risk: Welcoming refugees in challenging times*

Dr. Eric Jarvis—*Cultural consultation with refugees: Diagnostic assessment and case formulation*

Dr. Laurence Kirmayer: *Implications of research on cultural consultation for migration policy, advocacy and clinical practice*



Observed changes in the dentate gyrus in the normal human brain compared with a schizophrenic brain

Off-label prescription of gabapentinoid drugs

The gabapentinoid drugs gabapentin and pregabalin, which have long been approved to treat epilepsy and neuropathic pain, are also being prescribed by physicians for use against more generalized chronic pain as an alternative to dangerous and highly addictive opioids. Though these drugs have been in use since the 1990s, **Dr. Christel Renoux** was surprised to discover that the rate of patients newly treated with gabapentinoids in primary care has tripled over the past decade and, moreover, that 50% of gabapentinoid prescriptions were for off-label indications, and 20% of recipients had a co-prescription for opioids.

The data comes from the Clinical Practice Research Datalink (CPRD), a United Kingdom database that is the most comprehensive source for primary care medical records. Researchers identified nearly 400,000 patients newly treated with gabapentinoids. The results were published in *JAMA.*

"We know that these drugs are effective on neuropathic pain, but we don't have evidence to suggest they are effective or safe for all variety of chronic pain," said Dr. Renoux, "Gabapentinoids are being used as a general prescription for chronic pain when, in fact, they are intended specifically for neuropathic pain. Unfortunately, chronic pain is very difficult to treat. In trying to help suffering patients, doctors may employ medications for purposes for which they were not strictly intended in the hope that it will bring them relief."

She points out that gabapentinoids have sedative effects, not unlike opioids. Therefore, there is increased danger of adverse effects when they are taken together. Both drugs act on the central nervous system and have the unintended effect of depressing respiration. Hence, opportunities for misuse and addiction, as well as for overdose, is magnified when they are combined.

Because the dangers of opioids are well known, doctors sometimes prefer to prescribe an alternative, of which gabapentinoids are one. However, Dr. Renoux urges caution because the side effects for off-label use are improperly understood and require further investigation. There is a need, she points out, for more evidence regarding whether it is appropriate to use them against non-neuropathic pain.

Cancer Research Society Operating Grants

Applicants from the Lady Davis Institute succeeded at nearly double the national rate in the most recent competition for operating grants from the Cancer Research Society (31% to 17%).

Two year grants worth $120,000 were awarded to:

- **Dr. Mark Basik** for "Targeting chemotherapy resistance in triple-negative breast cancer" (funded in partnership with the Quebec Breast Cancer Foundation).
- **Dr. Koren Mann** for "Tungsten-induced leukemogenesis" (funded by the Cancer Research Society's Environment-Cancer Fund in partnership with Read for the Cure).
- **Dr. François Mercier** for "Identification of in vivo regulators of leukemic growth" (funded in partnership with the CIHR Institute of Cancer Research).
- **Dr. Miltiadis Paliouras** for "Targeting HER2 positive breast cancer using photo-ablative directed nanoparticles" (funded in partnership with the CURE Foundation).
- **Dr. Alan Spatz** for "Regulation of mRNA translation by PR70-PP2A in melanoma."

Dr. Celia Greenwood is co-principal investigator, receiving $660,512 in funding from Genome Centre: Génome Québec, for the project, "*Precision Medicine in Cellular Epigenomics*"

To mark the International Day of Women and Girls in Science, CIUSSS West Central Montreal created a video highlighting researchers at the Lady Davis Institute

Click here to watch the video

Dr. Phyllis Zelkowitz and the research of her Infotility team on male infertility was highlighted in a major feature on the topic in a recent issue of *Time* magazine.

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