Customer case study
Field of study: Rare Disease

GOSgene Scientists Generate Diagnoses for Ultra Rare Childhood Disease

At a translational genomics center in London, scientists combine next-gen sequencing, Ingenuity Variant Analysis, and dedicated funding to generate diagnoses for children with the rarest diseases. Their work is contributing to better healthcare for families around the world.

Patients with rare or novel diseases can spend years on diagnostic odysseys. Even after countless hypotheses, tests, and clinical observations, the likelihood of getting a correct diagnosis is still slim. It's about more than just getting an answer: the correct classification of a disease can open the doors to treatment options, support groups, and more.

Today, scientists at the Centre for Translational Omics in the University College London's Institute of Child Health have built a pipeline that takes even ultra-rare cases and consistently delivers answers with rapid turnaround. The center, known as GOSgene, may be as close as we can get to assembly-line processing of undiagnosed rare diseases, with results that give parents and children new hope for better health outcomes.

GOSgene functions in partnership with the Great Ormond Street Hospital, the largest pediatric research and clinical facility in Europe. Established in 2010 by UCL professor Philip Beales and funded by the hospital's Biomedical Research Centre, GOSgene was designed to take advantage of cutting-edge DNA sequencing technologies. By pairing exome sequencing with the filtering power and resolution of Ingenuity Variant Analysis, the GOSgene team has helped nearly 400 families and provided answers to more than 80 distinct clinical phenotypes.

Hywel Williams, manager of GOSgene, says that funding and scientific focus are two elements that set the center apart. Unlike many translational research facilities, GOSgene is not focused on a specific disease, so its team can help clinicians dealing with any kind of rare or undiagnosed phenotype. And with its own funding from the National Institute for Health Research, the center doesn't have to rely on charities or grants, which can be extremely hard to come by for studying rare and novel diseases. Together, the funding and broad remit give GOSgene scientists freedom to work on virtually any project brought to them by clinicians at Great Ormond Street Hospital.

GOSgene currently uses exome sequencing to analyze samples from families. "It allows us a hypothesis-free way to look at these genomes," Williams says. "We use the genetics to infer the candidate genes and see how they relate to the phenotype." Scientists at the center have begun exploring whole genome sequencing as well. "We've got data on about 40 whole genomes from various projects," he says, noting that this approach may be especially useful for acute cases, where whole genome data can be used to diagnose children in intensive care. The center's pipeline, including Ingenuity Variant Analysis, will be used for those efforts.

Williams says the variant filtering application is "absolutely essential to everything that we do." Given the center's work with so many different

phenotypes, he notes, "there's absolutely no way that you can be even a mild expert on all of those diseases." That's where Ingenuity Variant Analysis, and the Ingenuity Knowledge Base that powers it, come in handy. "It gives us the opportunity to filter down from a large list of potential variants to a small, compact list that's easily manageable for understanding potential pathogenicity," Williams says. "Without the Knowledge Base, we wouldn't be able to do what we do." It also enables GOSgene scientists to share data easily with clinicians, who can simply log in to view an analysis or run their own filters.

Two recent projects show the GOSgene pipeline in action. In one study, the team identified a novel syndrome that explained undiagnosed cases in three unrelated families. In the other, they managed to separate a complex phenotype into two distinct components, leading to a diagnosis for one of them and better management options for the other.

Three Families, One Answer

In a study published in the American Journal of Human Genetics ("Mutations in SNX14 Cause a Distinctive Autosomal-Recessive Cerebellar Ataxia and Intellectual Disability Syndrome"), Williams collaborated with scientific and clinical experts and identified a novel syndrome in three separate families. Each family had a previously undiagnosed disease thought to be unique, but the GOSgene team was able to link the conditions and characterize a new disease.

The project began with one sample from a patient in Portugal. The individual came from a consanguineous family and had a range of symptoms including microcephaly, hearing loss, and intellectual disability. Williams' team sequenced the exome of the patient, expecting to find an autosomal recessive mutation. Using standard filters for call quality and frequency with Ingenuity Variant Analysis, they were directed to a homozygous nonsense mutation in Sorting Nexin 14 (SNX14).

Comparing notes with colleagues, Williams learned that the same gene had been implicated in a previous family study with a phenotype that overlapped the first patient's. Since then, clinical geneticists at the Great Ormond Street Hospital located a third family with another mutation in that gene that causes the same syndrome. "By using the filtering in Ingenuity Variant Analysis, we were able to find the gene which then led to the identification of this syndrome," Williams says.

One Phenotype, Two Components

In the other study, published in the European Journal of Human Genetics ("The use of whole-exome sequencing to disentangle complex phenotypes"), the GOSgene team analyzed two siblings from a consanguineous family in Bangladesh with two affected and two unaffected children. The patients had a complex phenotype that involved both peripheral neuropathy — in this case, lack of typical movement and other motor problems

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— as well as bronchiectasis, leading to severe chest infections. "The combination of the two phenotypes clouded the ability to give a diagnosis to this family," Williams says.

At GOSgene, scientists were uncertain whether this was a single syndrome or two separate disorders. Williams used Ingenuity Variant Analysis to run two separate analyses, one for each phenotype, looking for loss-of-function variants. For peripheral neuropathy, the application immediately highlighted a mutation in PRX, a gene previously linked to diseases associated with that symptom. "It was an instant hit," he says. "As soon as you have the hit and it links back to previous manuscripts, you know that you've solved your case."

Results were not so straightforward for the bronchiectasis phenotype, which Williams says can be caused by environmental and other factors. None of the candidate mutations appeared to be causative, so "we just have to leave it there," he says.

"This was an interesting case because it shows how we're still very much reliant on a clinician making a phenotypic judgment on someone's symptoms," Williams notes. "We've taken a confused phenotype and broken it into two separate parts."

In the paper, Williams and his coauthors express their view that this case shows the clinical utility and cost-effectiveness of whole exome sequencing (WES). "We believe there are likely to be a great many patients who are currently undiagnosed who would benefit from the use of WES to disentangle their complex phenotypes to identify known disease genes," they write. "The identification of these specific phenotypic features will allow their targeted treatment, where therapies are available, which will have a positive impact on patient care and more generally it will lead to a better understanding of the illness holistically."

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