Discovery Of Novel CVID Loci Using The Exome SNP Chip Platform

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Technology description

Center for Applied Genomics (CAG) at CHOP

The Center for Applied Genomics is one of the world's largest genetics research programs, and the only center at a pediatric hospital to have large-scale access to high-throughput genotyping technology. There are over 50 active disease projects – both internally and in collaboration with researchers across North America, Europe, and Asia. This unique resource enables large-scale human genotyping studies: to date, genetic data from over 100,000 individuals has been analyzed. The Center for Applied Genomics is focused on detecting the genetic causes of some of the most prevalent childhood diseases including asthma, obesity, ADHD, autism, diabetes, inflammatory bowel disease, epilepsy, schizophrenia, and pediatric cancer, all of which are thought to involve multiple, interacting genes within the body. In addition, CAG has recently extended recruitment and genotyping efforts to adult disorders, in collaboration with the University of Pennsylvania.

Overview of Technologies

An example of a technology that derived from Dr. Hakonarson’ s work at the Center for Applied Genomics includes the discovery of six significant causal single nucleotide variations (SNVs) for common variable immunodeficiency (CVID)

which were discovered and quality controlled through the use of over 19,000 individual genomic sequences. Because these SNVs are thought to be causal, the SNVs can be used to not only diagnose CVID, but also to inform specific drug treatments based on the protein mutated as a result of the SNV. Common variable immunodeficiency (CVID) has a prevalence of approximately 1 in 25,000 in European populations. The immunological hallmark of CVID is the B cell defect with inability to produce adequate antibody responses. Patients also show other immunological abnormalities such as T cell dysfunction, monocyte/macrophage hyperactivity and signs of low-grade systemic inflammation. Use of this technology is a significant improvement for the diagnosis of CVID, which can be difficult, as it is currently based on clinical criteria with nonspecific laboratory findings suggestive of immune deficiency which are variable.

Similarly, Dr. Hakonarson’ s discovery of a causal SNV for cerebral palsy (CP) will allow for earlier diagnosis of this disease and inform the treatment of CP with a drug that modulates the mutated protein (Tech ID: 1005). CP is a common, heterogeneous group of early-onset disorders with no curative treatment. It is characterized by impaired motor function that adversely effects movement and

posture and, although it is thought to be non-progressive, the abnormal muscle tone, motor development, and coordination issues are associated with osteoporosis, increased pain, sleep disorders, communication difficulties, and urinary tract issues that continue through life in these patients. Earlier diagnosis of CP associated with this SNV will allow for earlier and more specific treatment with a drug that addresses the causal mutated protein.
The high-throughput sequencing resources and large genomic database of diseases available through the CAG are ripe for discovery of even more causal disease genes that could inform the diagnosis and treatment of many more childhood diseases.

Advantages

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• Enables early and specific diagnosis of disease
• Genetic diagnosis will inform treatment selection (precision medicine)

Institution

The Children's Hospital of Philadelphia

Inventors

Hakon Hakonarson
Director
Center for Appliced Genomics
Jin Li

联系我们

叶先生

电 话：021-65679356

手 机：13414935137

邮 箱：yeyingsheng@zf-ym.com