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Gillessen-Kaesbach-Nishimura syndrome: prenatal and postnatal findings

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Objective

Gillessen-Kaesbach-Nishimura syndrome (GIKANIS) is a congenital disease of glycosylation (CDG) linked to the ALG9 gene. GIKANIS is a lethal disorder characterized by atypical facial features, generalized skeletal changes with shortening of the long bones with broad, round metaphyses, round ilia, and deficient ossification of the skull, cervical spine and pubic bones, and visceral abnormalities including polycystic kidneys and congenital cardiac defects. GIKANIS is caused by a homozygous splic- ing variant (c.1173 + 2 T > A) leading to skipping of exon 10, frameshift, and prema- ture termination codon of the ALG9 gene. We present the ultrasonographic features and postnatal findings of two cases with GIKANIS which were polycystic kidneys, short tubular bones, decreased ossification frontoparietal bones, lack of mineralization pubic bones, thoracal vertebral body and thoracal ribs, unbalanced atrioventricular septal defekt (AVSD), transposition of great arteries and atypical facial features.

Methods

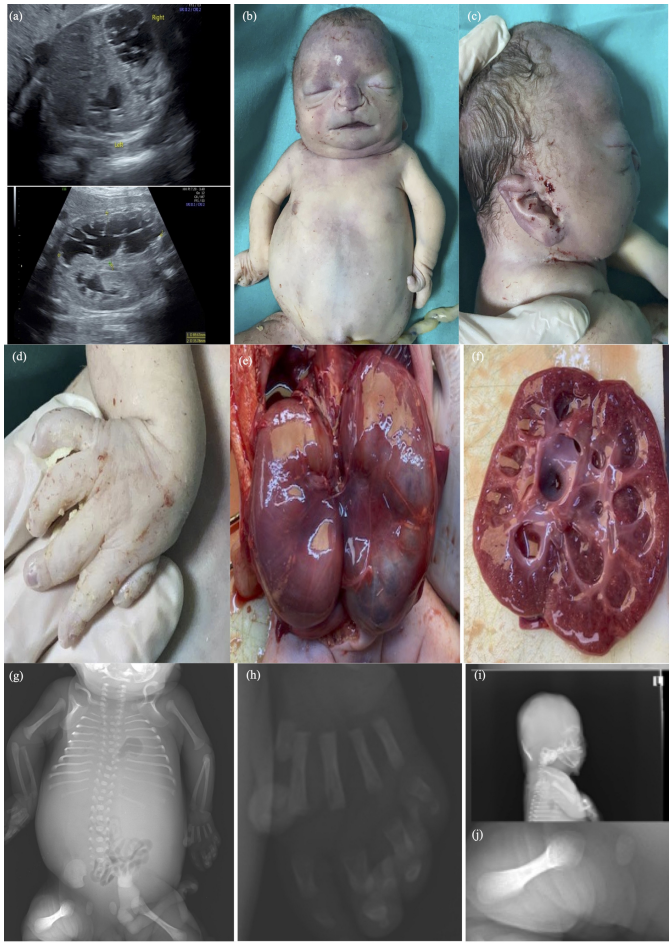
For the diagnosis of GIKANIS we used whole exam sequence test (WES).

