A Mutation in Human Histidyl-tRNA Synthetase Causes Type IIIB Usher Syndrome

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Recently, a genetic mutation in human histidyl-tRNA synthetase (hHARS) was linked to a neurological disorder in children of an Old Order Amish population in Lancaster, Pennsylvania. With the use of autozygosity mapping and exome sequencing techniques hHARS has been linked to a Type III Usher-like syndrome, which clinically presents as deaf-blindness. This is the first example of Mendelian inheritance linking cytoplasmic hHARS to a neurological disease. The substitution encodes for an Y454S mutation that is localized specifically on the surface of the anticodon-binding domain juxtaposed with the catalytic domain. It is known that hHARS is linked to autoimmune diseases, however the biochemistry of the human enzyme is not well developed. Preliminary aminoacylation studies of mouse HARS (mHARS) with purified human placental tRNA suggested that the Y454S mutant has slightly lower V_{max} and K_m values than wild-type (WT) hHARS. We have developed an expression system to purify *in vitro* transcribed human $tRNA^{His}$ and homogenous human HARS enzyme to allow for the biochemical characterization of WT hHARS and the Y454S mutant. Initial studies demonstrate that the WT and Y454S mutant hHARS enzymes have considerable aminoacylation activity, suggesting that the mutation does not significantly compromise enzyme activity. edProteomic data has previously demonstrated that residues in hHARS undergo limited post-translation modification. Among other possible models, we hypothesize that the Y454S mutation may alter recognition by specific kinases; and therefore are investigating the effects of PTMs on hHARS. With this work, we seek to understand the biochemical reasoning behind this substitution and how it results in hearing loss.