Unprecedented data sharing driving new rare disease diagnoses in Europe

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Sergi Beltran and Leslie Matalonga pictured in front of a supercomputer and servers that hosts the RD-Connect GPAP platform. The platform is located at the CNAG-CRG facilities in the Parc Cientific de Barcelona. Credit: Centro Nacional de Análisis Genómico (CNAG-CRG)

Rare disease experts detail the first results of an unprecedented collaboration to diagnose people living with unsolved cases of rare diseases across Europe. The findings are published today in a series of six papers in the *European Journal of Human Genetics*.

In the main publication, an international consortium , known as Solve-RD, explains how the periodic reanalysis of genomic and phenotypic information from people living with a rare disease can boost the chance of diagnosis when combined with data sharing across European borders on a massive scale. Using this new approach, a preliminary reanalysis of data from 8,393 individuals resulted in 255 new diagnoses, some with atypical manifestations of known diseases.

A complementary study describes the method in more detail and four accompanying case studies showcase the advantages of the approach. In one case study, researchers used the method to identify a new genetic form of pontocerebellar hypoplasia type 1 (PCH1), a genetic disease that affects the development of the brain. PCH1 is normally linked to mutations in four known genes. The researchers used the method to identify a new variant in a fifth gene.

In another case study, researchers used the method on an individual with a complex neurodevelopmental disorder and found the disease was caused by a new genetic variant in mitochondrial DNA. This went previously undetected because the patient did not present typical symptoms of a mitochondrial disorder. The diagnosis will help tailor treatment for the individual, as well as inform their family members on the possibility of passing it on to future generations.

Key to the reanalysis of unsolved cases is the RD-Connect Genome-Phenome Analysis Platform, which is developed, hosted and coordinated by the Centro Nacional de Analisis Genomico (CNAG-CRG), part of the Center for Genomic Regulation (CRG), based in Barcelona.

Recognized officially by the International Rare Diseases Research Consortium and funded by the EU, Spanish and Catalan governments, the RD-Connect GPAP provides authorized clinicians and researchers with secure and controlled access to pseudonymised genomic data and clinical information from patients with rare diseases. The platform enables the secure, fast and cost-effective automated re-analysis of the thousands of undiagnosed patients and relatives entering the Solve-RD project.

According to Sergi Beltran, co-leader of Solve-RD data analysis and Head of the Bioinformatics Unit at CNAG-CRG, "Solve-RD has shown that it is possible to securely share large amounts of genomics data internationally for the benefit of the

patients. The work we are publishing today is just the tip of the iceberg, since many more patients are being diagnosed thanks to the innovative methods developed and applied within Solve-RD."

An estimated 30 million people in Europe are affected by a rare disease during their lifetime. More than 70% of rare diseases have a genetic cause. However, around 50% of patients with a rare disease remain undiagnosed even in advanced expert clinical settings that use techniques such as genome sequencing.

At the same time, scientists around the world are finding an average of 250 new gene-disease associations and 9,200 variant-disease associations per year. As scientific understanding expands, reanalysing data periodically can help people receive a diagnosis.

The consortium, which consists of more than 300 researchers and clinicians in fifteen countries, and who collectively see more than 270,000 rare disease patients each year, aims to eventually diagnose more than 19,000 unsolved cases of rare diseases with an unknown molecular cause. Their preliminary findings are an important first step for the development of a European-wide system to facilitate the diagnosis rare diseases, which can be a long and arduous process.

More information: Zurek, B., et al. Solve-RD: systematic pan-European data sharing and collaborative analysis to solve rare diseases. Eur J Hum Genet (2021). doi.org/10.1038/s41431-021-00859-0

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