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In vitro studies of disease-linked variants of human tRNA nucleotidyltransferase reveal decreased thermal stability and altered catalytic activity

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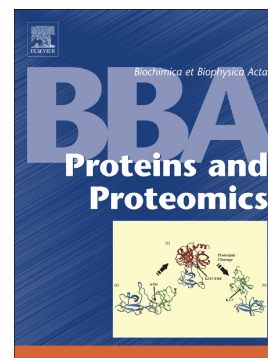
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**Title: *In vitro* studies of disease-linked variants of human tRNA nucleotidyltransferase reveal decreased thermal stability and altered catalytic activity**

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**Abstract**

Mutations in the human TRNT1 gene encoding tRNA nucleotidyltransferase (tRNA-NT), an essential enzyme responsible for addition of the CCA (cytidine-cytidine-adenosine) sequence to the 3'-termini of tRNAs, have been linked to disease phenotypes including congenital sideroblastic anemia with B-cell immunodeficiency, periodic fevers and developmental delay (SIFD) or retinitis pigmentosa with erythrocyte microcytosis. The effects of these disease-linked mutations on the structure and function of tRNA-NT have not been explored. Here we use biochemical and biophysical approaches to study how five SIFD-linked amino acid substitutions (T154I, M158V, L166S, R190I and I223T), residing in the N-terminal head and neck domains of the enzyme, affect the structure and activity of human tRNA-NT *in vitro*. Our data suggest that the SIFD phenotype is linked to poor stability of the T154I and L166S variant proteins, and to a combination of reduced stability and altered catalytic efficiency in the M158V, R190I and I223T variants.

**Keywords:** tRNA nucleotidyltransferase; TRNT1; SIFD; thermal stability; CCA

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