



Customer case study
Field of study: Translation research

In Genetic Study, Mount Sinai Researcher Aims to Parse Complexity of Craniofacial Disorders



Physician-scientist Bryn Webb is using Ingenuity Variant Analysis to interpret sequence data from patients with rare congenital facial paralysis disorders. Her quest could provide more accurate diagnosis and, eventually, better treatment options for patients around the world.

Children born with congenital facial paralysis disorders struggle on two fronts: interacting normally with other kids when they can't use facial expressions to convey emotion, and getting a clear diagnosis. A number of disorders present with some form of facial paralysis and other overlapping symptoms, making it challenging for physicians to accurately pinpoint the right disorder during diagnosis.

It doesn't help that these conditions see little research. Just a few labs around the world specialize in these rare congenital paralysis disorders, which include Moebius syndrome and other forms of facial palsy.

One of these labs is led by Bryn Webb, an instructor in genetics and genomic sciences as well as pediatrics at the Icahn School of Medicine at Mount Sinai and at the Icahn Institute for Genomics and Multiscale Biology. Though she is still early in her career, Webb has already won awards for her genetic research in craniofacial disorders. With Ingenuity Variant Analysis from QIAGEN in her arsenal, she is poised to add even more to the body of knowledge around these disorders.

Ultimately, establishing clear genetic markers for these disorders will not only enable physicians to clearly diagnose them — and therefore provide better treatment for patients — but may even contribute to the discovery of prenatal treatments that could detect anomalies and help steer cells toward healthy development.

Gene Candidates

Webb came to genome science from a medical background, earning her MD at the University of Texas Southwestern Medical School. She joined Mount Sinai for her residency, working with Moebius syndrome expert Ethylin Jabs and genomics pioneer Eric Schadt. Today, she spends most of her time conducting research but continues to see patients with craniofacial disorders.

The world of craniofacial disorders is fairly large, but Webb's specialty of congenital facial paralysis is an extremely small community — so patients seek her out from all over the world. Many times, these patients have been misdiagnosed because of the biological complexity involved, particularly when there are other symptoms such as heart defects or autism. "These disorders are extremely heterogeneous; some overlap, or one disease can be a collection of disorders," Webb says. "It's not simple and Mendelian." To confound things further, environmental factors can play a role as well.

But Webb is on a mission to unravel that complexity and make it more straightforward to diagnose people with congenital facial paralysis and associated conditions. Relying on samples from the patients who come looking for her expertise, she is taking a candidate gene approach with next-gen sequencing to elucidate the genetic underpinnings of these disorders. Her gene panel is 2.5 Mb and includes 436 genes she chose based on candidates from animal models in the literature, variants known to be involved in these disorders, and results from her own research that merited additional interrogation. So far, she has sequenced nearly 100 probands, running new samples as they arrive and confirming next-gen results with Sanger.

Webb interprets all her sequencing results using Ingenuity Variant Analysis. She uses the platform to exclude the most variable exonic regions and focus on changes that are predicted to be deleterious. “Not only can I sort variants, but then I can also start to look at more complex features,” Webb says. “I look at whether any variants are common to multiple persons, and then use burden analysis and association features.” She notes that being able to upload sequence results for all 98 probands and then analyze variants across them has been especially helpful. “I can see how many variants are common for two people, three people, four people, and so on,” she adds.

Key advantages of Ingenuity Variant Analysis are its user-friendliness and time savings, Webb says. “It’s great, easy-to-use software and I love the web-based interface,” she adds.

Without the platform, she would have to manually sort each variant, gathering dbSNP frequencies and predictions from SIFT and PolyPhen. “That would have taken a lot longer,” Webb says.

Because she used Ingenuity Variant Analysis, Webb also had access to a built-in database of control samples. She used genomic data from the Personal Genome Project and the 1,000 Genomes Project, both available within the QIAGEN platform, to help with the burden analysis interpretation and provide more power than just using dbSNP frequencies.

Functional Follow-Up

Based on the analysis, Webb found that a few patients had mutations already linked to congenital facial paralysis disorders. She also identified compelling new variants in other genes on the panel and is performing functional studies. “I’m trying to prove that these variants, which are in genes not known to be disease-causing, are in fact causative,” she says. Her research now involves protein modeling, studying variants in zebrafish, and more.

If history is any gauge, patients may have cause for optimism now that Webb is on the case. She has already won awards for her work, including the Rappaport Memorial Resident Research Award, the Kurt Hirschhorn Clinical Science Award, and an award from the Moebius Syndrome Foundation. But it’s the medical treatment opportunities rather than the accolades that motivate Webb, who

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notes that the only treatment option for patients today is smile surgery, and success rates vary greatly. "The aim is to identify the molecular cause of symptoms in these patients so that we can provide accurate genetic counseling and allow families to know what their genetic risk is if they're trying to have more children," she says. "And if you have the etiology, then you can study the condition to get to molecular therapies."

The big hope is eventually to detect the disorders in utero and offer prenatal treatment to encourage healthy development. "That would be the ultimate goal," Webb says.

he says, adding that these results have given the team enough confidence in being able to solve the heterogeneity dilemma that they are now moving on to human studies. They're currently collaborating with a pediatrician from a region of Canada with a high FASD prevalence."

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