Deep data dive helps predict cerebral palsy

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The pioneering technique UD Professor Adam Marsh developed to analyze the genetic activity of Antarctic worms is proving valuable for human health care research. Credit: University of Delaware/ Jeffrey Chase

When University of Delaware molecular biologist Adam Marsh was studying the DNA of worms living in Antarctica's frigid seas to understand how the organisms managed to survive—and thrive—in the

extremely harsh polar environment, he never imagined his work might one day have a human connection.

But it turns out that the genome of these Antarctic worms is very similar to ours in terms of the number and types of genes present. And the pioneering technique Marsh developed to analyze their genetic activity is proving valuable for human health care research.

Marsh and a business partner established a biotechnology company to make that technique available for such study. Specifically, Marsh's method uses next-generation genetic sequencing data to measure how cells control the way genes are turned on or off, a process known as DNA methylation.

Now, a Delaware team has released a study in the peer-reviewed journal *BMC Bioinformatics* showing that DNA methylation patterns in circulating blood cells can be used to help identify spastic cerebral palsy (CP) patients.

The interdisciplinary work is a collaborative effort between researchers at UD, Marsh's company Genome Profiling LLC (GenPro for short), and Nemours/Alfred I. duPont Hospital for Children.

Co-authors on the study include Marsh; Robert Akins, the project principal investigator, who directs the Center for Pediatric Clinical Research and Development at Nemours/Alfred I. duPont Hospital for Children and is an affiliated professor at UD; Erin Crowgey, the paper's lead author and associate director of Bioinformatics at Nemours; Karyn Robinson, Akins' laboratory manager, and Stephanie Yeager, project research coordinator, from Nemours Biomedical Research.

Seeking solutions that enable earlier intervention

Spastic CP is a lifelong condition characterized by joint stiffness, jerky movements and muscle tightness that affects the movement and posture and restricts the activity of affected children. CP is the most common physical disability arising in childhood and the Centers for Disease Control and Prevention (CDC) estimates that 1 in every 323 children has CP.

In the study, the research team profiled blood samples collected in a blinded study from adolescents ranging from 9 to 19 years old to explore whether orthopedic surgery patients with spastic CP show differences at the cellular level that routine orthopedic patients (with ACL tears, spine alignment or other surgeries) do not. The researchers identified a strong set of methylation markers, or patterns, that indicate differences in the genome between children with spastic CP and those without it.

These methylation patterns— found in the DNA sequencing data—allowed the scientists to distinguish groups of children that had spastic CP from those that did not. In a second study, using samples from a separate group ranging in age from 2 to 5 years old, the researchers were able to validate their results and predict with 73 percent accuracy whether the blood samples came from children who already had CP.

"The evidence suggests that there is some epigenetic or genetic connection," said Crowgey, a bioinformatician with Nemours Biomedical Research who earned her UD doctoral degree in bioinformatics and systems biology in 2016 and is an affiliated faculty member at UD. "If we can do a better job of screening for these at time of birth versus waiting for the disorder to be diagnosed say, at two years of age, then potentially we'll be able to deliver earlier therapeutics and have better outcomes and lower medical costs."

Medicaid data show that annual medical costs for a child with CP are 10

to 26 times higher than those without CP, imparting a high burden on patients, families and society. In 2003, the CDC estimated that lifetime costs of caring for an individual with cerebral palsy are approximately $1 million, in addition to normal living costs. This amount equaled approximately $1.3 million in 2014 when adjusted for inflation.

The power of data science, analytics and machine learning

The UD/Nemours study leverages a unique statistical method and software platform developed by Marsh at UD, and licensed by GenPro, to measure methylation patterns in DNA (a cell's genetic code) using next generation sequencing (NGS) data.

NGS is a modern technique that enables scientists to decode DNA faster and more cheaply than traditional DNA sequencing techniques. Each person's genome, or complete set of DNA, is like a word that's the length of 3 billion characters; but spelled with only the letters A, T, C or G. Traditional DNA sequencing techniques decode sections of DNA 700 characters at a time, while NGS takes advantage of parallel computing capabilities to enable scientists to simultaneously decode millions of DNA fragments.

According to Marsh, in the human health applications he is studying, subtle changes in a patient's physical health are paralleled by changes in DNA methylation, making it a useful tool to understand disease.

