Using AI to improve diagnosis of rare genetic disorders

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Diagnosing rare Mendelian disorders is a labor-intensive task, even for experienced geneticists. Investigators at Baylor College of Medicine are trying to make the process more efficient using artificial intelligence. The team developed a machine learning system called AI-MARRVEL (AIM) to help prioritize potentially causative variants for Mendelian disorders. The study is published in *NEJM AI*.

Researchers from the Baylor Genetics clinical diagnostic laboratory noted that AIM's module can contribute to predictions independent of clinical knowledge of the gene of interest, helping to advance the discovery of novel disease mechanisms.

"The diagnostic rate for rare genetic disorders is only about 30%, and on average, it is six years from the time of symptom onset to diagnosis. There is an urgent need for new approaches to enhance the speed and accuracy of diagnosis," said co-corresponding author Dr. Pengfei Liu, associate professor of molecular and human genetics and associate clinical director at Baylor Genetics.

AIM is trained using a public database of known variants and genetic analysis called Model organism Aggregated Resources for Rare Variant ExpLoration (MARRVEL) previously developed by the Baylor team. The MARRVEL database includes more than 3.5 million variants from thousands of diagnosed cases. Researchers provide AIM with patients' exome sequence data and symptoms, and AIM provides a ranking of the most likely gene candidates causing the rare disease.

Researchers compared AIM's results to other algorithms used in recent benchmark papers. They tested the models using three data cohorts with established diagnoses from Baylor Genetics, the Undiagnosed Diseases Network (UDN) and the Deciphering Developmental Disorders (DDD) project. AIM consistently ranked diagnosed genes as the No. 1 candidate in twice as many cases than all other benchmark methods using these real-world data sets.

"We trained AIM to mimic the way humans make decisions, and the machine can do it much faster, more efficiently and at a lower cost. This method has effectively doubled the rate of accurate diagnosis," said co-corresponding author Dr. Zhandong Liu, associate professor of pediatrics—neurology at Baylor and investigator at the Jan and Dan

Duncan Neurological Research Institute (NRI) at Texas Children's Hospital.

AIM also offers new hope for rare disease cases that have remained unsolved for years. Hundreds of novel disease-causing variants that may be key to solving these cold cases are reported every year; however, determining which cases warrant reanalysis is challenging because of the high volume of cases. The researchers tested AIM's clinical exome reanalysis on a dataset of UDN and DDD cases and found that it was able to correctly identify 57% of diagnosable cases.

"We can make the reanalysis process much more efficient by using AIM to identify a high-confidence set of potentially solvable cases and pushing those cases for manual review," Zhandong Liu said. "We anticipate that this tool can recover an unprecedented number of cases that were not previously thought to be diagnosable."

Researchers also tested AIM's potential for discovery of novel gene candidates that have not been linked to a disease. AIM correctly predicted two newly reported disease genes as top candidates in two UDN cases.

"AIM is a major step forward in using AI to diagnose rare diseases. It narrows the differential genetic diagnoses down to a few genes and has the potential to guide the discovery of previously unknown disorders," said co-corresponding author Dr. Hugo Bellen, Distinguished Service Professor in molecular and human genetics at Baylor and chair in neurogenetics at the Duncan NRI.

"When combined with the deep expertise of our certified clinical lab directors, highly curated datasets and scalable automated technology, we are seeing the impact of augmented intelligence to provide comprehensive genetic insights at scale, even for the most vulnerable

patient populations and complex conditions," said senior author Dr. Fan Xia, associate professor of molecular and human genetics at Baylor and vice president of clinical genomics at Baylor Genetics.

"By applying real-world training data from a Baylor Genetics cohort without any inclusion criteria, AIM has shown superior accuracy. Baylor Genetics is aiming to develop the next generation of diagnostic intelligence and bring this to clinical practice."

More information: AI-MARRVEL: A Knowledge-Driven Artificial Intelligence for Molecular Diagnostics of Mendelian Disorders, *NEJM AI* (2024). dx.doi.org/10.1056/AIoa2300009

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