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Comprehensive Expression Analysis of a Large Family with Diamond Blackfan AnemiaReveals a Loss of Coordination between RPL11 and Mitochondria

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Diamond Blackfan Anemia (DBA) is an inherited disease predominantly caused by mutations in ribosomal protein genes. Loss-of-function variants causing DBA have been associated with incomplete penetrance yet the mechanism of variability despite alterations to a core biological process remains enigmatic. Here, we report the first detailed RNA expression and splicing analysis from a large family with an intronic RPL11 variant with incomplete penetrance and partial expressivity. Our analysis revealed a complex pattern of disruptions with many novel junctions of RPL11. These include an RPL11 transcript that is translated with a late stop codon in the 3' untranslated region (3'UTR) of the main isoform and an antisense exon-exon junction variant present only in carriers. We observed that RPL11 transcript abundance is comparable among carriers regardless of symptom severity. In contrast, both the small and large ribosomal subunit transcripts were significantly overexpressed in individuals with more prominent DBA symptoms. Finally, we discovered that coordinated expression between mitochondrial components and RPL11 was lost in all carriers, which may lead to variable expressivity. Overall, this study highlights the importance of large-scale RNA expression analyses in families with intronic genetic variants associated with Mendelian disorders with variable penetrance and expressivity.