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Arthrogryposis and pterygia as lethal end manifestations of genetically defined congenital myopathies.

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Abstract

Arthrogryposis multiplex congenita affects approximately 1 in 3,000 individuals of different ethnic backgrounds and displays an equal incidence in males and females. The underlying mechanism for congenital contracture of the joints is decreased fetal movement during intrauterine development. This disorder is associated with over 400 medical conditions and 350 known genes that display considerable variability in phenotypic expression. In this report, four fetal or perinatal autopsy cases of arthrogryposis were studied by gross morphology, microscopic histopathologic examination, and whole genome sequencing of postmortem DNA. Two stillborn sibling fetuses with arthrogryposis, pterygia, and amyoplasia had compound heterozygous pathogenic variants in NEB. A neonate with a histopathologic diagnosis of nemaline myopathy had a heterozygous de novo pathogenic variant in ACTA1. Another stillborn infant with pterygia and arthrogryposis had a heterozygous de novo likely pathogenic variant in BICD2. These cases demonstrate the utility of whole genome sequencing as the principal diagnostic method of lethal forms of skeletal muscle disorders that present with arthrogryposis and muscle amyoplasia/hypoplasia. Molecular diagnosis provides an opportunity for studying patterns of inheritance and for family counseling concerning future pregnancies.

KEYWORDS: arthrogryposis; autopsy; fetal akinesia; myopathy; whole genome sequencing

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