IN THIS ISSUE

NIPS provides clinically relevant information for mom as well as baby

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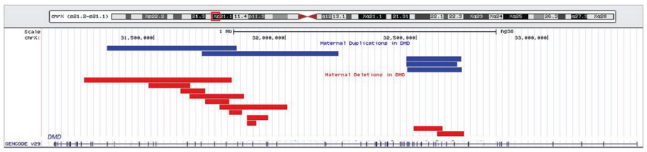

Noninvasive prenatal screening (NIPS) of cell-free DNA from maternal serum enables detection of fetal aneuploidies. Although the screening typically aims to uncover viable, fetal trisomies, the analysis can also detect maternal copy-number variations (CNVs) that may be clinically actionable. In this issue, Brison and colleagues report a review of cases in which NIPS revealed maternal CNVs involving the *DMD* gene. Loss-of-function variants in the *DMD* gene can lead to dystrophinopathies, including Duchenne muscular dystrophy (DMD), a severe neuromuscular disorder. The researchers examined NIPS results from more than 26,000 pregnant women who underwent the screening at the Center for Human Genetics in Leuven, Belgium, between 1 July 2017 and 30 June 2018. The analysis detected 16 maternal CNVs in the *DMD* gene, which corresponds to an incidence of 1 in 1632 pregnant women. Using DNA extracted from maternal white blood cells, the scientists validated the size and position of all 16 maternal CNVs by chromosomal microarray analysis. Phenotypic databases allowed correct interpretation and classification of variants in nine families. Of the remaining five detected variants, segregation analysis enabled classification of two. A recurrent in-frame duplication of exons 10–27 in unrelated women from three families was also present in clinically unaffected adult male relatives, leading Brison and team to classify this variant as likely benign. Paternal inheritance of an in-frame deletion in exons 54–55 in another family allowed classification of this variant as likely benign as well. Finally, the researchers classified a novel out-of-frame duplication of exons 51–62 for which segregation analysis was uninformative as likely pathogenic for DMD. Variants detected in two families remain unclassified. The authors conclude that NIPS can provide relevant and clinically actionable *DMD* variants to the mother and present a strategy for return of results. *V. L. Dengler, News Editor*

Scientists uncover links between lysosomal storage diseases and cancer

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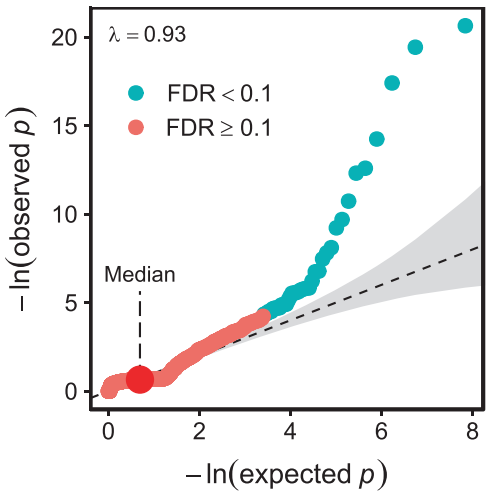

Lysosomal storage diseases (LSDs) are a group of more than 50 mostly autosomal recessive monogenic lysosomal catabolism disorders that affect 1 in 5000 live births. Defects in lysosomal proteins lead to the accumulation of macromolecules and ultimately cellular stress, dysfunction, and death in many cases without treatment. As a result, patients with LSDs suffer impaired organ function and many have short life expectancy. Additionally, clinical observations have revealed that patients with two LSDs are at increased risk of cancer, and disruption of lysosomal homeostasis is linked to several cellular processes that can induce malignancies. Yet scientists remain uncertain about the relationship between lysosomal dysfunction and cancer. Now, in an extensive association analysis between cancer and germline variants in 42 causal LSD genes, Shin and colleagues show that carriers of potentially pathogenic variants (PPVs) in LSD genes not only are at increased risk of cancer but also develop the malady earlier than noncarriers. The researchers compared sequencing and clinical data from more than 2500 cancer patients from the Pan-Cancer Analysis of Whole Genomes (PACWG) to publicly available variant call sets of about 2500 genomes in the 1000 Genomes Project and more than 53,000 exomes from a subset of the Exome Aggregation Consortium. The analysis revealed that the proportion of individuals carrying PPVs was significantly higher in the Pan-Cancer cohort (20.7%) than in the 1000 Genomes cohort (13.5%). Additional association analyses revealed that 19 cancer types harbor PPVs in at least 1 LSD gene and that PPVs in 18 genes were associated with at least one cancer type. When the researchers assessed age at cancer diagnosis in PPV carriers versus noncarriers, they found that cancer developed earlier in carriers. For example, PPV carriers developed chronic myeloid disorder at a median age of 45.5 years, whereas median age of diagnosis for noncarriers was 58.5 years. The researchers conclude that carriers of PPVs in LSD genes are at increased risk of cancer. *—V. L. Dengler, News Editor*

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