Molecular Dynamics Simulation Of Mutant Tyrosyl-Trna Synthetase Accociated With Charcot-Marie-Tooth Neuropathy Reveals The Stabilization Of Enzyme Dimer Interface.

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Aminoacyl-tRNA synthetases are key enzymes of protein biosynthesis which are also implicated in other cellular processes. Charcot-Marie-Tooth disease (CMT) is a group of heterogeneous inherited disorders, that is characterized by degeneration of peripheral nerve fibers.

Identified p34-p35 locus in human chromosome 1, associated with the CMT disease, corresponds to YARS gene , encoding human cytoplasmic tyrosyl-tRNA synthetase. TyrRS is α2-dimer, 2x59 kDa, that catalyze the aminoacylation of cognate tRNA by L-tyrosine. Currently, two heterozygous missense mutations (G41R and E196K) and one de novo deletion (153-156delVKQV) in human TyrRS were identified in patients with CMT disease.

3D structures of all 3 human TyrRS mutants were constructed in silico. Molecular dynamics simulations were carried out in GROMACS 4.0.2. All computations were carried out on computer clusters of Ukrainian academic grid-infrastructure in the frame of MolDynGrid Virtual Laboratory which was established for interdisciplinary research in computational biology requiring high processing power and immense storage space. MD simulations of all 3 human TyrRS mutants were performed for 10 ns. It was found that H11 a-helix of the G41R mutant reveals the partial melting and helix structure distortion. The stabilization of TyrRS dimer interface was revealed in E196K mutant due to the formation of H-bonds between Lys154 and Leu160 in A-monomer and between Lys496 and Leu502 in B-monomer of enzyme dimer. Due to these interactions the antiparallel b-structure is formed at unstructured region between H9 and H10 a-helices. This novel structure significantly restricts the movements of enzyme dimer interface. Correlated motions between dimerisation interfaces and anticodon binding regions are significantly lower in E196K in comparison to wild-type protein structure.

Conclusion: The effects of CMT-causing mutations in human TyrRS could be understood in terms of long-range structural effects on the dimer interface of enzyme.