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IN UTERO BASE EDITING AMELIORATES PATHOLOGY IN A MOUSE MODEL OF MUCOPOLYSACCHARIDOSIS TYPE I

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Purpose

Mucopolysaccharidosis I (MPS-IH) is a congenital disease caused by a G-to-A mutation in the IDUA gene which results in non-functional IDUA enzyme and the buildup of glycosaminoglycan (GAG). MPS-IH causes significant progressive musculoskeletal morbidity often requiring multiple orthopedic surgeries. Children develop these pathologies early in life. Current treatments include enzyme replacement therapy and hematopoietic stem cell transplantation both of which have significant morbidity and cost. Investigative postnatal gene therapies are limited by inefficient skeletal correction. In contrast, prenatal gene correction offers the potential to correct the mutation before the onset of debilitating pathology.

Methods

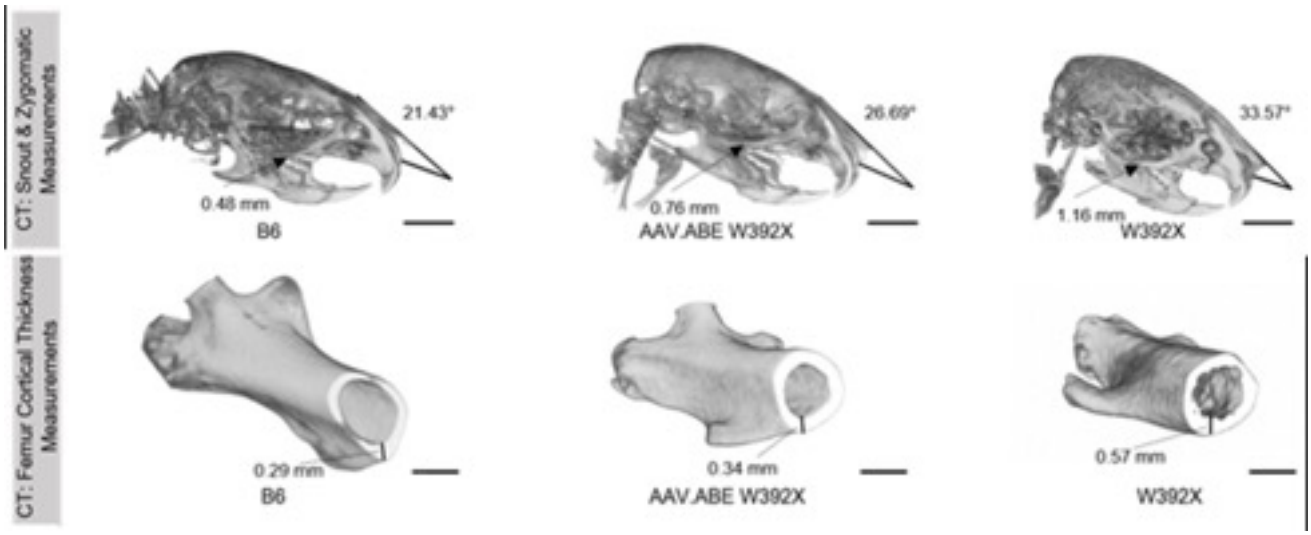
We delivered an adenine base editor and guide RNA targeting the murine MPS-IH mutation in embryonic day 15.5 fetuses (n=10) via the vitelline vein. Micro-computed tomography (μCT) of the whole skeleton was conducted at 6 months-of-age. Analysis of the CT scans was performed using Dragonfly v4.1. Bone and muscle tissue were assayed for editing, IDUA enzyme function, and GAG levels. Forelimb grip strength was assessed using a force gauge. Controls included age and sex-matched MPS-IH disease mice (n=14) and healthy C57Bl/6 mice (n=14).

Results

Next generation sequencing at 6 months demonstrated gene editing in the muscle (1.65%) and bone (0.29%). Compared to untreated Idua-W392X mice, treated mice had increased bone and muscle IDUA enzyme levels and decreased bone and muscle GAG levels ($p < 0.0001$). μCT demonstrated statistically significantly improved parameters of skull and femur cortical bone deposition such as cortical and zygomatic thickness, snout angle, and skull width/length (Figure 1). Finally, grip strength demonstrated significant improvement ($p < 0.0001$).

Conclusion

Correction of the pathologic mutation in the MPS-IH mouse via in utero base editing leads to improvement in musculoskeletal parameters. Due to early onset of musculoskeletal pathology associated with significant morbidity, in utero treatment of MPS-IH has significant relevance for clinical translation.


CT: Snout & Zygomatic Measurements
21.43°
0.48 mm
B6
26.69°
0.76 mm
AAV.ABE W392X
33.57°
1.16 mm
W392X
CT: Femur Cortical Thickness Measurements
0.29 mm
B6
0.34 mm
AAV.ABE W392X
0.57 mm
W392X