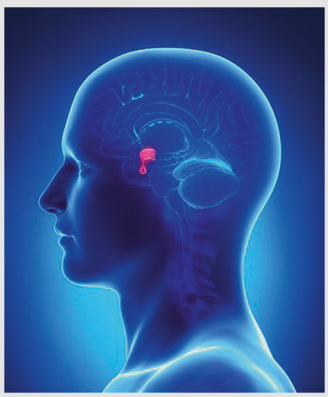
NEWS

Reporter assay uncovers splicing variants underlying pituitary hormone deficiency



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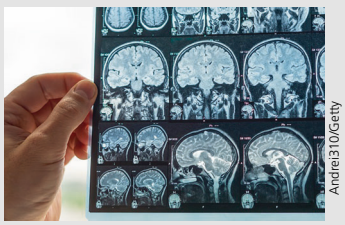
Pituitary hormone deficiency, which affects about 1 in 4,000 live births, impacts growth, development, and energy levels. Three percent of pituitary hormone deficiency cases result from variants in the alpha isoform of *POU1F1*, a gene that encodes a pituitary-specific transcriptional activator. Loss of *POU1F1* function often results in deficient growth and thyroid-stimulating hormones. Alternative splicing of *POU1F1* predominately produces the alpha isoform. However, an alternative splice variant, *POU1F1* beta, which can act as a transcriptional repressor, comprises as much as 3% of *POU1F1* transcripts in the human pituitary gland. In a study recently published in the *American Journal of Human Genetics* (https://www.cell.com/ajhg/fulltext/S0002-9297(21)00237-8), Gergics and colleagues identified splice variants in *POU1F1* beta that lead to pituitary hormone deficiency. The researchers exome-sequenced individuals with hypopituitarism from cohorts in Europe and South America to identify causal variants. They identified four heterozygous missense variants in exon 2 of the *POU1F1* beta isoform in four unrelated individuals. Transient transfection of cells with a *POU1F1*-luciferase reporter gene revealed that the newly identified variants retain repressor activity. Using an exon trapping assay, the researchers found that the variants shift splicing of *POU1F1* to favor nearly exclusively expression of the beta isoform. The researchers then set out to identify splice-disrupting variants in exon 2 of *POU1F1*. They generated a library of every possible single-nucleotide variant across the exon and used a high-throughput splicing reporter assay to test the impact of splicing on more than 1000 single-nucleotide variants. The analysis uncovered 132 *POU1F1* variants that result in exon skipping, isoform switching of cryptic isoform use. Nearly 100 of the variants, including 14 synonymous variants, disrupted splicing and increased usage of isoforms other than alpha by at least threefold. With this catalog, the researchers evaluated additional families with hypopituitarism. They identified two unrelated individuals with isolated growth hormone deficiency who carried synonymous *POU1F1* variants that affected splicing and increased beta isoform usage to a degree similar to that with the four missense variants. The authors conclude that the findings underscore the importance of evaluating the impact of variants on splicing. —*V. L. Dengler, News Editor*

Early trial shows gene delivery is safe and feasible for rare genetic disorder



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Patients with aromatic L-amino acid decarboxylase (AADC) deficiency, a rare recessive neurodevelopmental disorder, have deficient catecholamines and serotonin and cannot normally metabolize levodopa to dopamine. The disorder, which presents in early infancy, causes severe developmental and intellectual disability, including lifelong motor, behavioral, and autonomic symptoms such as oculogyric crises, emotional lability, sleep disruption, and excessive sweating. In a recently published study in *Nature Communications* (https://www.nature.com/articles/s41467-021-24524-8), Pearson and colleagues investigated the safety and efficacy of a novel gene therapy for AADC deficiency. The researchers used magnetic resonance to guide bilateral delivery of an adeno-associated virus type 2 encoding *DDC*, the aromatic L-amino acid decarboxylase gene (AAV2-hAADC), to the substantia nigra (SN) and ventral tegmental area (VTA) of seven children aged 4 to 9 years old. Subjects received one of two doses. The AAV2-hAADC delivery achieved target coverage of nearly all of the SN and the majority (70%) of the VTA. None of the subjects showed adverse effects in the short or long term following the surgical procedure. Beginning 3–4 weeks after gene therapy delivery, several symptoms, including irritability, sleep dysfunction, and dyskinesia, worsened but then improved to better than baseline over the following weeks and months. Six of the subjects tapered dopaminergic and anticholinergic medications, and three subjects stopped dopaminergic medication altogether. By 2 years post-treatment, three subjects had no residual dyskinesia. Oculogyric crises, a cardinal feature of the disorder, resolved completely in six of seven subjects by 3 months postsurgery. Dopamine metabolism increased in all subjects, and they exhibited enhanced uptake of 6-[^{18}F]-fluoro-L-DOPA within the midbrain and the striatum. By 12 months after surgery, six of seven subjects had gained normal head control and more than half (four of seven) could sit independently. At 18 months post-treatment, two subjects could walk with support. The rate of improvement varied between subjects and was not related to dose or age. Together the findings indicate that the gene therapy is well tolerated and helps restore brain AADC activity. The authors conclude that direct midbrain gene delivery of AAV2-hAADC in children with AADC deficiency is not only safe and feasible but also leads to clinical improvements in symptoms and motor function. —*V. L. Dengler, News Editor*

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