Researchers identify gene variations that predict chemotherapy side effects

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Seemingly benign differences in genetic code from one person to the next could influence who develops side effects to chemotherapy, a Mayo Clinic study has found. The study identified gene variations that can predispose people to chemotherapy-induced peripheral neuropathy, a condition that is hard to predict and often debilitating enough to cause cancer patients to stop their treatment early. Results of the research were presented today at the American Association for Cancer Research Annual Meeting 2013 in Washington, D.C.

The study, which implicates the genes EPHA5, ARHGEF10, and PRX, is the first to mine large swaths of the human genome for predictors of chemotherapy side effects. Further research into these genes and others may enable clinicians to use genomic information to more safely deliver these potentially toxic treatments.

"Our study creates a path for how to approach the whole genome in order to tailor cancer treatments," says Andreas Beutler, M.D., an oncologist at Mayo Clinic Cancer Center and senior author of the study. "That is important because we would not only like to cure people's cancer or help them live longer, but we also wish to provide them with the best quality of life."

Chemotherapy-induced peripheral neuropathy affects an estimated 20 to 30 percent of cancer patients treated with chemotherapy agents. The symptoms can be as mild as a light tingling or numbness, but can progress to a loss of feeling in the hands and feet, or to the point where

patients can no longer walk normally and are left with a permanent feeling of numbness or pain. Currently, there is no way to predict which patients undergoing chemotherapy will develop this side effect or to what degree.

There are approximately 50 genes linked to a hereditary form of peripheral neuropathy. However, many of the people who have a mutation in one of these genes experience no symptoms until they are exposed to chemotherapy. Dr. Beutler decided to first consider those 50 genes as the most likely suspects, and then expand his search to the wider human genome for other predictors of chemotherapy-induced peripheral neuropathy.

Dr. Beutler's approach relied on exome sequencing, a type of DNA sequencing that focuses on the exonic regions of the genome that code for functional proteins. These protein-coding regions are believed to harbor about 85 percent of all disease-causing mutations.

Dr. Beutler and his colleagues performed exome sequencing on 20,794 genes from 119 cancer patients, over half of whom had developed chemotherapy-induced peripheral neuropathy during the course of a chemotherapy clinical trial.

First, they looked at the 50 hereditary neuropathy genes and found one—EPHA5—that appeared to predispose the patients to chemotherapy-induced peripheral neuropathy. Next, researchers analyzed the remaining 20,000 genes and discovered two new genes—ARHGEF10 and PRX—that are also associated with chemotherapy-induced peripheral neuropathy. They validated those findings in another group of 75 cancer patients.

The results suggest that the two conditions, hereditary neuropathy and chemotherapy-induced peripheral neuropathy, may share genetic roots in

some patients. They also point to ways that clinicians can improve cancer treatment. For instance, if clinicians know which patients are at risk for a particular chemotherapy side effect, they can use the information to individualize treatment.

Dr. Beutler and his team plan to expand their study to look at the entire genome, not just the protein-coding regions, in as many as 1,000 cancer patients. Dr. Beutler says any additional genes they find will add to the larger picture of symptom control in cancer treatment.

"What we are doing at Mayo is much larger than just uncovering a handful of genes," says Dr. Beutler. "We are using cutting-edge genomics research to enhance our strengths in clinical trials and develop new methods to individualize medicine."

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