NEWS

Damaging de novo variants involved in cerebral palsy


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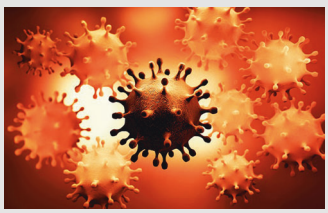
Cerebral palsy (CP) is the most common childhood motor disability, affecting about 1 in 300 kids. The condition, a nonprogressive impairment of motor function, was historically attributed to brain damage caused by a lack of oxygen before or during birth. Although environmental factors such as prematurity, maternal infection, and pre- and perinatal stroke are known risk factors, up to 40% of CP cases have an associated congenital anomaly, suggesting a genetic component. In an article recently published in *Nature Genetics* (https://www.nature.com/articles/s41588-020-0695-1), Jin and colleagues report evidence for CP risk genes that disrupt early neuronal connectivity. The researchers exome sequenced 250 CP trios from the United States, China, and Australia. A third of the cases had a known environmental insult, and 63% were classified as idiopathic. In parallel, the team analyzed sequencing data from nearly 1800 unaffected siblings of autism cases and their unaffected parents. The analysis uncovered an enrichment of damaging de novo variants in CP cases. The researchers attributed nearly 12% of CP cases to an excess of damaging de novo variants, and found that this enrichment was greater in idiopathic versus environmental cases. Overall, the analysis uncovered nearly 440 putative CP risk genes. In addition to genes previously associated with CP phenotypes, the analysis revealed that two unrelated cases harbored identical damaging de novo variants in *RHOB*. *RHOB* is known to control dendritic spine outgrowth but has not been implicated in human disease before this. Likewise, another two unrelated cases harbored identical damaging de novo variants in *FBXO31*, a gene that plays critical roles in axonal and dendrite outgrowth and neuronal migration during development. STRING-based clustering and pathway analyses of candidate genes revealed an overrepresentation of genes involved in extracellular matrix biology, cell matrix interactions, cytoskeletal dynamics, and Rho GTPase function. The researchers then performed a reverse genetics screen in *Drosophila*, prioritizing genes with known roles in brain development or neurodevelopmental disorders, and found that 71% (10/14) of genes showed a locomotor phenotype, suggesting that candidate CP genes involved in cytoskeletal, Rho GTPase, and cell projection pathways may have a role in motor development. The researchers conclude that, contrary to dogma, damaging genomic variants may be a major contributor to CP and propose that the findings carry clinical implications for guiding preventive health care and patient management and treatment. *—V. L. Dengler, News Editor*

Rare loss-of-function variants may underlie pneumonia in COVID-19 patients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The novel coronavirus SARS-CoV-2 has infected millions worldwide, with clinical manifestations ranging from silent to lethal. Researchers have identified that being older, male, and having one or more underlying conditions increases the risk of severe infection, yet substantial clinical variability exists, even between people with the same risk factors. In a recently published article in *Science* (https://science.sciencemag.org/content/370/6515/eabd4570), researchers from the COVID Human Genetic Effort show that inborn errors of immunity can underlie potentially fatal COVID-19. The researchers sequenced more than 650 patients hospitalized for life-threatening pneumonia due to SARS-CoV-2 infection and assessed 13 loci that confer susceptibility to potentially fatal influenza pneumonia. They found that 3.5% (23/659) of patients in the study cohort carried 24 deleterious variants across eight genes, including *IRF7*, *TLR3*, and *IFNAR1*. In follow-up assays using patient cells, the team showed that not only did cells from *IRF7*-deficient patients have low IRF7 expression levels but they also did not produce detectable type I or type III interferon (IFN) in response to SARS-CoV-2 infection. Similarly, T cells from an *IFNAR1*-deficient patient showed impaired IFNAR1 expression and did not respond to interferon (IFN)-α2 or β. Additionally, cells deficient in *IRF7*, *TLR3*, or *IFNAR1* displayed higher levels of SARS-CoV-2 infection than cells from healthy donors, but transduction with wild-type *IRF7* or *IFNAR1* rescued the defect. Together the findings show that *IRF7*, *TLR3*, or *IFNAR1* deficiency impairs type I IFN immunity to SARS-CoV-2 infection. In vivo analyses corroborated the cellular assays. IFN-α levels from patient blood samples taken during the acute phase of COVID-19 showed that nearly half of tested patients (10/23) had IFN-α serum levels below 1 pg/ml, substantially lower than levels in patients hospitalized with unexplained severe COVID-19. Together, the data suggest that at least 23 of the patients with life-threatening COVID-19 pneumonia have genetic defects involving eight loci implicated in TLR3- and IRF7-dependent type I IFN production, according to the authors. The findings suggest that type I IFN cell–intrinsic immunity is essential to managing SARS-CoV-2 infection in the lungs and that patients with life-threatening COVID-19 pneumonia may have variants in other type I IFN–related genes. The authors conclude that, at least early during the course of infection, administration of type I IFN may be of therapeutic benefit to some patients. *—V. L. Dengler, News Editor*

Genetics in Medicine (2020) https://doi.org/10.1038/s41436-020-01036-2