Researchers develop new approach to analyzing complex genetics underlying spina bifida

December 20 2021

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Weill Cornell Medicine researchers are using machine learning, a form of artificial intelligence, to shed light on genetic mutations associated with spina bifida. In this birth defect, the neural tube that forms the spinal cord during pregnancy, does not close so that spinal nerves are

exposed, resulting in paralysis and high risk of other complications.

Their new study, published online Dec. 16 in *PNAS*, "brings us closer to being able to provide a precision medicine approach to families who are looking to ensure healthy birth outcomes and the greatest potential for infants affected by spina bifida," said senior author Dr. Margaret Elizabeth Ross, director of the Center for Neurogenetics and professor of neuroscience in the Feil Family Brain and Mind Research Institute and the Nathan Cummings Professor in Neurology at Weill Cornell Medicine.

Spina bifida is a complex genetic disorder, meaning it's not generally caused by malfunction in a single gene but usually requires an interplay of several genes that have been altered in relatively small ways. Environmental conditions such as nutrition and the medications and supplements women are taking can also impact fetal health. "The challenge is to understand the role of genetic variation in individual families, coupled with the environmental factors, so we can do our best to ensure a healthy baby," said Dr. Ross, who also heads the Laboratory of Neurogenetics and Development at Weill Cornell Medicine.

Studying the genes involved in causing spina bifida has been challenging. Mouse models bearing specific gene mutations have helped researchers gain insight into genetic pathways that may be important to neural tube closure, and researchers have looked for alterations to these genetic pathways in humans. However, the problem with this approach to scientific investigation is bias. "You tend to get what you look for," Dr. Ross said.

In order to find ways to prevent and treat complex genetic disorders, it is necessary to reduce this bias inherent in a "candidate gene search", that is, to avoid limiting the search for clinically relevant genes to those already implicated in experimental models. One way to look at our genes

without a preconceived notion of what causes disease is to search across the complete set of genes in a genome-wide association study (GWAS). A successful GWAS requires thousands of patients to find specific mutations related to a disease. While such large patient collections have been gathered for common complex disorders like autism spectrum that affects 1 in 54 children in the United States, a GWAS approach is really challenging for spina bifida that affects one in every 2,758 live births in the United States or 1,427 babies born each year, according to the Centers for Disease Control and Prevention. "We need to devise new ways for genome-wide investigations of complex genetic conditions that are less common but still impact many families." Dr. Ross said.

Tackling these obstacles, Dr. Ross and her colleagues, including at Weill Cornell Medicine-Qatar, Baylor College of Medicine, and Stanford Medicine, developed an unbiased approach to study a smaller number of people to find genes that distinguish patients with spina bifida versus individuals without the condition, and apply further systems biology tools to assess relevance of those genes to human spina bifida. The researchers examined the genomes of 149 people with spina bifida and 149 healthy controls with similar genetic backgrounds. Because spina bifida is rare, studying people from around the globe is necessary to obtain enough data, Dr. Ross said. This is why the researchers evaluated genetic information from people in both the United States and Qatar. Using machine learning, in which a computer algorithm sorts through and categorizes data, they were able to determine which genes bearing predicted function-changing variants had the greatest potential for distinguishing cases from controls.

The researchers then analyzed how these genes relate to activities at the molecular level. The pathways that were most highly significant involved glucose and lipid metabolism, meaning the body's ability to break down and use sugar and fats for cell energy and function. "These processes are relevant to conditions like diabetes and obesity," Dr. Ross said. Diabetes

and obesity during pregnancy are both known risk factors for neural tube defects. "This really gave us a lot of encouragement that our machine learning approach was coming up with clinically relevant information," she said, and the method is identifying additional significant molecular pathways that underpin the condition.

"We continue to build an international consortium of clinicians and families to increase the power of this approach toward understanding human spina bifida," Dr. Ross said. Ultimately, she hopes it will be possible to analyze the genomes of couples who want to conceive, to identify their optimal strategies for preventing spina bifida. For example, for some couples, additional folic acid may be an excellent preventive measure, while for others, taking a supplement like inositol—that can support cell membrane function—may help lower the risk of spina bifida, according to some studies. "One day we will be able to counsel individual couples on what is the most effective route for them to have a healthy birth outcome, and for a child affected by spina bifida, to optimize their development and quality of life into adulthood," she said.

More information: Vanessa Aguiar-Pulido et al, Systems biology analysis of human genomes points to key pathways conferring spina bifida risk, *Proceedings of the National Academy of Sciences* (2021). DOI: 10.1073/pnas.2106844118

Provided by Weill Cornell Medical College