

SHORT COMMUNICATION

SUCCESSFUL GENE THERAPY IN UTERO FOR LETHAL MURINE HYPOPHOSPHATASIA

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Perinatal HPP is the most severe form and the patients usually die in utero or shortly after birth. In Japan, the lethal perinatal HPP is more common than in other countries and the fifth major disease among fetal-diagnosed skeletal dysplasias. The perinatal HPP can be diagnosed by prenatal ultrasound sonography, but there is no therapeutic option for this form. In this study, we investigated the feasibility of fetal gene therapy for lethal HPP model mice. HPP model mice (*Akp2*^{-/-}) phenotypically mimic the severe infantile form of human HPP; they appear normal at birth but die by two weeks of age due to growth failure, hypomineralization, and epileptic seizures. On day 15 of gestation, the fetuses of HPP model mice underwent

transuterine intraperitoneal injection of AAV serotype 9 expressing bone-targeted TNALP. Treated animals showed good weight gain, normal mineralization, and seizure-free survival until at least 8 weeks when sacrificed for analysis (figure A). ALP activity in plasma and bone was consistently high, and enhanced mineralization was demonstrated on X-ray images of the chest and forepaw. Vector sequence was also detected in systemic organs including bone (figure B), especially in the growth cartilage area. Our data suggest that fetal injection of AAV9 vector represents a potential breakthrough for gene delivery into bone cells to treat life-threatening HPP or systemic skeletal diseases after prenatal diagnosis.

