Customer case study
Field of study: Cancer Genomics

To Track Cancer Predisposition, City of Hope's Slavin Uses Ingenuity Variant Analysis

At City of Hope, a pioneering research and clinical institution near Los Angeles, Assistant Clinical Professor and Clinical Geneticist Thomas Slavin specializes in the diagnosis and treatment of hereditary cancers. When he's not seeing patients at the National Cancer Institute-designated comprehensive cancer center, Slavin conducts research into these types of cancer to better understand risk alleles, therapy response biomarkers, and more.

Slavin's work is guided by a strong interest in personalized medicine. He aims to use genomics, epidemiology, and other types of data to identify the best treatment plan for each patient — with the ultimate

goal of translating these advances into preventive medicine to keep people healthier despite their genetic risks.

In recent studies, Slavin has reported results from investigations of hereditary breast, pancreatic, and gastric cancers. For each of these efforts, he and his team relied on QIAGEN's Ingenuity Variant Analysis tool to filter and interpret the slew of variants detected. The analysis tool automatically computes and classifies variants according to guidelines from the American College of Medical Genetics and Genomics (ACMG), making it much easier for scientists and clinicians to report results in required categories. "As of right now, to my knowledge, there is no other software program like this on the market that uses ACMG guidelines to categorize variants," Slavin says. "In today's era of research you really need to be publishing using ACMG guidelines, but hand curating all of these variants using those guidelines is so time-consuming that it would be nearly impossible."

Cancer Predisposition

Three recent studies illustrate how Slavin and his colleagues use Ingenuity Variant Analysis to characterize and understand genetic risk factors for cancer. "I've used it from large-scale studies with common genes all the way to smaller studies looking at very obscure and candidate cancer predisposition genes," he says, "and it's worked well in both."

In an analysis of more than 2,100 women with familial cancer who had already tested negative for known mutations in BRCA1 and BRCA2, his research team used targeted NGS to detect single nucleotide and copy number variants in 26 genes believed to be associated with cancer. The case-control information, including nearly 2,900 variants, was compared to data in the Exome Aggregation Consortium to identify unexpected allele frequencies. The team uncovered mutations in 8.2% of women with familial breast cancer; after detailed analysis, they estimated that about 4.7% of these women had "mutations in genes statistically associated with breast cancer," according to the paper. Through this work, they found high-risk mutations in PALB2 and TP53, moderate-risk mutations in ATM and BARD1; and low-risk truncating mutations in CHEK2.

For variant analysis, the team used two separate classification strategies and then implemented an expert review step to reconcile results. One strategy deployed Ingenuity Variant Analysis, using the ACMG interpretation pipeline to sort variants into pathogenic, likely pathogenic, benign, likely benign, and unknown significance categories. Ultimately, 96% of variants identified were classified as unknown or benign/likely benign, while the remaining 4% — a total of 114 variants — were interpreted as pathogenic or likely pathogenic.

In a separate effort, Slavin and his team studied patients with hereditary pancreatic cancer to find predisposition mutations that could eventually be used to identify patients at high risk of this cancer and get them on enhanced screening and early detection programs. The team analyzed germline DNA from 53 patients, including 49 without a known genetic risk mutation, through targeted sequencing of 706 candidate genes. Sixteen patients harbored variants considered pathogenic or likely pathogenic for predisposition to hereditary pancreatic cancer, including several genes not previously associated with this type of cancer. Variants were interpreted with Ingenuity Variant Analysis and classified with the tool's ACMG algorithm; the mutations considered most likely to be deleterious were followed up individually by the research team.

Finally, Slavin and his team reported results from an analysis of susceptibility mutations for gastric cancer. The study included 51 adults with gastric cancer, 43 of whom lacked a previously identified germline mutation associated with cancer predisposition. Again, the team used a panel of 706 candidate genes, emerging from Ingenuity Variant Analysis and follow-up evaluations with 20 variants classified as pathogenic or likely pathogenic in 18 people. For this and the other two studies, the scientists suggest that larger cohorts will be necessary to hone our understanding of these mutations.

Analysis Tool

Slavin began using Ingenuity Variant Analysis about three years ago, at the recommendation of City of Hope's bioinformatics director, Yate-Ching Yuan. He says the tool's ease of use is an important factor; while he has bioinformatics training, the tool could be deployed by just about anyone familiar with genomics research.

For large-scale studies, Slavin says it's handy to be able to put all detected variants into one or two VCF files, load them into Ingenuity Variant Analysis, and let the tool do the heavy lifting. For smaller studies, he notes, the product is helpful "to really get into the weeds of variants and genes that don't have a lot of information."

It's the wealth of information Ingenuity Variant Analysis offers that makes it so helpful to Slavin and his team as they attempt to find clinically actionable mutations for hereditary cancer. In addition to direct links to important sources such as ClinVar, "it has such a big literature backbone" from QIAGEN Knowledge Base, he says. "You can see all the literature on a particular variant, even if that variant's name has changed over the years. It's a very valuable resource."

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Publications cited:

- The contribution of pathogenic variants in breast cancer susceptibility genes to familial breast cancer risk
- The spectrum of genetic variants in hereditary pancreatic cancer includes Fanconi anemia genes
- Genetic Gastric Cancer Susceptibility in the International Clinical Cancer Genomics Community Research Network

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