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Dysregulated Gene Expression in Friedreich's Ataxia and Response to Treatment with Nomlabofusp

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Background and Objectives

Friedreich's ataxia (FRDA) is a hereditary neurodegenerative disease caused by guanine adenine adenine repeat expansions in the frataxin (hFXN) gene, resulting in hFXN protein deficiency. As a rare disease affecting clinically inaccessible tissues, FRDA lacks a minimally invasive, repeatable molecular readout directly linked to therapeutic target engagement. Furthermore, distinguishing primary hFXN-driven gene expression changes from secondary disease adaptations remains a key challenge.

Nomlabofusp is a protein therapy intended to address the root cause of FRDA by delivering hFXN. The goal of this study was to determine FRDA-associated buccal gene expression alterations and evaluate the effect of nomlabofusp treatment on these alterations in subjects with FRDA.

Methods

Throughout the nomlabofusp clinical development program spanning 2 clinical studies, buccal epithelial cells from subjects with FRDA and healthy volunteers were collected for gene expression profiling using NanoString nCounter® and RNA sequencing.

Results

The study identified 68 differentially expressed genes, predominantly downregulated, with pathway analyses implicating cellular, immune, and neurological processes consistent with established FRDA biology. Co-expression network analysis revealed a discrete 8-gene interactome (BASP1, BTG2, CD44, EGR1, LRRK2, LY96, SOD2, XPO6) highly coordinated in healthy volunteers but markedly disrupted in FRDA. After treatment with nomlabofusp, directional reversal of abnormal gene expression toward healthy-volunteer levels was observed in 27 differentially expressed genes. Further analysis using orthogonal approaches confirmed 7 genes (SOD2, SLC25A37, EGR1, BTG2, LRRK2, XPO6, MGAM) that trended towards normalized expression with nomlabofusp treatment, with partial restoration of co-expression network connectivity. SOD2 and SLC25A37 emerged as the strongest FRDA-linked transcriptional markers.

Discussion and Conclusion

Consistent with prior reports, gene expression is altered in patients with FRDA. Reversal of these alterations was observed in subjects with FRDA treated with nomlabofusp. Buccal transcriptomics is a scalable, minimally invasive platform for monitoring pharmacodynamic effects of hFXN replacement therapy.