Synergistic Enhancement of PTC Readthrough in PGRN-Linked FTD via mRNA Stabilizing Compounds

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Frontotemporal dementia (FTD) is a progressive neurodegenerative disease and a leading cause of early-onset dementia, characterized by profound changes in behavior, personality, and language. A subset of FTD cases is caused by heterozygous nonsense mutations in the GRN gene, which encodes a secreted glycoprotein named progranulin. Progranulin , a secreted glycoprotein that plays key roles in neuronal survival, lysosomal homeostasis, and regulation of neuroinflammation. Nonsense mutations introduce premature termination codons (PTCs), which not only lead to truncated protein but also trigger nonsense-mediated mRNA decay (NMD), resulting in significantly reduced levels of progranulin and subsequent neuronal dysfunction. The resulting progranulin haploinsufficiency is a well-established driver of disease pathogenesis in GRN associated FTD. The aminoglycoside G418 has been shown to induce ribosomal readthrough of PTCs and restore partial expression of full-length progranulin, but the high concentrations required for efficacy are toxic and limit its therapeutic potential. To address this, we screened for compounds that synergize with low-dose G418 and identified three hits that significantly enhanced progranulin levels only in the presence of low-dose G418. Our data suggest these compounds may stabilize mutant GRN mRNA, increasing its availability for translational readthrough and thereby boosting functional progranulin production. This combination approach offers a promising path toward safer and more effective readthrough therapies for FTD caused by GRN nonsense mutations.

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