

A patient-specific *ADAMTSL2* variant causes Geleophysic Dysplasia connective tissue changes in a preclinical mouse model

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Introduction:

Geleophysic dysplasia (GD) is caused by recessive mutations in *ADAMTSL2* (a disintegrin and metalloprotease with thrombospondin type I motifs-2; GD1), and is characterized by severe short stature and other skeletal abnormalities, characteristic facial features, thick skin, and hyper-muscular build. Progressive heart valve disease and narrowing of the large airways results in approximately 33% mortality before the age of 5 years. Despite high childhood mortality and significant morbidity, no disease-modifying treatments exist for GD.

Methods:

To model disease progression and enable efficacy testing of mechanism-based therapeutic approaches, a mouse model for severe GD1 was generated by introducing the patient-specific *ADAMTSL2* c.499G>A (p.D167N) mutation into the mouse *Adamtsl2* locus. X-ray, histology and antibody staining were undertaken to determine changes in extracellular matrix and molecular signaling.

Results:

Homozygous *Adamtsl2*^{D167N/D167N} (D167N) mice had reduced postnatal survival and short stature. Radiographs demonstrated significantly shortened hind limb and forelimb bones with delayed mineralization and abnormally shaped vertebrae. Histologic investigation revealed a shortened growth plate, suggesting abnormalities in chondrogenesis. Cardiac histomorphometry revealed dysplastic aortic heart valves, consistent with progressive heart valve disease observed in patients with GD1. In the lungs, bronchial obstruction was observed, as previously reported for global *Adamtsl2* knockout mice, likely resulting in occlusion of the affected airways. TGFβ signaling was increased in D167N mice as compared to control.

Conclusion:

D167N mice recapitulate key clinical manifestations of patients with GD1 and can be utilized further to determine the molecular mechanisms of GD1 towards therapeutic intervention.