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# Disrupted Growth Plate Hypertrophy in X-Linked Hypophosphatemia: Insights from 3D Morphological Analysis

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X-linked Hypophosphatemia (XLH) is a rare disorder ranking among the most common inherited forms of rickets. XLH arises from mutations in the PHEX gene which leads to increased levels of the phosphaturic hormone FGF23, disrupting vitamin D metabolism and causing an imbalance in phosphate homeostasis. This cascade of events manifests in characteristic features including short stature, leg bowing, dental anomalies, and bone deformities. While growth impairment is a prominent feature, limited research focuses on the mechanism underlying this growth arrest.

The Growth Plate (GP) cells undergo differentiation and hypertrophy, ultimately transforming into bone-forming cells or providing space for new bone formation. Although final length is directly related with final chondrocyte size, in XLH and other growth disorders, little is known about the hypertrophy process, likely due to the GP heterogeneity and complexity. This study utilized advanced three-dimensional morphological analyses of the growth plate of young XLH mice, providing a comprehensive view growth plate mineralization. The integrated approach revealed that growth plate can be divided in more than the 3 classical zones and determines molecular signatures mainly affecting hypertrophy zone in XLH. Indicating that these cells are not able to final differentiate and hypertrophy and therefore synthesize matrix proteins properly, forming eventually an aberrant extrapolation of cells identified as cluster 8 in confocal microscopy. Therefore, these findings highlight an alteration of ECM, in turn, changes the biomechanical environment of articulations independently of grade of bone bowing. This further will drive the progression of degenerative disease as Osteoarthritis even in presence of bone surgery correction. This study enhances our comprehension of XLH's impact on skeletal development and illuminate the underlying molecular mechanisms governing longitudinal bone growth.