Interview with Dr. Catrina Loucks

Unravelling genomic factors behind opioid side effects in children

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The Human Genome Project began in 1990 and was a groundbreaking initiative to sequence the human genome, taking over a decade and approximately 3 billion USD to complete.[1] Since then, genomics technologies have advanced so rapidly that a human genome can be sequenced in as little as one day for approximately 200 USD.[2] Today, a variety of sequencing technologies are available, allowing researchers to analyze not only entire genomes but also exomes (protein-coding regions) and RNA. The impact of the Human Genome Project is long lasting, as it simultaneously revealed both the simplicity and complexity of the human genome. Remarkably, as humans we share 99.9% of our genetic makeup, yet it is the remaining 0.1% that gives rise to our individuality.[1] This tiny fraction accounts for a diverse array of traits, from varying hair and eye colours to differences in heights and personalities. It also plays a critical role in health, influencing susceptibility to certain diseases and the likelihood of experiencing adverse effects to medications.

The field of pharmacogenomics focuses on understanding how variability within the human genome influences individual responses to medications. It is well known that individuals can respond differently to the same medication doses, even something as simple as the caffeine in a cup of coffee. Some individuals can drink a cup of coffee and feel energized, while others may not notice any effect, and some may even feel anxious or jittery. This variability in response can be influenced by several factors, such as age and/or sex, but genetic factors also play a significant role.[3] Researchers in pharmacogenomics use a variety of genomics techniques to study this variability, enabling them to uncover genetic factors that influence individual responses to drugs and impact overall safety and effectiveness. As a result of this field of research, several drug labels now include warnings about the potential impacts of genetic factors on the metabolism or effect of a drug, and any recommended genetic testing to ensure its' safety and efficacy for a particular individual.[4]

Dr. Catrina Loucks is an Assistant Professor in the Division of Translational Therapeutics, Department of Pediatrics, and the Department of Anesthesiology, Pharmacology and Therapeutics at the University of British Columbia. Additionally, she is an Investigator at the British Columbia Children's Hospital Research Institute. In these roles, she leads a team of pharmacogenomics researchers that are using genotyping and sequencing techniques to delineate the factors underlying poor pain relief and side effects of opioids used to treat pain in children.

Dr. Loucks' interest in genetics research began during her Bachelor of Health Sciences (Honours) degree and subsequent Master's degree in Medical Sciences at the University of Calgary. As a doctoral student at Simon Fraser University, she uncovered novel biological roles for disease-related genes using the model organism *Caenorhabditis elegans*.[5,6] *C. elegans*, a microscopic worm whose genome was mapped shortly before the completion of the Human Genome Project[1], shares remarkable genetic similarities with humans, with over 50% of its genes having counterparts in the human genome.[7] This genetic connection makes *C. elegans* a valuable model in genetics research. By manipulating the *C. elegans* version of a gene, scientists can explore the effects of specific genetic markers identified in humans, providing valuable insights into their potential implication in human health and disease.

As genomics technologies continued to advance, Dr. Loucks became interested in pursuing research in the human genomics field, particularly in pharmacogenomics. She came to the University of British Columbia to work as a postdoctoral fellow at the

https://doi.org/10.29173/hsi492
Received 28 March 2025
Accepted 1 July 2025

Canadian Pharmacogenomics Network for Drug Safety led by Dr. Bruce Carleton, a Canada-wide network of clinicians and researchers focused on identifying genetic factors underlying adverse reactions to medications.[8] Now, as an Assistant Professor at the University of British Columbia, she combines her previous experiences of conducting genetics research in humans and *C. elegans* to improve the lives of children experiencing severe pain. According to Dr. Loucks, "every person carries genetic characteristics that influence their responses to medications, putting them at an unknown risk of drug-induced harm or ineffectiveness. It is an immense privilege to contribute to pharmacogenomic knowledge that can ultimately empower patients to help choose medications that are both safe and effective for them."

