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105 additional genetic errors that cause cystic fibrosis pinpointed

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Of the over 1,900 errors already reported in the gene responsible for cystic fibrosis (CF), it is unclear how many of them actually contribute to the inherited disease. Now a team of researchers reports significant headway in figuring out which mutations are benign and which are deleterious. In so doing, they have increased the number of known CF-causing mutations from 22 to 127, accounting for 95 percent of the variations found in patients with CF.

In a summary of their research to be published online in *Nature Genetics* Aug. 25, the scientists say that characterizing those additional mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene will not only bring certainty to families about a CF diagnosis or carrier status, but will also accelerate the design process for new drugs tailored to a particular mutation. There already is one such individualized drug on the market.

"Since not all mutations cause disease, sequencing the DNA in both copies of your CFTR gene and finding an abnormality in one wouldn't tell us if you are a carrier for CF unless we knew if that abnormality causes CF," says Garry Cutting, M.D., professor of pediatrics in the McKusick-Nathans Institute of Genetic Medicine at the Johns Hopkins University School of Medicine. "Until this new work, more than a quarter of couples in which both partners were found to carry a CFTR mutation were left wondering if their mutations were going to affect their offspring. Now it's down to 9 percent," he says.

CF is the most common, lethal, recessive genetic disease affecting Caucasians, with approximately 70,000 to 80,000 cases worldwide. When two copies of a defective CFTR gene are inherited, one from each parent, a child's body will not be able to create working CFTR proteins, resulting in the production of thickened mucus, which clogs the lungs and digestive system. Modern treatments to unclog the lungs and address other symptoms have allowed patients to survive into adulthood, but most will still die prematurely of lung disease.

One in 30 Caucasians in the United States is a "carrier" of the disease, meaning their genomes include one abnormal copy of the CFTR gene but they experience no symptoms of the disease, and as many as a million Americans are tested each year for carrier status. If two carriers have children together, each child has a 1-in-4 chance of inheriting two bad copies of CFTR and suffering from the disease. The severity of the disease will depend on which particular gene variations are inherited and how they affect the functioning of the CFTR protein.

In 2012, a drug (ivacaftor) that enhances the function of one specific mutant form of the protein became available. Although the particular mutation targeted is only found in 4 percent of patients with CF, drug companies are already working on drugs to target mutant proteins resulting from other mutations.

"There is very important information in each of these naturally occurring mutations that teaches us more and more about the disease," says Patrick Sosnay, M.D., assistant professor of pulmonary and critical care medicine. "We want to get to a point where we can say, 'This is your mutation, this is what it means and this is how you can treat it.'"

The team began its study with a database containing the genetic information of nearly 40,000 patients with CF. It then examined the 159 mutations that occurred in the database at a frequency of at least 0.01

percent. (Most of the more than 1,900 known mutations are even more rare than that.) The research team analyzed each of these mutations to determine its clinical relevance and its effect on the work of the CFTR protein.

The impact of each mutation on patients' health was assessed by first examining data on the salt concentrations in the sweat of patients bearing each particular mutation. CF causes unusually high amounts of salt to appear in sweat, so a mutation was deemed clinically significant if patients carrying that mutation had high reported salt concentrations.

The team then looked at how each genetic error affected the protein made by the CFTR gene. Eighty of the mutations would prevent the production of any CFTR protein based on the location of the mutation. These were classified as disease-causing, Cutting said. The remaining 77 mutations were tested biochemically in cells to determine the amount of damage sustained by the CFTR protein in each case.

In total, 127 of the 159 mutations were shown to cause CF, if inherited with another CF-causing mutation. Of those, 105 had never before been characterized.

"This new information will give clear answers to tens of thousands of people each year: those being screened as potential carriers, parents of infants who have been flagged during newborn screening and children and adults who are looking for a diagnosis," says Karen Siklosi, M.G.C., a genetic counselor involved in the study.

"It's our hope that the functional data we have provided for these other mutations can be used to find additional drugs for specific CF mutations," says Cutting. "We also believe that the process we followed in this study can be repeated to help characterize many other rare genetic disorders."

This data is already being used by CF clinicians to aid in diagnosis, by public health experts to refine newborn screening and by researchers investigating new therapeutics. The team is also continuing to analyze the rest of the mutations in the database—those with a frequency of less than 0.01 percent—and has already found 49 more that are CF-causing. Updates can be found at the project's website. "We don't want to stop where we are and forget about the patients with the rarest mutations. We will leave no one behind," says Cutting.

More information: Defining the disease liability of variants in the cystic fibrosis transmembrane conductance regulator gene, dx.doi.org/10.1038/ng.2745

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