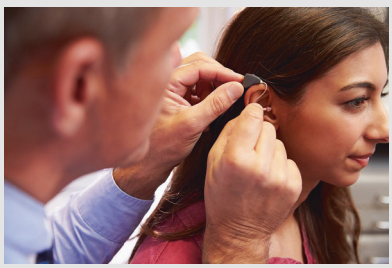
NEWS

Antisense oligonucleotides are a possible therapy for hereditary deafness



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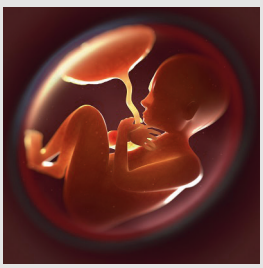
Patients with a form of sensorineural hearing loss called DFN9A progressively lose hearing and suffer balance problems that interfere with daily life. Researchers estimate that most people with DFN9A, which manifests in the third to fifth decades of life, carry a heterozygous variant, c.151C>T (p.Pro51Ser), in *COCH*, a gene encoding cochlin, one of the most abundant proteins in the cochlea. The variant leads to cytotoxic cochlin dimers and oligomers that sequester wild-type cochlin. In a recent proof-of-concept study published in *Molecular Therapy—Nucleic Acids* (https://doi.org/10.1016/j.omtn.2021.02.033), de Vrieze and colleagues report that antisense oligonucleotides (AONs) are a viable therapeutic possibility for DFN9A. The researchers employed long-read single-molecule real-time (SMRT) sequencing of the *COCH* genomic sequence from three DNF9A patients to identify 11 deep-intronic variants specific to the c.151C>T allele. As intronic variants, the identified disease-associated transcripts are only amenable to pre-mRNA degradation by AONs, and not RNA interference strategies. The team then designed AONs against the variants. In silico thermodynamic analyses revealed differences in binding affinity of AONs for wild-type versus variant-carrying alleles. Because patient-derived primary fibroblasts express only very low levels of *COCH*, making the effect of AONs difficult to determine, the researchers next generated two stable transgenic cell lines that express either wild-type or variant-carrying minigenes. Compared with a scrambled AON control, six of seven AONs directed against the c.151C>T variant and four of seven AONs directed against a deep-intronic variant reduced variant transcript levels. Further analysis of four AONs—three directed against the c.151C>T variant and one against the deep-intronic variant—showed that three did not affect wild-type transcript levels. To best discern allele specificity, the researchers then isolated a variant *COCH* minigene clone with *COCH* expression similar to endogenous levels. When the researchers treated the cells with 25 nM of an AON against the c.151C>T variant, they found that the therapeutic nucleotide reduced variant *COCH* levels by four- to sixfold without affecting wild-type levels. The findings suggest that this AON has a stronger affinity for the variant transcript than for wild type. Altogether, the research identifies a highly effective AON against the c.151C>T variant as a promising candidate for further preclinical development in animal models of DFN9A. The authors conclude that the use of AONs is a feasible strategy for treating inherited hearing impairment and vestibular dysfunction. *—V. L. Dengler, News Editor*

Mosaicism is a typical feature of placental development



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The placenta, a temporary organ that supplies the fetus with nutrients and eliminates waste, can harbor chromosomal aberrations that are not identified in the fetus. Although the basis of this genetic segregation remains unknown, confined placental mosaicism may contribute to placental dysfunction and associated diseases, including pre-eclampsia, intrauterine growth restriction, and stillbirth. In an article recently published in *Nature* (https://www.nature.com/articles/s41586-021-03345-1), Coorens and colleagues show that mosaicism is a characteristic feature of placental development. The researchers sequenced the whole genomes of 86 bulk placental samples from 37 term placentas as well as umbilical cord tissue derived from the inner cell mass and maternal blood. Placentas came from normally progressing pregnancies as well as complicated pregnancies. The analysis revealed a high substitution burden within bulk samples. The median variant allele frequency (VAF) within each bulk placental sample was 0.24, suggesting that variants permeated nearly half of cells. In contrast, umbilical cord samples did not contain detectable clonal expansions. Nearly half of substitutions in the bulk placental samples corresponded to single-base substitution mutational signatures that are rare in healthy tissues. Nearly half of bulk samples also contained a copy-number change. Most somatic changes in bulk samples from the same placenta were seen in single samples, indicating that the placenta is a collection of independent genetic units. To determine the origin of mosaicism in the bulk samples, the researchers whole-genome sequenced trophoblast clusters and fetal mesenchymal cores derived from the inner cell mass. They found that the median VAF of mesenchymal cores was 0.20, compared with 0.39 for trophoblast clusters, indicating that the trophoblast clusters were monoclonal. Phylogenetic analysis revealed that pairs of trophoblast clusters shared more than half of somatic variants, indicating a long developmental ancestry. The findings suggest that expansions of single-trophoblast progenitors underpin the clonality and confined mosaicism in bulk placental samples. Further comparison of the VAF of early embryonic variants across bulk and microdissected samples revealed that at least one genetic bottleneck occurred in about half of placentas to segregate genomic changes between placental and fetal lineages. On the basis of the research, the authors conclude that the placenta is a patchwork of genomic alterations and that larger-scale genomic studies of the placenta may help to explain how placental genomic aberrations impact human pregnancy complications. *—V. L. Dengler, News Editor*

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