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A *DYNC1H1* MUTATION IN AUTOSOMAL DOMINANT SPINAL MUSCULAR ATROPHY SHOWS THE POTENTIAL OF PHARMACOLOGICAL INHIBITION OF HISTONE DEACETYLASE 6 AS A TREATMENT FOR DISEASE ASSOCIATED CELLULAR PHENOTYPES

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Spinal muscular atrophy with lower extremity predominance (SMA-LED) is an autosomal dominant congenital form of motor neuron disease. The most common cause of SMA-LED are mutations in dynein cytoplasmic 1 heavy chain 1 (*DYNC1H1*), which encodes the largest subunit of the retrograde motor cytoplasmic dynein 1. As is typical in other cases of SMA-LED, patients harbouring the *DYNC1H1* p.R399G mutation exhibit lower limb weakness as a consequence of muscle atrophy and also show a degree of cognitive impairment. However, the underlying molecular pathogenesis remains unknown. In addition to its characteristic function in retrograde trafficking, the dynein complex is increasingly understood to be involved in other cellular processes including growth cone dynamics and regulation of the Golgi apparatus. Here, we show that fibroblasts with the *DYNC1H1* p.R399G mutation exhibit a striking loss of Golgi apparatus integrity as measured by increased fragmentation, which correlates with increasing zygosity of the mutation. Importantly, we also see a decrease in the localisation of the dynein complex to the Golgi cisternae and a significant decrease in the acetylation of microtubules in the perinuclear region. Excitingly, the treatment of mutant fibroblasts with tubacin, an HDAC6 inhibitor, caused a striking amelioration of the Golgi apparatus integrity by increasing microtubule acetylation. This highlights for the first time a perturbed dynein-mediated regulation of microtubule acetylation and the fragmentation of the Golgi apparatus as a contributory factors in the pathogenesis of SMA-LED. Importantly, these data also illustrate that ameliorating the microtubule acetylation is sufficient to rescue the Golgi integrity, thereby providing a potential therapeutic target for this pathology.