Rare Diseases Congress 2019: New therapies in genetic skeletal diseases achieved through drug repurposing - Michael Darren Briggs- Newcastle University, UK

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Abstract

Genetic skeletal diseases (GSDs) are an extremely diverse and complex group of diseases that development and homeostasis of the skeleton. There are more than 450 unique and well-characterised phenotypes that range in severity from relatively mild to severe and lethal forms and although individually rare, as a group of related orphan diseases, GSDs have an overall prevalence of at least 1 per 4,000 children, which represents a large unmet medical need. Our studies have focussed on a group of clinically-related GSDs that present with disproportionate short stature and early onset OA and result from dominant-negative mutations in a range of cartilage structural proteins including cartilage oligomeric matrix protein (COMP), matrilin-3, aggrecan and types II, IX and X collagens. We have unequivocally established that endoplasmic reticulum (ER) stress, induced in chondrocytes as a result of accumulated misfolded mutant proteins, is the primary cause of growth plate dysplasia and reduced bone growth in a broad group of GSDs. Moreover, we have recently demonstrated that reducing ER-stress, through the administration of a repurposed anti-epileptic drug carbamazepine (cbz), in both cell and mouse models, restores cell homeostasis and bone growth in metaphyseal chondrodysplasia, type Schmid (MCDS) resulting from collagen X mutations.

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