Personalising whole genome sequencing doubles diagnosis of rare diseases

November 7 2022

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Tailoring the analysis of whole genome sequencing to individual patients could double the diagnostic rates of rare diseases, finds a new study led by UCL researchers.

In 2018, the UK's department of health announced an NHS Genomic Medicine Service, which allows patients with rare diseases to have their entire genetic code read in the hope of providing a much-needed diagnosis.

However, the interpretation of this data can be extremely challenging and many people with complex, rare genetic diseases still do not receive a molecular answer to the cause of their problems.

In the study, published in *Nature Communications*, researchers at The London Mitochondrial Center at UCL Queen Square Institute of Neurology and UCL Great Ormond Street Institute of Child Health sought to offer such patients an improved chance of receiving a genetic diagnosis.

To do so, they tested how using a genomic medicine team of specialist doctors, bioinformaticians, and scientists could boost the capabilities of NHS diagnostic laboratories beyond the standard semi-automated analysis of data. The UCL team re-evaluated undiagnosed cases to identify clues that might help direct further, more personalized analysis. They subsequently applied additional bioinformatic approaches, using advanced computer technologies to identify genetic alterations in a patients' DNA which may be causing disease but had been overlooked during routine testing.

The work included 102 undiagnosed patients, suspected of having a primary mitochondrial disease (a large group of incurable genetic disorders that affect children and adults, associated with a broad spectrum of medical problems, severe disabilities, and reduced lifespan), who had undergone whole genome sequencing via the NHS's 100,000 Genomes Project.

This personalized approach increased the diagnostic rate from 16.7% to

31.4%. It also detected potential disease-causing variants in a further 3.9% of patients.

Lead author, Dr. Robert Pitceathly (co-lead for the London NHS Highly Specialized Service for Rare Mitochondrial Disorders and a research group leader at UCL Queen Square Institute of Neurology), said: "The NHS has invested heavily in advanced genetic technologies. Consequently, the UK has established itself at the forefront of diagnostic whole genome sequencing. That said, some people with rare genetic diseases remain without a molecular diagnosis after their genome is analyzed.

"We believe investing in specialist genomic medicine teams is crucial, ensuring equitable access to dedicated multidisciplinary expertise and maximizing diagnoses. On average, patients in our study waited over 30 years for a diagnosis—we now have the capability to solve such cases but need adequate workforce planning to support NHS diagnostic genetic laboratories in achieving this goal."

Receiving a genetic diagnosis is important as it allows patients to receive access to family planning, specialized IVF, and drugs trials. It can also permit targeted screening of known disease complications and access to drug studies.

Dr. Pitceathly said: "In this study, every new genetic diagnosis had a direct impact on patient care. This included additional check-ups for heart problems, hearing loss, and diabetes, and access to clinical trials."

Professor Michael Hanna, Director of UCL Queen Square Institute of Neurology said: "This work is a significant step forward in developing the best ways to maximize the benefits of genome analysis for patients. It clearly demonstrates that by combining automated approaches to genome analysis with data interpretation by a skilled multidisciplinary

team the diagnostic rates doubles. This is an important finding that will influence how genomic medicine diagnostic services should evolve world-wide."

Co-author, Dr. James Davison (Metabolic Medicine Department at Great Ormond Street Hospital and chair of the British Inherited Metabolic Diseases Group), said: "The journey to reaching a diagnosis for children and adults with rare, complex, medical conditions can be a very long process, and genomic medicine provides a transformative and powerful tool in helping reach that goal.

"This study highlights the importance of the collaboration between specialist clinicians and genetic scientists in interpreting the results of genome sequencing to maximize the opportunity of reaching a diagnosis which can then help guide medical management and treatment options."

Patient story

Rachel North was one of the patients involved in the trial and described getting a diagnosis as "life changing". It has since allowed her to be screened for disease complications such as osteopenia, and these have been treated.

She said: "I had attended so many hospitals over the past 20 years and had been searching so long, I never thought I'd get a diagnosis.

"Wondering about it took up so much energy, and I was worried about my 12-year-old son, and if my condition would affect him. So, getting a rare recessive diagnosis was a relief and takes away fear of the unknown.

"Having a diagnosis allows me to research my condition and be very proactive in managing it.

"Anything that helps me understand and make sense of what is happening to my body helps me come to terms with it and gives me confidence that I am managing it as well as possible."

More information: Specialist multidisciplinary input maximises rare disease diagnoses from whole genome sequencing, *Nature Communications* (2022). DOI: 10.1038/s41467-022-32908-7

Provided by University College London

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