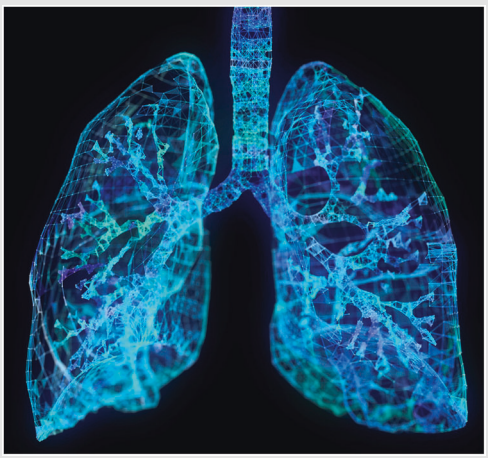
Genetics inMedicine | NEWS

NEWS

Cystic fibrosis carriers have increased risk for associated conditions



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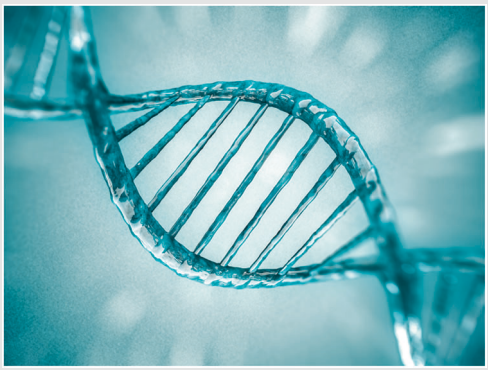
Cystic fibrosis (CF) carriers, those with only one pathogenic variant in the *CFTR* gene, in the recent past were commonly thought to have no health effects related to their heterozygote status. As an autosomal recessive disease, it is only when two pathogenic variants are inherited that people experience persistent lung infections and other adverse health effects related to CF. But as reported in a recent article in *PNAS* (https://doi.org/10.1073/pnas.1914912117) Miller et al. found in a cohort of nearly 20,000 CF carriers that they are at increased risk for virtually every condition that affects people with CF, compared with noncarriers. The researchers evaluated the prevalence of 59 CF-related diagnostic conditions among CF carriers in the Truven Health MarketScan Commercial Claims database, matching each of the CF carriers with five controls and calculating odds ratios for each condition. Carriers were found to be significantly more likely to experience 57 of the CF-related conditions, with a trend toward greater likelihood of experiencing the remaining two as well. Previous studies had already tentatively linked some conditions, such as pancreatitis, male infertility, and bronchiectasis, to CF carriers, but the majority of conditions are associated with CF carriers for the first time: diabetes, constipation, cholelithiasis, short stature, and failure to thrive, among others. A comparison to more than 23,000 subjects with CF matched with controls additionally showed that as the relative odds ratio of a specific condition increased among those with CF, it also did so among CF carriers. The increased risk of CF conditions among carriers was also confirmed in a smaller cohort of mothers of children with CF. Although ~70% of carriers have the same F508del *CFTR* variant, the team notes that their results may not be generalizable to all CF carriers due to other variants. While the absolute risk of an individual carrier having a CF-related condition is very low, with 10 million carriers in the United States, a significant number of people are likely affected. Awareness of CF carrier risk can inform screening and preventive treatment, and provide motivation for avoiding other disease risk factors. The researchers conclude that studying carriers of recessive genetic diseases is now possible thanks to widespread availability of genetic testing, and combining genetic and health information from large databases is a powerful way to identify population-level health risks.
—A.N. Grennell, News Editor

New autoinflammatory disease caused by a *RIPK1* missense variant



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A previously undescribed autoinflammatory disorder has emerged in members of three families, marked by fevers, swollen lymph nodes, severe abdominal pain, gastrointestinal problems, headaches, and sometimes enlarged spleen and liver. From birth or shortly thereafter, the seven affected patients experienced periodic flares of symptoms, often with increased levels of inflammatory markers in between flares. After ruling out infections and cancer, researchers turned to the patients' genomes. In a recent article in *Nature* (https://doi.org/10.1038/s41586-019-1828-5) Lalaoui et al. found a different missense variant in *RIPK1* in each family and determined that variants in *RIPK1* explained the autoinflammatory response. Unable to find the same or similar *RIPK1* variants among 554 people with unexplained periodic fevers and 250,000 people in public sequence databases, the team named the new condition cleavage-resistant RIPK1-induced autoinflammatory (CRIA) syndrome. *RIPK1* is a key regulator of immune signaling pathways, but is modified post-translationally by, among other things, caspase-8-mediated cleavage to achieve an optimal inflammatory response. RIPK1 cleavage is thought to limit inflammatory response by inhibiting RIPK3 activation and necroptosis. The researchers examined the mechanism of the disease with a cleavage-resistant *RIPK1* mouse model, and found that homozygous mice died during embryogenesis and heterozygous mice were viable but hyperresponsive to inflammatory stimuli. This is consistent with CRIA patients, who have one variant copy and one normal copy of *RIPK1*, while unaffected family members have two normal copies. Further experiments in cleavage-resistant mice showed that RIPK1 cleavage limits tumor necrosis factor (TNF)-induced cell death and inflammatory responses. The researchers propose a new hierarchy of cellular responses to TNF signaling: cell survival, then caspase-8-mediated apoptosis, and finally necroptosis. So far, only the heterozygous missense variants D324N, D324H, and D324Y are associated with CRIA syndrome. While CRIA patients did not respond to several TNF inhibitors known to reduce inflammation, five of the seven did respond to the interleukin-6 inhibitor tocilizumab. The researchers conclude that caspase-mediated RIPK1 cleavage maintains inflammatory homeostasis throughout life and that specific RIPK1 inhibitors currently being developed may help treat CRIA and other inflammatory conditions.
—A.N. Grennell, News Editor