



Genomics Research Center Discovers Sources of Childhood Epilepsy Using Twist Custom Panels

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Genetic tests for epilepsy in children from remote reaches of South America conducted by the Center for Applied Genomics at the Children's Hospital of Philadelphia lead to faster, effective treatment.



The Center for Applied Genomics at the Children's Hospital of Philadelphia is world-renowned for its work detecting the genetic causes of some of the most prevalent childhood diseases. As one of the world's largest genetics research and analytical facilities, the Center collaborates with researchers in the academic, public, and private sectors; and has access to state-of-the-art, high-throughput genotyping technology. Its scientists have processed genetic samples from more than 100,000 people.

The mission of the Center is to translate its findings into drug discovery, treatment and clinical paths that address a variety of ailments; including epilepsy, asthma, obesity, ADHD, autism, diabetes, inflammatory bowel disease, schizophrenia, and pediatric cancers.

Renata Pellegrino, PhD, the Center's technical director, believes there is no greater calling for her than connecting the discovery of genetic causes of diseases with real world treatments that can save lives. "Our work in genomics is helping treat rare diseases and often saving children," Pellegrino said. "I feel very emotional about these kids. They are the reason why I do my job."

Researchers Challenged to Work with Poor Quality, Dry Blood Samples

In 2017, the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo in Brazil asked Dr. Pellegrino, a native of Brazil, for help in the discovery of potential variants related to epilepsy in children with rare manifestations of the disease from remote areas of South America.

"The group in São Paulo had a project for epilepsy and other neurological disorders with which they are trying to help people

in very poor and inaccessible areas that don't have medical treatment so that they would at least receive diagnostics," Dr. Pellegrino said. "The Brazilian team is trying hard to get any source of material to develop the test, and they only had very poor quality, aged blood spots."

The Brazilian team provided a list of genes they wanted to examine for epilepsy-associated variants, as well as for structural variants for early onset epilepsy panels. "The clinical criteria for enrolment was basically the manifestation of seizure in patients aged between two- and four-years-old and also various types of epilepsy," Dr. Pellegrino said. "They did a very good job on the phenotype of the samples and ensured they came from different areas, such as remote mountain villages with children who are totally missed in diagnostics from centers like us who can help them."

Cutting-Edge Innovation from the Center for Applied Genomics

The Center for Applied Genomics has 85 employees and is a hybrid lab, with half its resources devoted to research and half to diagnostics/clinical operations, Dr. Pellegrino explained. Its Next Generation Sequencing (NGS) capabilities deliver high-quality sequencing services to the scientific community and to external partners worldwide. According to Dr. Pellegrino, the Center's "Biobank" is the largest repository in the world for biospecimens of children, with about 300,000 genotype samples cataloging more than 70 diseases. The facility integrates clinical research programs with molecular profiling technologies, enabling large-scale genomics and functional research programs for targeted diagnostics and therapies. It also uses a robotic platform and automation applied to laboratory molecular biology protocols to

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Renata Pellegrino, PhD

TECHNICAL DIRECTOR AT PHILADELPHIA RESEARCH CENTER

achieve high throughput sample processing for DNA sequencing, genomics and other biological applications.

The lab is designed not just for gene discovery but treatment as well: “We want to work with the patients and so the phenotype provided to us is so important,” Dr. Pellegrino explained. “We do a lot of functional studies. Our lab is not focused solely on finding variants. We don’t only locate mutations. We want to see what they do so that it can be addressed.”

Because the dry blood samples are often very poor in quality, this current work presents significant challenges to genetic identification. In order to combat these challenges, the Center asked Twist Bioscience to provide custom target enrichment panels rather than seeking to sequence a whole genome or whole exomes, Dr. Pellegrino said, as target enrichment procedures isolate specific genomic regions of interest before next-generation sequencing. Dr. Pellegrino explained, “We do the majority of our research in exome sequencing, but at the end of the day the technology is still based on short reads in sequencing and a panel would be more cost effective and focused in specific candidate variants.”

Searching for, and Locating, Epilepsy Variants

“The challenge of this project was to work successfully with the blood specimens,” Pellegrino said. “To do a very good capture with very bad samples is very difficult.”

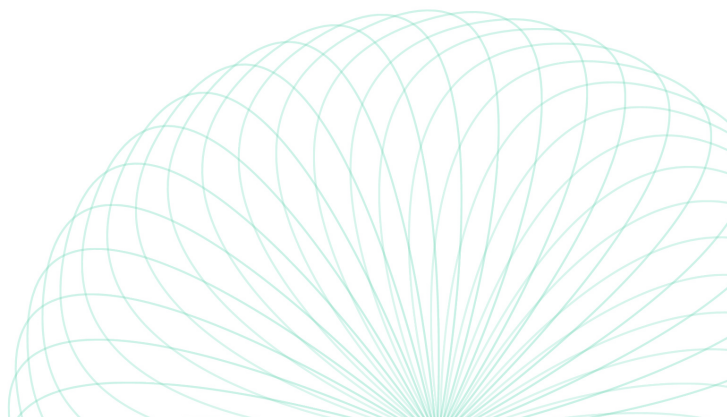
“Twist Custom Panels allowed us to focus on important, medically relevant genes instead of forcing us to work with a whole genome,” Pellegrino added. “The panel was concise, with a simple protocol. The cost was reasonable with very good candidate variants already curated by the literature.”

“We saw high performance with challenging samples, and we did this not only in regular dry blood spots but in much compromised dry blood spots,” Dr. Pellegrino added. “As a technical director, this gives me hope that I can now take samples from different countries and different situations/conditions. We are confident to we can handle not only the DNA extraction with successful downstream results, but also that we can work with Twist to extend this to other types of NGS target enrichment panels in challenging specimens.”

Dr. Pellegrino said it’s important to keep in mind the real-world treatments that may result from the Center’s findings.

“We’re very lucky as genomics researchers in that we can do a fast turnaround where you know the results of our investigation,” Dr. Pellegrino said. “Our work examining rare and common diseases over the years has resulted in saving hundreds of patients with our discoveries.”

“I wake up and go to work for long hours and I’m happy about it,” Dr. Pellegrino said, “because I know the impact we’re having on people’s lives.” ■





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