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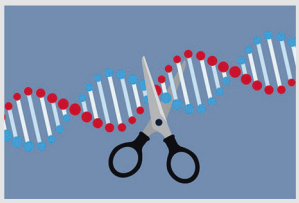
NEWS

Gene editing shows promise for treating fatal monogenic disorder



In patients with transthyretin amyloidosis, a progressive and fatal disease, amyloid fibrils of misfolded transthyretin (TTR) protein accumulate in tissues, especially the nerves and heart. Transthyretin amyloidosis, which is also known as ATTR amyloidosis, may be acquired or hereditary, with more than 100 pathogenic variants in *TTR* contributing to the disease. Patients primarily experience amyloid polyneuropathy and/or cardiomyopathy although other organ systems may also be affected. Current treatment strategies focus on reducing amyloid formation. As a monogenic disease, however, ATTR amyloidosis is an ideal target for CRISPR–Cas9 in vivo gene editing. In a recently reported study in *The New England Journal of Medicine* (https://doi.org/10.1056/NEJMoa2107454), Gillmore and colleagues presented interim results of a phase I trial testing the safety and efficacy of an intravenously administered CRISPR–Cas9-based in vivo gene editing therapy known as NTLA-2001, which edits *TTR* in hepatocytes where it is nearly exclusively produced. The therapy resulted in decreased production of wild-type and mutant TTR after a single administration. Preclinical studies revealed a dose-dependent and durable effect of NTLA-2001 in murine and primate animal models. In transgenic mice, circulating serum TTR protein levels dropped to the lowest levels within 4 weeks and remained there for 12 months following the single dose administration. The researchers saw a similar effect in cynomolgus monkeys, with a greater than 94% reduction in serum TTR protein levels. Possible off-target editing sites were minimal, and no evidence of off-target editing was seen in primary human hepatocytes when treated with NTLA-2001. In addition, the treatment was not associated with any adverse events. The researchers then initiated an open-label, single-dose, proof-of-concept study of hereditary ATTR amyloidosis patients with polyneuropathy. Three of the six enrolled patients experienced mild adverse events during or after the treatment, and one patient had an infusion-related reaction. No serious adverse events were seen. In the three patients who received a dose of 0.1 mg per kilogram, mean TTR serum levels dropped by half compared with baseline. In the remaining three patients who received a dose of 0.3 mg per kg, serum levels fell to nearly 90% below baseline by day 28. The study is ongoing, but together the results provide clinical proof-of-concept data for in vivo CRISPR–Cas9-mediated gene editing as a therapeutic strategy for ATTR amyloidosis. *—V. L. Dengler, News Editor*

SNIP1 variant causes recessive neurodevelopmental disorder prevalent in Amish community

Nearly a decade ago, researchers described three Old Order Amish individuals with symptomatic epilepsy and skull dysplasia and homed in on a likely causative variant in the gene *SNIP1*. Now, in a study recently published in *PLOS Genetics* (https://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1009803), Ammous and colleagues describe a neurodevelopmental disorder marked by seizures that is prevalent in the Amish community and identify a variant in *SNIP1* that causes the recessive condition. The researchers identified more than 50 individuals from over 20 interrelated Old Order Amish families. Thirty-five individuals were included in the study and evaluated clinically. Affected individuals displayed substantially varied phenotypes including between sibships. Cardinal features of the disorder include hypotonia, global developmental delay, intellectual disability, seizures, skull abnormalities, and a characteristic facial appearance. More than half of affected individuals also displayed congenital cardiac defects, with 12% developing cardiomyopathy. Nearly a quarter of individuals exhibited spinal abnormalities such as tethered cord and scoliosis. In the neonatal period, upper-airway respiratory troubles were common and poor feeding was universal. Endocrine abnormalities and ophthalmic and auditory features were also present. The researchers investigated four affected individuals from two nuclear families to ascertain a genetic cause. They first performed a genome-wide screen to identify putative autozygous genomic regions. The inspection revealed a single region of homozygosity greater than 1 Mb common to the four individuals. Whole-exome sequencing data in this region isolated a single potentially pathogenic variant in exon 4 of the *SNIP1* gene. A follow-up analysis confirmed homozygosity of the variant in all 35 individuals as well as heterozygosity in all parents. The researchers then performed whole-transcriptome sequencing on six affected individuals along with sex-matched unaffected control individuals. Reactome pathway analysis of the 75 significantly upregulated and 109 significantly downregulated genes identified 30 overrepresented pathways. Transforming growth factor-β receptor signaling in the epithelial to mesenchymal transition pathway was the most overrepresented pathway. An additional assessment using GTex data revealed that several of the upregulated genes are highly expressed in the brain. Altogether, the findings reveal that biallelic variants in *SNIP1* cause a neurodevelopmental disorder that is prevalent in the Amish. The authors conclude that preventing life-threatening complications and optimizing psychomotor development are top clinical management strategies for affected individuals. *—V. L. Dengler, News Editor*

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