

The Case of the Missing Limbs!

New Delhi, Aug 26: Embryonic development and organogenesis and the genetic and non-genetic factors that regulate them, have always been areas of extensive research and have aroused a great deal of interest amongst basic scientists as well as clinicians across the world.

A number of genes that play a vital role in embryonic development have been identified primarily through studies based on animal models. For some of these developmental genes, phenotypic predictions based on studies of knock-out models of mice and other organisms are available. However, human syndromes with the expected phenotype (manifestations) related to variants in these genes are yet to be reported.



The T-box4 (TBX4) gene is one such gene known to be a crucial regulator of embryonic hindlimb development. Animal models in which the TBX4 gene is knocked out have been reported to have complete absence of hindlimbs. In humans, a syndrome called Small patella syndrome, associated with skeletal defects of the pelvis and lower limbs, has been known to be caused by heterozygous mutation (single mutation in only one copy of the gene) in the TBX4 gene. However, the defects are relatively less severe: there are no reports in humans of complete absence of lower limbs associated with mutations in this gene.

Recently, scientists at the Department of Biotechnology's Centre for DNA Fingerprinting and Diagnostics (DBT-CDFD), Hyderabad, identified a fetus with a hitherto undescribed multiple malformation syndrome associated with complete absence of both lower limbs along with sacrococcygeal agenesis, left heart hypoplasia, bilateral lung hypoplasia, hydrouretero nephrosis and hydrops.

The findings were noted in the antenatal scan and then confirmed through fetal autopsy evaluation following termination of the pregnancy. It was the third pregnancy of a consanguineous couple who had two previous similarly affected pregnancies. With the help of the powerful tool of next generation sequencing-based Whole Exome Sequencing, the researchers identified a homozygous mutation (same mutation on both copies of the gene) in the TBX4 gene in the fetus and subsequently through Sanger sequencing technique, both parents were confirmed to be heterozygous carriers for the mutation.

Interestingly, both the carrier parents had features of Small patella syndrome, the milder TBX4-associated disorder. The syndrome reported in this fetus is a novel monogenic syndrome with an autosomal recessive inheritance pattern with a 25% risk of recurrence in each offspring of the carrier couple.

Identification of the mutations in the family led to accurate recurrence risk assessment for the couple and based on this, it is possible to provide definitive prenatal or preimplantation genetic diagnostic testing for their subsequent pregnancies. The study has also provided valuable confirmation about the role of the Tbx4 factor in development of lower limbs in human embryos also, similar to that identified in animal models in previous research studies.

The findings have been published in the international journal European Journal of Human Genetics in January 2020.

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