Mutant mice provide clues on cause of cleft palates, other severe deformities in humans

Deficiency in a crucial gene causes gross deformities and early death

Medical specialists in a multinational project combined some old-fashioned sleuthing with sophisticated genetic research to solve a longstanding medical mystery over why some babies are stillborn and others are delivered with cleft palates or other severe developmental disabilities. Reported in the online journal *Nature Medicine*, the research could have far-reaching implications for the study of human developmental biology.

The study was a collaborative effort by scientists from RIKEN, led by Shiro Ikegawa, as well as those from Tokyo Metropolitan Kiyose Children's Hospital, Tokyo Medical and Dental University, Cedars-Sinai Medical Center, the David Geffen School of Medicine at the University of California at Los Angeles, Freiburg University Hospital, University Medical Center Utrecht, Chiba University, Japan Science and Technology Agency, and Tokyo Metropolitan Institute of Medical Science.

Geneticists first stripped a gene, called solute carrier-35 D1 (SLC35D1), from specially bred lab mice, observed the subsequent deformity of the bones and cartilage passed on to successive generations, then closely analyzed the mouse DNA for clues as to why the deformity was occurring. They determined that SLC35D1 plays a key role in skeletal development during prenatal growth. Mice with the gene deficiency were born with skeletal dysplasia, a lethal form of skeletal deformity with severe shortening of limbs and facial structures. Detailed analysis of cartilage under a microscope revealed distinctive characteristics of the cellular structure, including connective protein lattices that were severely shortened and misshapen.

Members of the research team then located six patients with a developmental condition known as 'Schneckenbecken dysplasia,' another severe form of skeletal dysplasia and a recessive trait that can be passed on to subsequent generations. Analysis of their DNA identified that in all cases they too were deficient in the crucial gene. Schneckenbecken dysplasia is a very rare genetic disorder involving defective bone and cartilage development that causes a cleft palate, short neck and short stature.
Other hallmarks include a misshapened rib cage, severe flattening of backbone vertebra, and short, thick long bones. The condition generally results in stillbirth or death soon after birth.

The near-perfect match of the DNA samples - patient-to-patient as well as patient-to-mouse - was telling evidence, the study authors believe, that they had found the cause not only for Schneckenbecken dysplasia but possibly for a range of developmental ailments seen in newborns. The finding could eventually lead to a 'genetic fix' of irregular chromosomes in fetuses found to be expressing the trait while still in the womb.

As well, the use of 'mouse models' to replicate other genetic abnormalities in humans gives medical specialists an ideal tool for first uncovering the cause, then developing treatments to directly cure it or reduce the likelihood of it being passed down in family lines. Such an approach provides opportunities for genetic studies that cannot be performed on human patients.

Researchers from more than a dozen facilities in Japan, the U.S., Germany and the Netherlands participated, coordinated by researchers at the Laboratory for Developmental Genetics at the RIKEN Research Center for Allergy and Immunology in Yokohama and the Laboratory of Bone and Joint Diseases at the Single Nucleotide Polymorphism Research Center in Tokyo.

**Original work:**

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