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A MASTERMIND STORY

Rady Children's Institute for Genomic Medicine

Mastermind Uncovers Baby's Rare Immunodeficiency

RADY CHILDREN'S INSTITUTE FOR GENOMIC MEDICINE®

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When a child needs a genome-driven diagnosis fast, clinicians turn to Rady Children's Institute for Genomic Medicine (RCIGM) in San Diego. More than 50 children's hospitals nationwide rely on the Institute for ultra-rapid genetic analysis, diagnosis, and treatment recommendations.

Associate Lab Director Kasia Ellsworth sees the difference they make every day. "About 4% of children or neonates born in hospitals require critical care", she said. "There they start interim empirical treatment, and a search for etiological diagnosis begins. We can expect that 20 to 50% of those kids will end up having a genetic diagnosis, and from many of those diagnoses we can devise precision treatment. That leads to lower mortality and long-term morbidity, shorter clinical stays, and decreased hospital costs."

With young lives in the balance, time is of the essence. And RCIGM delivers; they have set the world speed record for WGS twice. For medically urgent cases, the Institute's typical turnaround time from sample to preliminary diagnosis is less than three days.

The process starts at the referring hospital, where consent, enrollment, information gathering, and sample collection take place. At Rady Children's Institute, the samples are sequenced in their CAP/CLIA certified laboratory. The data then goes through the bioinformatics pipeline using a variety of computational tools. The resulting data files are annotated, filtered, and interpreted using data analysis software.

Then, Dr. Ellsworth and her board certified colleagues step up to the final challenge. The analysis and interpretation team *prioritizes* variants with respect to phenotypes; *curates* the evidence for clinical relevance; and *classifies* them according to guidelines set forth by the ACMG (American College of Medical Genetics & Genomics). "This is where we spend a lot of time," says Dr. Ellsworth. "By improving and automating some of the variant curation steps, we're able to decrease turnaround time. That's where Mastermind comes into play."

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THE GENOMIC SEARCH ENGINE

MASTERMIND IN ACTION

"Based on the rapid, precise results, the patient's care was tailored appropriately. There were stunning results because Mastermind provided additional information not available anywhere else for variant classification in a timely manner."

Dr. Kasia Ellsworth
Rady Children's Institute
for Genomic Medicine

The need for speed was evident when a week-old baby showed signs of an immune deficiency (SCID, or severe combined immunodeficiency): He was doing well in the neonatal ICU, but was at risk of developing severe recurrent viral bacterial and fungal infections, along with failure to thrive.

A blood sample obtained from the patient indicated an absence of T and B-cells, prompting a search for the genetic cause to confirm the diagnosis and better define the treatment strategy. Among the many genetic data-points that required review, they discovered a large deletion encompassing three exons within the DCLRE1C gene, which the OMIM (Online Mendelian Inheritance in Man) catalog confirmed is associated with autosomal recessive SCID.

Diligent further analysis revealed another anomaly within this gene: a single DNA letter change that changed a single molecular component of the protein encoded by this gene - otherwise known as a missense variant; these can be among the most challenging to interpret without direct evidence from previous cases or functional studies to support the variant's role in causing disease. An immunologist noted that DCLRE1C is notoriously difficult to sequence. Could it be relevant to the case? A search for references characterizing the variant in previous cases in HGMD (the Human Gene Mutation Database) came up empty.

But where other research tools failed, Mastermind succeeded.

"When Mastermind indicated there was a single reference that had cited the exact variant found in our patient, we could then quickly access and read the data, which showed that in vivo and in vitro studies were performed", said Dr. Ellsworth. "Rather than gene name, this variant was found in the literature under the protein's name — Artemis. It turned out that this amino acid position is essential for the protein catalytic activities, and therefore we were able to evoke functional evidence for classification."

Based on the patient's clinical presentation and molecular findings, the RCIGM clinical team agreed on the patient's diagnosis — crucially, prior to onset of severe symptoms. As a result, the baby's medical treatment was adjusted to match the child's disease-specific needs.

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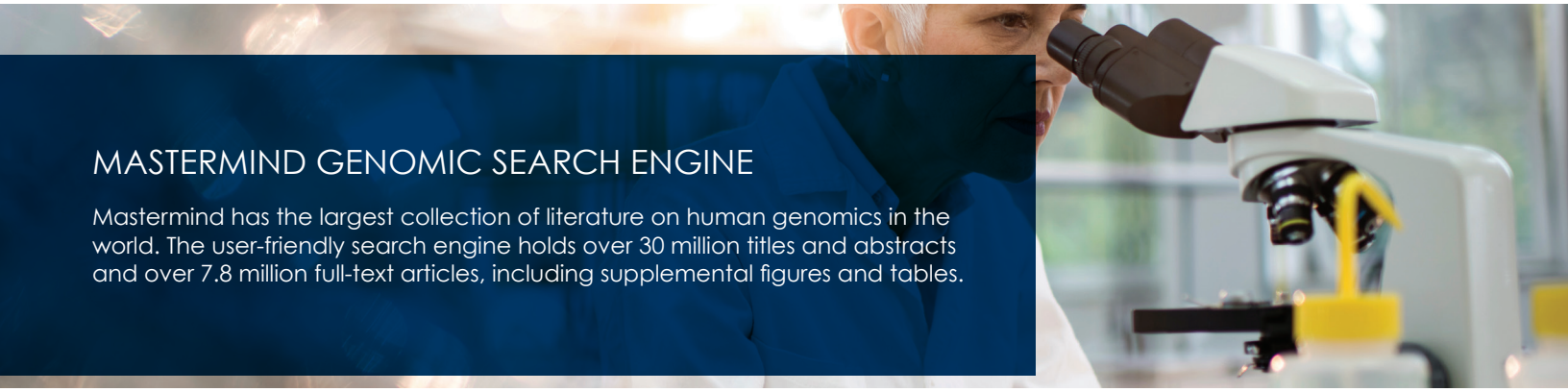

MASTERMIND GENOMIC SEARCH ENGINE

Mastermind has the largest collection of literature on human genomics in the world. The user-friendly search engine holds over 30 million titles and abstracts and over 7.8 million full-text articles, including supplemental figures and tables.

Rady Children's® Institute Genomic Medicine

The result of this diagnostic journey? The baby is healthy and thriving.

Dr. Ellsworth said that this wasn't the only time that Mastermind came through for her. In 11 recent cases, Mastermind handily beat out HGMD in five of them in terms of number of references, finding more information for 11 out of 23 genes. In contrast, HGMD never returned more references.

She further reported that many of the references that Mastermind found "were very useful for classification of the variants that were ultimately noted in the clinical report."

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