Format: Abstract

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Cystic kidneys in fetal Walker-Warburg syndrome with POMT2 mutation: Intrafamilial phenotypic variability in four siblings and review of literature.

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Abstract

Walker-Warburg syndrome (WWS) is a severe form of congenital muscular dystrophy secondary to α-dystroglycanopathy with muscle, brain, and eye abnormalities often leading to death in the first weeks of life. It is transmitted in an autosomal recessive pattern, and has been linked to at least 15 different genes; including protein O-mannosyltransferase 1 (POMT1), protein O-mannosyltransferase 2 (POMT2), protein O-mannose beta-1,2-N acetylglucosaminyltransferase (POMGNT1), fukutin (FKTN), isoprenoid synthase domain-containing protein (ISPD), and other genes. We report on a consanguineous family with four consecutive siblings affected by this condition with lethal outcome in three (still birth), and termination of the fourth pregnancy based on antenatal MRI identification of brain and kidney anomalies that heralded proper and deep clinical phenotyping. The diagnosis of WWS was suggested based on the unique collective phenotype comprising brain anomalies in the form of lissencephaly, subcortical/subependymal heterotopia, and cerebellar hypoplasia shared by all four siblings; microphthalmia in one sibling; and large cystic kidneys in the fetus and another sibling. Other unshared neurological abnormalities included hydrocephalus and Dandy-Walker malformation. Whole exome sequencing of the fetus revealed a highly conserved missense mutation in POMT2 that is known to cause WWS with brain and eye anomalies.In conclusion, the heterogeneous clinical presentation in the four affected conceptions with POMT2 mutation expands the current clinical spectrum of POMT2-associated WWS to include large cystic kidneys; and confirms intra-familial variability in terms of brain, kidney, and eye anomalies.

KEYWORDS: Walker-Warburg syndrome; cystic kidneys; whole exome sequencing

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