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# 41 MOLECULAR DYNAMICS SIMULATIONS OF TYROSYL-tRNA SYNTHETASE MUTANT FORMS ASSOCIATED WITH CHARCOT-MARIE-TOOTH NEUROPATHY

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Certain mutations in aminoacyl-tRNA synthetases lead to Charcot-Marie-Tooth disease (CMT) – a group of heterogeneous inherited disorders that are characterized by degeneration of peripheral nerve fibers, loss of muscle tissue and touch sensation. There are some of possible mechanisms: loss of charging function, aggregation, mischarging, nucleolar dysfunction, dimerization, non-canonical functions, novel interactions resulting from mutations, mitochondrial toxicity or dysfunction, impaired axonal transport that leads to deficits in local translation (Motley, 2009). The common mechanism is still unknown. Two heterozygous missense mutations (G41R, E196K) and one *de novo* deletion (153-156delVKQV) in *Homo sapiens* tyrosyl-tRNA synthetase (*Hs*TyrRS) were identified in different families of patients with DI-CMTC (Jordanova, 2006).
All thee mutants of *Hs*TyrRS, structural complexes with cognate $tRNA_{Tyr}$ and translation elongation factor eEF1A2 were constructed *in silico* using Modeller 9.7 software. Molecular dynamics (MD) simulations were carried out for all *Hs*TyrRS mutants for 100 ns using GROMACS package. All MD simulations and trajectories analysis were performed using the grid services of MolDynGrid virtual laboratory (*http://moldyngrid.org*) (Savytskyi et al., 2011).

The melting of H9 helix (T141-A148) and subsequent partial melting of H11 helix were observed in 153-156delVKQV mutant of TyrRS. A novel $\beta$-sheet formation was observed in K147-E157 region in G41R and in 153-156delVKQV mutants for 20-100 ns time interval of MD simulation in CP1 region of Rossmann fold, which is a specific part for recognition with $tRNA_{Tyr}$. Calculation of hydrogen bonds for region K147-E157 with $tRNA_{Tyr}$ shows (lifetime more >10%): E151:C75 – 38.71%, Q155:A76 – 12.90%, K147:G72 – 12.90%, K147:G71 – 9.68%. MD simulations showed the attraction of the chloride ion instead of potassium ion for G41R mutant (active side localization), which has functional role replacing the second lysine of the catalytic KMSSS loop (KMSKS motif) that affects the catalytic properties of human TyrRS. Our results confirm the similar effect as for glycyl-tRNA synthetase mutation (G526R) and propose the idea of conformational changes in both enzymes in the active site after mutations.