"Many of the signals that we are picking up are based on immune system shifts—meaning the way a person's immune system responds to external stress events," said Marsh, GenPro's chief science officer and an associate professor in UD's College of Earth, Ocean, and Environment. "We are able to pick up that epigenetic response, or signal, found in the

genetic sequencing and use it to provide another line of evidence for clinicians to use in making decisions."

The approach uses sophisticated machine learning techniques and algorithms to sort through hundreds of gigabytes of NGS data looking for these distinct DNA methylation patterns.

"The data is massive," Crowgey said. "It's not something a human can do, you need infrastructure, machine learning and data analysis, and data science."

It's the kind of research and training that will be possible through UD's newly announced Data Science Institute, which will be led by Cathy Wu, who advised Crowgey's UD doctoral studies.

Results are promising, but researchers say more testing is needed

While the study findings indicate that there is a consistent signal present in circulating blood cells of children with spastic CP that remains from early childhood to teenage years, the researchers say further study is needed of samples from different age groups, including teenagers, toddlers and infants from birth to two years old. Better understanding these methylation signals also could provide researchers new clues to understanding the cellular processes involved in advancing CP, and consequently, new therapeutics to manage the disease.

"We're still in the early phases, but the results are extremely promising and we're excited about the sensitivity of the test that we are seeing in our retrospective analysis," Crowgey said. If successful, the researchers say the blood test also may be useful for other disorders, including infant leukemia.

"This blood test could be a game changer," said Dr. M. Wade Shrader, who leads the Cerebral Palsy Center at Nemours/Alfred I. duPont Hospital for Children. "The earlier the diagnosis, the earlier we can direct therapies at the child. Specifically, high intensity physical therapy and possibly early surgery to prevent more significant problems in the future, and hopefully improve overall function and quality of life."

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The birth of a biotechnology startup

Marsh credits his unique background in computational biology, marine science and academia with helping him to approach problems in human health in a non-traditional way.

In Antarctica, Marsh was trying to understand how environmental forces epigenetically altered DNA methylation patterns in invertebrate worms. Specifically, he was studying how stress from low temperatures and low food availability stimulated chemical changes at the cellular level to help cells survive, and how those changes were passed along to future generations.

At the time, available techniques to do this work were expensive and focused on human model systems, so Marsh developed his own method and platform to measure DNA methylation patterns using NGS data. Once the platform was working, Marsh realized it could be applied to any organism, including the human genome.

"Genomes are genomes, but I needed more funding support to push the tool further," Marsh said.

David Weir, then director of UD's Office of Economic Innovation and Partnerships (OEIP), helped Marsh protect his idea and introduced him to Jeb Connor, whose expertise lies at the nexus of software and life sciences. Early on, Connor peppered Marsh with questions about the technology before arranging meetings for Marsh to speak with others about the project. Fast forward 100 or so presentations and the pair knew they were on to something worthwhile.

Marsh and Connor co-founded the biotech startup company GenPro in 2011 and commercialized in 2014. Today, GenPro has a core team of five professionals and the GenPro software platform provides a fast, cost-effective and more accurate way to measure DNA methylation patterns over traditional techniques.

Marsh called OEIP an incredible resource that helped him "stay on track, make the right contacts in the business community and push [his] ideas further" than he could alone. And there were others too, from Connor who helped Marsh develop his analytics platform into a product with a solid business plan, to the health care systems and other partners the GenPro team has developed along the way.

"I've been impressed by Delaware's ecosystem," Marsh said. "It wasn't just us at GenPro with an idea, we had help from UD, agencies and other companies. From small things like people who were willing to give us feedback about our idea, to state funding through Delaware Bioscience Center for Advanced Technology grants to do the genetic sequencing."

Last fall, GenPro and researchers at Christiana Care Health System announced a promising new blood assay, or test, that may improve the ability to detect breast cancer when used in conjunction with routine monitoring, such as mammography.

The assay leverages the GenPro analytics to identify epigenetic

biomarkers that can be used to detect subtle changes in the immune response in women with different stages of breast cancer. The work is a collaborative project with Christiana Care immunologist Jennifer Sims-Mourtada, director of translational breast cancer research at the Helen R. Graham Cancer Center and Research Institute. The team completed its first pilot study in 2016 and has raised funds from various sources to support ongoing preclinical work.

More information: Erin L. Crowgey et al, Epigenetic machine learning: utilizing DNA methylation patterns to predict spastic cerebral palsy, *BMC Bioinformatics* (2018). DOI: 10.1186/s12859-018-2224-0

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