Artificial intelligence can accelerate clinical diagnosis of fragile X syndrome

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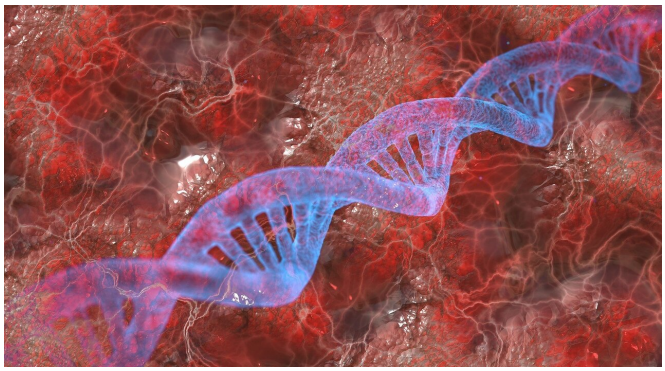

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An analysis of electronic health records for 1.7 million Wisconsin patients revealed a variety of health problems newly associated with fragile X syndrome, the most common inherited cause of intellectual disability and autism, and may help identify cases years in advance of the typical clinical diagnosis.

Researchers from the Waisman Center at the University of Wisconsin–Madison found that people with fragile X are more likely than the general population to also have diagnoses for a variety of circulatory, digestive, metabolic, respiratory, and genital and urinary disorders. Their study, published recently in the journal *Genetics in Medicine*, the official journal of the American College of Medical Genetics and Genomics, shows that machine learning algorithms may help identify undiagnosed cases of fragile X syndrome based on diagnoses of other physical and mental impairments.

"Machine learning is providing new opportunities to look at huge amounts of data," says lead author Arezoo Movaghar, a postdoctoral fellow at the Waisman Center. "There's no way that we can look at 2 million records and just go through them one by one. We need those tools to help us to learn from what is in the data."

Machine learning is a form of artificial intelligence that uses computers to analyze large amounts of data quickly and efficiently. Movaghar and Marsha Mailick, emeritus vice chancellor of research and graduate education at UW–Madison and a Waisman investigator, employed machine learning to identify patterns among the various health conditions of a huge pool of records collected over 40 years by Marshfield Clinic Health System, which serves northern and central Wisconsin.

Though fragile X symptoms vary, the AI-generated model successfully predicted diagnoses of fragile X as much as five years earlier than receipt of a clinical diagnosis of FXS in patients with symptoms such as developmental delay, speech and language disorders, attention deficit hyperactivity disorder, anxiety disorder, and intellectual disability.

The algorithm could alert physicians to the risk of fragile X and reduce the time to reach a clinical diagnosis. The typical path to a genetic test confirming a fragile X diagnosis can take as long as two years after initial concerns arise.

"A lot of people are still not getting the proper diagnosis or, they have to go through a really long process before being diagnosed," Movaghar says. "Just knowing and receiving the proper diagnosis gives you the answers to this question that you always had of why you're experiencing these health conditions or what's happening to your child."

By using the lifetime medical history of patients and a discovery-oriented approach, the researchers were able to expand their investigation beyond known neurological and mental co-occurring conditions and characterize the full spectrum of health risks associated with fragile X. For example, the researchers found an alarming number of heart-related comorbidities, which confirm that regular

screening for circulatory disease is critical for fragile X patients. Heart valve disorders were five times more frequent among fragile X cases than the general population, according to the new study.

While there is not yet a cure for fragile X, earlier diagnosis will allow for more timely interventions, genetic counseling and family planning.

"There are patterns in the data in the electronic health records that can reveal important clinical interventions," Mailick says.

The study has strong implications not just for individuals with fragile X, but for their families. A diagnosis of the syndrome for one person in a family is a strong indication that relatives should also be tested. But in many cases, families have a second child with fragile X before receiving a diagnosis for their first child.

"Because this is a condition that's inherited across generations, it's expressed in other members of the family," Mailick says. "When a child is diagnosed, other members of the family can choose to be tested and identify if there are others who have fragile X syndrome or other conditions related to the mutation."

The researchers would like to expand their study to include data from medical records within other health care systems.

"Now we have to see whether those new conditions also appear if we were to ask the same question in another data source," Mailick says.

Other Waisman researchers involved in the study include Danielle Scholze, Jinkuk Hong, Leann Smith DaWalt and Murray Brilliant. David Page of Duke University and Finn Kuusisto and Ron Stewart from the Morgridge Institute for Research also contributed to the study.

"This is really the meeting of the minds of many, many different disciplinary points of view," Mailick says. "And I truly believe this is a great example of why the Waisman Center is such a good place to do really interesting work and how grateful we are to be able to do that at Waisman."

More information: Arezoo Movaghar et al. Artificial intelligence–assisted phenotype discovery of fragile X syndrome in a population-based sample, *Genetics in Medicine* (2021). DOI: 10.1038/s41436-021-01144-7

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