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Unveiling novel players in HSPB8 pathology caused by frameshift mutations

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Autosomal dominant mutations in heat shock protein B8 (HSPB8) cause a spectrum of diseases, including neuropathy, myopathy and cardiomyopathy. HSPB8 plays a pivotal role in striatal muscles and neurons, by facilitating the removal of damaged and aggregating-prone proteins in response to cellular stress. This function is mediated by its involvement in chaperone-assisted selective autophagy (CASA), alongside the BAG cochaperone 3 (BAG3), HSPA family members, and the E3-ubiquitin ligase STUB1. Recently, we defined a molecular mechanism through which HSPB8 frameshift mutations (fs) in the last exon of HSPB8 lead to this spectrum of diseases. These fs mutations cause a +1 or +2 nucleotide shift in the open reading frame, resulting in the expression of elongated HSPB8 proteins. In overexpressing cell models, both fs mutants exhibit similar pathological behaviors, including HSPB8 aggregation, sequestration of wild-type HSPB8, recruitment of CASA components, and proteostasis impairment. Intriguingly, analyses on patient-derived fibroblasts carrying an HSPB8 fs+1 mutation (c.515dupC) revealed the absence of the elongated HSPB8 protein and downregulation of the HSPB8 mRNA from the mutated allele. This suggests the activation of quality control (QC) mechanisms at the translational level. To investigate this further, we examined components of the ribosome-associated and protein QC systems, focusing on NEMF, the ubiquitin ligase LTN1, and valosin-containing protein (VCP). Using an HSPB8 fs+1 mutant as a reference in cell models, we observed upregulation of core RQC components NEMF and LTN1 at the transcript level, although their protein levels remained unchanged. In contrast, VCP was sequestered by HSPB8 mutants, and its silencing exacerbated protein aggregation, likely contributing to HSPB8-pathology. In summary, our findings define shared pathogenic mechanisms among various HSPB8 fs mutations and highlight novel molecular players involved in HSPB8-associated disease pathology.