Web-based resource provides precise classification of dual genome variants of primary mitochondrial disease

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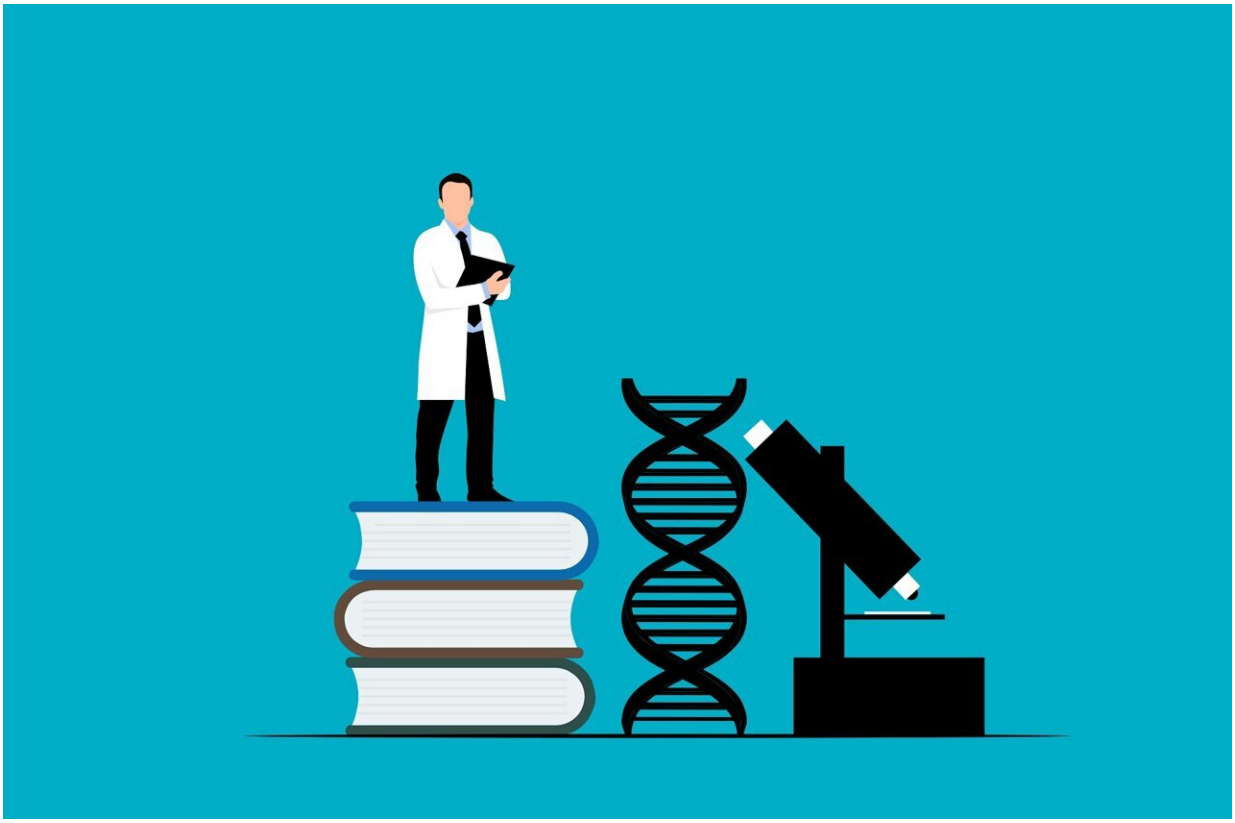

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A multi-institutional team of researchers led by teams at Children's Hospital Los Angeles and Children's Hospital of Philadelphia (CHOP)

has developed a user-friendly, web-based genomic dataset analysis platform to help researchers more easily identify likely disease-causing gene variants in patients with suspected mitochondrial disease.

The findings were recently published online by the journal *Current Protocols*.

While other web-based resources to analyze exome and genome datasets exist, they are often not directly available for researchers to upload and readily analyze their raw data in the context of clinical features of individual patients.

In addition, most genomic data analysis pipelines do not address the dual genome nature of primary mitochondrial diseases, which are multi-system disorders that may result from gene variants in either the nuclear DNA of cells or, uniquely, in the DNA genomes that exist outside the nucleus within mitochondria (mitochondrial DNA, or mtDNA).

Hundreds of pathogenic variants in more than 400 genes across both genomes have now been associated with a variety of primary mitochondrial diseases, creating a greater need to provide resources to research underlying genetic diagnoses of these individually rare but collectively common sets of energy deficiency diseases.

"While great advancements have been made in web-based tools designed to identify pathogenic variants associated with disease, these resources are often very general and designed to encompass all diseases associated with variants in nuclear DNA," said senior author Xiaowu Gai, Ph.D., Director of Bioinformatics in the Center for Personalized Medicine in the Department of Pathology and Laboratory Medicine at Children's Hospital Los Angeles.

"We wanted to design a resource that supported the special

characteristics of primary mitochondrial disease and the broad community of mitochondrial disease researchers."

Empowering the mitochondrial disease community with bioinformatics has been the aspiration of the lead author, Lishuang Shen, Ph.D., who is also the lead bioinformatician of the Mitochondrial Disease Sequence Data Resource (MSeqDR) consortium, ever since MSeqDR's inception.

To help provide a widely available resource that takes primary mitochondrial diseases and their dual genome nature into account, the study team developed MSeqDR Quick-Mitome, which offers an automated variant interpretation of whole-exome sequencing datasets for primary mitochondrial diseases.

In this study, the researchers found that the Mitochondrial Disease Variant Classifier, developed for use with Quick-Mitome (QM), correctly classified more than 98% of variants. It further predicted primary mitochondrial disease-causing variants with 94% precision based on performance benchmarks.

"Quick-Mitome represents a significant effort from the international mitochondrial disease research community to create an automated and user-friendly experience for researchers who want to be able to directly analyze raw genomic datasets in the context of specific medical features of individual primary mitochondrial disease patients," said senior study co-author Marni Falk, MD, executive director of the Mitochondrial Medicine Frontier Program at CHOP.

"While hundreds of causal genes across both nuclear and mtDNA genomes have already been identified to cause primary mitochondrial disease, many more are discovered every year."

"This web platform serves as an equalizer to allow those researchers who

know individual patients best to directly upload, query, and consider in their existing genomic data the potential relevance to their patient's disease symptoms of machine learning prioritized variants identified in both known and novel disease genes."

The MSeqDR QM Web server has been running and continuously upgraded since June 2017 and is freely accessible for research use. Overall, MSeqDR QM represents a significant effort of the international MSeqDR consortium to empower automated, user-friendly, research-based genetic diagnoses for the broad, highly heterogeneous, and continually growing group of primary mitochondrial diseases.

The MSeqDR Quick-Mitome Web server is publicly available for non-commercial, non-clinical research use. Quick-Mitome is a resource built by and for the international Mitochondrial Disease Sequence Data Resource (MSeqDR) Consortium.

More information: Lishuang Shen et al, MSeqDR Quick-Mitome (QM): Combining Phenotype-Guided Variant Interpretation and Machine Learning Classifiers to Aid Primary Mitochondrial Disease Genetic Diagnosis, *Current Protocols* (2024). DOI: 10.1002/cpz1.955

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