# IN THIS ISSUE

## Low-pass genome sequencing is effective in prenatal diagnostic testing

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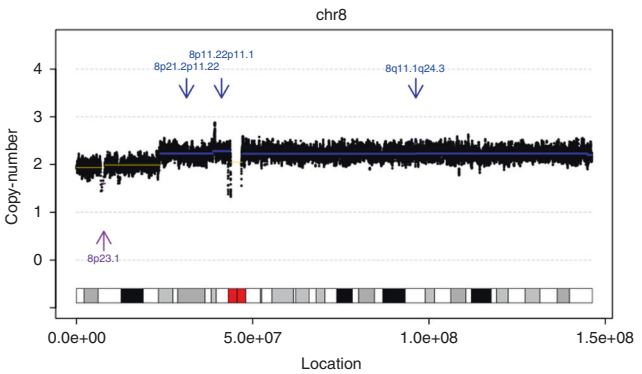


Prenatal diagnostic testing can detect genetic conditions such as copy-number variants (CNVs) as early as in the first trimester. Currently, chromosomal microarray analysis (CMA) is recommended as a first-tier test for high-risk pregnancies. However, variation in CMA platforms across genetic testing centers and different detection approaches are barriers to cross-laboratory validation of results and genetic counseling. In this issue, Wang and colleagues show that low-pass genome sequencing (GS) is equivalent to CMA and, in fact, surpasses the method in prenatal diagnostic testing. It offers a higher diagnostic yield and greater sensitivity to mosaicism, helps to reduce the need for repeat testing, requires less input DNA, and runs at a higher throughput. Previous work by this team demonstrated that low-pass GS could detect CNVs and be used in a clinical setting. In the current work the researchers directly compared results of CMA and low-pass GS tests on chorionic villi, amniotic fluid, and cord blood from more than 1000 women undergoing prenatal diagnosis. While CMA identified 87 numerical disorders, 37 clinically relevant CNVs (pathogenic or likely pathogenic), and 47 variants of uncertain significance, low-pass GS returned the same results plus an additional 17 cases of relevant CNVs and 6 more variants of uncertain significance. The additional CNVs were verified by quantitative polymerase chain reaction (PCR); insufficient probe coverage was responsible for some CNVs not detected by CMA. A majority of the additional CNVs found by low-pass GS (83%) were Southeast Asian type α-thalassemia, and a subset of CNVs were missed by CMA due to low-level mosaicism. The experimental repeat rate for low-pass GS was only 0.4%, compared with 4.6% for CMA. The authors conclude that with genome-wide resolution, low-pass GS has advantages over CMA in identifying genetic conditions prenatally. *—A. N. Grennell, News Editor*

## A new genomic landscape for fetal akinesia

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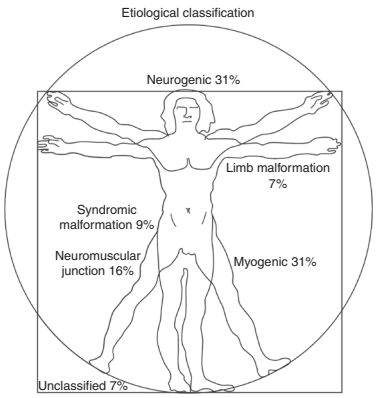


Fetal akinesia (FA) covers a broad spectrum of disorders linked by a decrease or absence of fetal movement. Related phenotypes range from mild musculoskeletal defects to lethal prenatal abnormalities. Associated disorders include intrauterine growth restriction, arthrogryposis multiplex congenita (AMC), multiple pterygium syndrome, and fetal akinesia deformation sequence (FADS). Pathogenic variants in more than 160 genes have been implicated in FA, and 20 clinical subtypes are described. Despite extensive testing, many patients have no causal genetic diagnosis identified. In this issue, Pergande and colleagues uncover novel genomic insights across this spectrum via next-generation sequencing (NGS), finding the underlying genetic cause for FA in 73% of previously unsolved cases. The team recruited 51 patients with multiple joint contractures at or before birth in whom no causative pathogenic variant had been identified. NGS was performed and variant identification was validated by dideoxy sequencing. Variants were then filtered with the Varbank pipeline and manually curated by gene function, known disease association, and severity of predicted effect, creating a list of potential candidates. These candidates were graded for pathogenicity, and in combination with deep clinical phenotyping, underlying causes of each case were evaluated. By this method, the researchers identified 41 novel likely pathogenic variants, 9 novel putative pathogenic variants, and 14 novel disease–gene associations for FA. Several genes known to cause disease phenotypes but not previously linked to FA were found. The candidate genes covered a wide range of molecular functions; however, the large majority were ion channel genes. The distributions of phenotype category, molecular functions, and etiological classifications support the heterogeneity of FA and offer a new perspective for analyzing and classifying patients. The authors conclude that exome sequencing combined with variant filtering and thorough clinical assessment of patients is useful in uncovering the genetic basis of complex diseases. *—A. N. Grennell, News Editor*

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