‘The Ingenuity Way’: Clinical Geneticist Relies on Easy-to-Use Data

Clinical geneticist and biotech entrepreneur Hugh Rienhoff is a longtime user of Ingenuity applications, trusting these tools for studies ranging from clinical trials of a new drug to understanding the genetic mysteries of his own daughter.

As a California biotech entrepreneur, Hugh Rienhoff has been familiar with Ingenuity technologies since the original company was first spun out of Stanford University. Indeed, one of the designers of the Ingenuity software reached out to Rienhoff years ago and asked him to be a test user to help the team make important choices about the user interface.

Today, Rienhoff is more than just familiar with Ingenuity’s applications. He has used the tools in several studies including a large sequencing research project — as well as to validate findings about the cause of a previously unknown genetic disease affecting his own daughter.

Rienhoff, trained as a hematologist and clinical geneticist, branched out to try venture capital investing in the 1990s but preferred a role mixing scientist and entrepreneur. He founded one of the earliest consumer genomics firms, DNA Sciences, in 1998. In 2007, he founded and served as CEO of FerroKin BioSciences, a company focused on therapeutics for iron-overload treatment, which was sold to Shire plc in 2012. Today, he is founder and CEO of Imago BioSciences, a biotech company developing therapeutics for genetic disorders.

Despite his history as a biotech pioneer, Rienhoff may be best recognized as the founder of MyDaughtersDNA.org and his quest to identify the genetic mutation underlying the clinically undescribed syndrome with which his daughter Beatrice was born in 2003. Nine years later, Rienhoff and a team of clinicians and scientists reported a never-before-seen variant in TGF-β3 that appears to explain the signs and symptoms of Beatrice’s syndrome. After years of hunting through stretches of Beatrice’s DNA, Rienhoff found the mutation — and loaded his exomes into Ingenuity Variant Analysis to confirm, and eventually publish, the results.

A BETTER IRON CHELATOR

At FerroKin BioSciences, Rienhoff worked to solve a serious medical challenge: some patients with hereditary anemias like sickle cell disease need regular transfusions to survive, but those very transfusions invariably result in iron overload, which can be fatal. His goal was to find an effective iron chelator without major side effects that could help these patients enjoy longer, more normal lives.

In one study, Rienhoff and his colleagues assessed 45 patients with thalassemia major, a heritable anemia in which too little hemoglobin is made. While patients were being studied on the new iron chelator, their exomes were sequenced with the goal of identifying genetic variants associated with specific clinical phenotypes such as transfusion requirements, pharmacokinetics, and pharmacodynamic responses. The data were analyzed in the Ingenuity Variant Analysis suite of tools. “I used the Ingenuity system extensively for that study,” Rienhoff says. “It was really the only analytical tool I could find to make sense of that data.” That work was absorbed by Shire when it acquired FerroKin, along with a promising drug currently in late phase 2 clinical trials.

For another project, Rienhoff collaborated with scientist and physician Renzo Galanello in Sardinia to explore the genetics behind a serious adverse event associated with a marketed drug used in the treatment for thalassemia. “I sequenced the exomes of those patients who experienced the adverse event and used our thalassemia patients as controls,” he says. Again, Rienhoff turned to Variant Analysis

to interpret the data. The results of this analysis are currently being prepared for publication.

HIS DAUGHTER'S DNA

When Rienhoff's daughter Beatrice (Bea) was born in 2003 there were a few clues she might not be completely healthy: long, narrow feet and contracted fingers were two examples. But as she grew older, her weight and strength did not keep up with those of her peers. It became clear that she had an undiagnosed medical condition.

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>
> *Hugh Reinhoff*

Rienhoff spent the next nine years chasing that diagnosis, working with longtime colleagues like Victor McKusick, his clinical genetics mentor at the Johns Hopkins Hospital, as well as complete strangers who were experts in relevant scientific or medical niches. During that odyssey, Rienhoff brought Bea's case to the attention of doctor after doctor, scientist after scientist, hunting down every lead that arose.

The syndrome was vexing in its refusal to be categorized. Certain symptoms fit with Marfan syndrome, but it wasn't Marfan. Other symptoms matched Loeys Dietz syndrome, but it wasn't that. While these syndromes did not provide a diagnosis, the overlap did help to narrow the search for which pathways might be affected and hence which genes might be at the root of Bea's condition.

When he had focused his quest on a select list of genes, Rienhoff wound up buying secondhand equipment and sequencing the genes himself because IRBs would not permit his friends in academia to do it for him. Years later, when exome sequencing became an option, Illumina performed that service, sequencing not just Bea's exome but also those of her two older siblings and both of her parents for comparative purposes. The sequencing company conducted analysis of the data, finding a likely candidate in the TGF-β signaling pathway — the same pathway implicated in Marfan and Loeys Dietz syndromes.

Based on his prior experience with the Ingenuity platform, Rienhoff says, "It seemed natural to load the exomes in and analyze them the Ingenuity way." Ingenuity Variant Analysis identified three mutations that were likely deleterious, one of which was the same TGF-β3 variant that Illumina's filtering had turned up. Rienhoff and his network of volunteer scientists followed up on the other variants, concluding that they were unlikely to be the primary cause of Bea's syndrome.

He says that getting familiar with Variant Analysis was quite simple. Ingenuity provided a quick tutorial showing him how to use filters, and after that, "it wasn't very hard at all," reports Rienhoff, who loaded the exome data himself. "Even a physician could use this, and that's critical."

The TGF-β3 mutation, which was reported in a 2013 publication in the American Journal of Medical Genetics, alters a critical cysteine to a tyrosine in the last exon of the gene. This stretch of DNA is highly conserved, showing conservation even in orthologous regions in C. elegans and D. melanogaster.

As part of the publication, Rienhoff and his coauthors made the exome data available through the Publish function of Variant Analysis, which permits free access for anyone else to comb through the data and re-analyze it. "That's part of what I consider to be publishing: all the data that supports the conclusions of the paper," says Rienhoff, who would not have been satisfied to release less of the data or to have it less straightforward to access. "I just think that's the right thing to do."

To see these data, go to https://variants.ingenuity.com/Rienhoff2013.

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