Novel enhancer mediates the *RPL36A-HNRNPH2* readthrough loci and *GLA* gene expressions associated with fabry disease

Mohammed A Al-Obaide [1], Saimul Islam [1], Ibtisam Al-Obaidi [1], Tetyana L Vasylyeva [1]

Affiliations expand

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Abstract

Fabry disease (FD) is a rare genetic condition caused by mutations in the *GLA* gene, located on the X chromosome in the *RPL36-HNRNPH2* readthrough genomic region. This gene produces an enzyme called alpha-galactosidase A (α-Gal A). When the enzyme does not function properly due to the mutations, it causes harmful substances called globotriaosylceramide (Gb3) and globotriaosylsphingosine (lyso-Gb3) to build up in the body's lysosomes. This accumulation can damage the kidneys, heart, eyes, and nervous system. Recent studies have shown that the *RPL36A-HNRNPH2* readthrough loci, which include *RPL36A* and *HNRNPH2* genes, as well as the regulatory sequence known as the *GLA-HNRNPH2* bidirectional promoter, may also play a role in FD. However, the involvement of enhancer RNAs (eRNAs) in FD is still poorly understood despite their known role in various diseases. To investigate this further, we studied an *RPL36A* enhancer called GH0XJ101390 and showed its genomic setting in the *RPL36-HNRNPH2* readthrough region; the eRNA is rich in Homotypic Clusters of TFBSs (HCTs) type and hosts a CpG Island (CGI). To test the functional correlation further with *GLA*, *RPL36A*, and *HNRNPH2*, we used siRNAs to knock down GH0XJ101390 in human kidney embryonic cells 293T. The results showed a significant decrease in *RPL36A* and *GLA* expression and a non-significant decrease in *HNRNPH2* expression. These findings could have important implications for understanding the regulatory mechanisms of GH0XJ101390

and its potential role in FD. A better understanding of these mechanisms may improve diagnostic and therapeutic methods for FD, which could ultimately benefit patients with this rare condition.

Keywords: bioinformatic; enhancer; fabry disease; lncRNA; readthrough locus; α-Gal A.