MedicalXpress

Ethnic differences in CF genetic coding not addressed in screening tests for nonwhite patients

December 16 2015

Cystic fibrosis (CF) occurs less frequently in nonwhites than in whites, and nonwhites tend to be diagnosed at a later age. This late diagnosis often comes only once they have become symptomatic, rather than through newborn screening programs or molecular diagnostic testing. Delaying diagnosis can result in postponed treatment and clinical deterioration. A new study in *The Journal of Molecular Diagnostics* found that one reason for this ethnic disparity in CF diagnoses is that the variants examined in the most common CF newborn screening panels do not sufficiently include the variants present in nonwhite populations.

"We think that this information can be used to optimize newborn screening programs, taking into account the ethnic composition of state populations, resulting in earlier diagnosis and intervention, timely clinical treatment, and enhanced prognosis," explained Iris Schrijver, MD, professor of pathology and, by courtesy, of pediatrics at the Stanford University School of Medicine, and director of the Stanford Molecular Genetic Pathology Service, Stanford, CA. "We believe it could propel equity in mutation detection for white and nonwhite CF patients."

As part of the study at Stanford University, the investigators examined CFTR genotyping of CF individuals in the CF Foundation Patient Registry across different racial and ethnic groups, including non-Hispanic whites (22,206), Hispanics (1,955), blacks (1,214), Asians

(156), and Native Americans (171).

Mutations in the 27-exon CFTR gene that encodes the CF transmembrane conductance regulator (CFTR) underlie CF. Disruption of CFTR production and/or function affects chloride ion channels and thus interferes with the transport of electrolytes. This defective ion transport in the respiratory tract leads to less airway surface liquid and the formation of thick and sticky airway secretions that block lung passages. Individuals with CF may also have higher than normal levels of salt in their sweat.

The researchers found that 90% of white patients and 83% of Native Americans with CF have a particular mutation (p.Phe508del), and about half of these individuals have two copies of these mutations. However, they found that 30% of Hispanics, 38% of blacks, and 41% of Asians did not even have one copy of the mutation. Patients of Hispanic, black, or Asian ancestry were also less likely to have two identified CFTR variants. "Our results confirm the widely held notion that the American College of Medical Genetics and Genomics list of 23 mutations that was specifically designed for carrier screening is inadequate for diagnostic testing, even though it is used widely," commented Dr. Schrijver.

When the investigators compared Registry results from 2008 to 2013, they documented that genetic analyses were reaching greater proportions of CF individuals. For instance, in 2008 21% of whites were not yet genotyped compared to 9% in 2013. Although similar trends were observed across all ethnic groups, significantly greater proportions of individuals in nonwhite ethnic groups remained not yet genotyped compared to whites (eg, 19% of blacks versus 9% of whites).

To learn more about the spectrum of CTFR variants in nonwhite individuals, the investigators used direct DNA sequencing to study 140 individuals in the Registry. They found that 89 had two CFTR variants,

including seven novel ones. Multiplex ligation-dependent probe amplification (MLPA) detected 14 rearrangements in the remaining 51 patients, six of which had not been described before. Because the investigators found that deletions and duplications were relatively common in the nonwhite CF patients, yet many were not previously reported, they suggest that testing should be expanded to include MLPA analysis.

CF, an inherited life-threatening disorder, affects the exocrine epithelial cells of multiple tissues and organs. Serious pulmonary problems occur, including chronic lung infections and airway inflammation. Other symptoms include failure to thrive, pancreatic insufficiency, infertility, and bowel obstruction. Its prevalence is approximately 1:2500 in whites, 1:15,000 in blacks, 1:35,000 in Asians, and 1:10,900 in Native Americans.

More information: *The Journal of Molecular Diagnostics*, dx.doi.org/10.1016/j.jmoldx.2015.07.005

Provided by Elsevier