Results

Case 1: A 29-year-old primigravid women was referred to our clinic at 30 weeks of gestation with suspicion of fetal anomalies on prenatal ultrasound (US). She and her husband had a first-cousin marriage and the family history was not contributory. Prenatal US at 30 weeks of gestation revealed shortening of the long bones (<2 SD) and enlarged bilateral polycystic kidneys with anhidramnios (Figure 1a) After multi-disciplinary team counseling, the family decided to continue the pregnancy. The female fetus was vaginally delivered spontaneously at 31 weeks of gestation. A newborn died shortly after birth and showed craniofacial abnormalities, including brachycephaly with temporal narrowing, hypertelorism, upslanted palpebral fissure, epicanthal folds, broad nasal bridge, hypoplastic nasal alae, low set and fleshy ears, long and flat philtrum and retromicrognathia, a distended abdomen, micromelia with joint contracture, and ulnar deviation of hands (Figure 1a–d). Postmortem radiograph revealed defective ossification of the frontoparietal bones and thickoccipital bones, absent/lack of mineralization of the cervical and dorsal vertebral bodies, round iliac bone with short greater sciatic notches, absent pubic ossification, shortening of the long bones with broad, rounded metaphyses, and defective ossification of ulnar phalanges, (Figure 1g–j). Autopsy confirmed bilateral polycystic kidneys (Figure 1e, f). A karyotype analysis yielded a normal 46 XX, and chromosomal microarray analysis no deletion or duplication. A homozygous pathogenic variant in exon 10 of the ALG9 gene, c.1173+ 2 T > A, was detected with whole exome sequencing (WES) test. The parents were found to carry one copy of c.1173 + 2 T > A mutation. Case 2: The same women was referred to our clinic again at 16 weeks of gestation with suspicion of fetal anomaly in her second pregnancy. Prenatal US revealed, bilateral hyperechoic enlarged kidneys with oligohydramnios, unbalanced AVSD with transposition of great arteries, shortening of the long bones (< 2 SD), and single umblical artery (Figure 2a, b). A female fetus was delivered by labor induction due to in utero ex fetus at 26 weeks of gestation. A malformed fetus showed the same dysmorphic features as those of her older sib, including brachycephaly with temporal narrowing, hypertelorism, upslanted palpebral fissure, epicanthal folds, broad nasal bridge, hypoplastic nasal alae, low set and fleshy ears, long and flat philtrum and retromicrognathia, a protuberant abdomen, and short limbs with joint contractures, (Figure 2c–e). Postmortem radiograph revealed the same skeletal changes as those of the older sib (Figure 2g, f). A homozygous pathogenic variant in exon 10 of the ALG9, c.1173 + 2 T > A, was detected.

Conclusion

This study reported the third family with the ALG9-related-GIKANIS phenotype caused by a biallelic pathogenic variant, c. (1173 + 2 T > A). CDG should be considered in the differential diagnosis for malformed fetuses with skeletal abnormalities and polycystic kidneys. WES is a useful and important diagnostic tool especially in consanguineous marriages with multiple prenatal lethal anomalies.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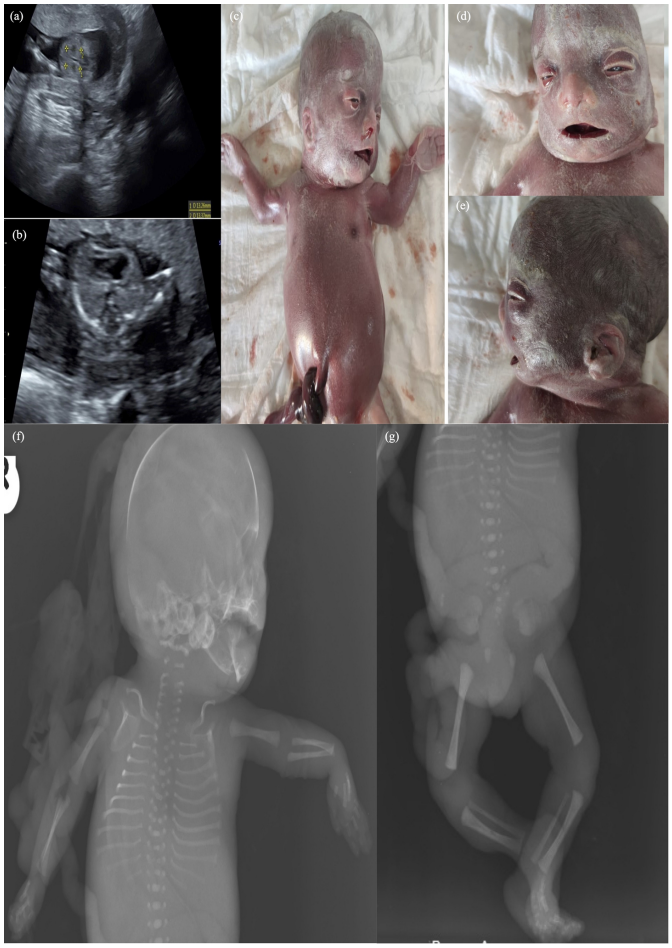
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