Children undergoing invasive medical procedures or who have severe cancer-related pain often receive opioids, such as morphine or fentanyl, as the first line of treatment.[9–11] However, treatment with opioids can have three different outcomes: good pain relief, poor pain relief, or side effects such as vomiting, breathing problems, or allergic reactions.[12] Poor pain relief and side effects are especially devastating in children as chronic pain can affect brain development, which can lead to behavioural problems as children grow older.[13,14] The opioid crisis has led to a hesitancy to prescribe opioids due to concerns about abuse and overdose[11,15,16], however, opioids are effective pain relievers for many children. "If we can balance the safety and effectiveness of opioids, such that only those who will benefit from them are treated with them, we can effectively treat pain without increasing the harmful effects of opioids," says Dr. Loucks. Dr. Loucks' research team at the University of British Columbia and British Columbia Children's Hospital Research Institute works closely with clinicians to identify and recruit opioid-treated children from hospitals across Canada. They use genomics technologies, such as genome-wide genotyping and exome sequencing, combined with advanced bioinformatic tools, to identify genetic markers that influence how children respond to opioids. As *C. elegans* have recently been shown to be ideal model organisms for opioid pharmacogenomics research[17], Dr. Loucks' team tests genetic markers in *C. elegans* models to better understand how they affect the body's opioid response. Ultimately, her team plans to develop genetic tests that could be administered before opioid use to better predict treatment outcomes. Patients who are expected to experience poor pain relief or side effects to opioids could then be offered alternative pain-relieving medication.

Similar genetic tests are already available for adults for codeine, an opioid that is metabolized to morphine by the enzyme *CYP2D6* to exert its pain-relieving effect. Depending on the genetic markers that an individual carries within the *CYP2D6* gene, they can be classified as a poor metabolizer (where reduced morphine formation leads to poor pain relief), a normal metabolizer (where expected morphine formation leads to good pain relief), or an ultrarapid metabolizer (where increased morphine formation leads to side effects).[18,19] Individuals classified as poor or ultrarapid metabolizers are then recommended other opioids that are not metabolized by the *CYP2D6* enzyme so that they can experience adequate pain relief with minimal side effects.[18,19] However, for opioids other than codeine, there may be other genetic markers that can interfere with pain-relieving abilities. For example, there are currently no genetic markers with strong evidence for affecting the pain-relieving abilities of morphine and fentanyl, and thus no such genetic tests to predict treatment outcomes in these cases. Dr. Loucks' work therefore aims to develop such tools that would ensure patients who require pain management with opioids receive sufficient pain relief while minimizing adverse effects.

Nevertheless, uptake of these genetic tests in the clinic can be challenging. Since genetic testing is a relatively recent addition to clinical practice, some clinicians may not have adequate training to know how or when to use it.[4,20] Some clinicians may also not fully understand, or have easy access to, the evidence for genetic testing in certain contexts.[4,20,21] Dr. Loucks' team hopes to overcome these barriers by creating clinical practice guidelines – essentially, a manual for clinicians.[4] These guidelines provide information about which genetic markers to test for, what the results of the test mean, and whether an alternative medication or dose should be used based on the test results.

Dr. Loucks is enthusiastic about the future of the pharmacogenomics field. In the few decades since the completion of the Human Genome Project, initiatives such as the publicly available genetic data in the 1000 Genomes Project[22], UK Biobank[23], and Genotype-Tissue Expression[24] databases have made it increasingly easier for researchers to investigate genomic variation in large

populations. However, these populations are typically comprised primarily of patients with European ancestry. In response, Genome Canada recently launched an initiative to sequence the genomes of at least 100,000 Canadians, with the aim to reflect Canada's diversity so that these data can be used to improve the health of all Canadians.[25] "Patients of diverse ancestries have historically been underrepresented in pharmacogenetics research, so I'm excited to see more genetic markers discovered in diverse populations," says Dr. Loucks. In addition, advanced machine learning techniques are making it easier to model and find genetic markers for complex drug reactions.[26] Dr. Loucks envisions a future where the insights gained from innovative technologies and diverse genomic data will empower patients and healthcare providers to make well-informed treatment decisions, shaping a future where pharmacogenomics can truly cater to the unique needs of every individual.

Erika Scott is a postdoctoral researcher at the University of British Columbia where she is working to identify genetic predictors of variable responses to morphine treatment in infants and children to better manage pain in these vulnerable patient populations.

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