LOCAL *β*-SHEET FORMATION IN G41R MUTANT OF HUMAN TYROSYL-tRNA SYNTHETASE ASSOCIATED WITH CHARCOT-MARIE-TOOTH DISEASE

Oleksandr V. Savytskyi[1], Semen O. Yesylevskyy[2] and Alexander I. Kornelyuk[1]

1 – Institute of Molecular Biology and Genetics, National Academy of Sciences of Ukraine, Kyiv, Ukraine

2 – Institute of Physics, National Academy of Sciences of Ukraine, Kyiv, Ukraine

savytskyi@moldyngrid.org

Aminoacyl-tRNA synthetases (aaRS) are key enzymes of protein biosynthesis, which are also implicated in other cellular processes. Certain mutations in human TyrRS (*Hs*TyrRS) lead to Charcot-Marie-Tooth disease (CMT) – a group of heterogeneous inherited disorders that are characterized by degeneration of peripheral nerve fibers. Currently, three heterozygous missense mutations (G41R, E196K, K265N) and one *de novo* deletion (153-156delVKQV) in *Hs*TyrRS were identified in patients with CMT disease.

Three-dimensional structures of all 4 CMT *Hs*TyrRS mutants are still unknown and their models were constructed *in silico* using Modeller v9.7 software. Molecular dynamics (MD) simulations were carried out for all 4 *Hs*TyrRS mutants for 100 ns each using GROMACS 4.0.7 package with GROMOS 53A6 and AMBER99SB-ILDN force fields. All MD simulations and analysis of trajectories were performed in Ukrainian National Grid (UNG) environment using the resources of MolDynGrid virtual laboratory (http://moldyngrid.org). Time-resolved RMSF calculations, facilitated by the Pteros molecular modeling library (http://sourceforge.net/projects/pteros/), were used to detect possible changes of residues mobility in the course of MD simulations.

The significant changes of conformational dynamics were revealed for all *Hs*TyrRS mutants. In general, mutant structure revealed less relaxed states with higher values of root-mean square fluctuations and lower values of radii of gyration data analyses. Analysis of spatial contacts between 2 monomers in enzyme revealed the longer distance of enzyme interfaces in *Hs*TyrRS mutant with partially confirmed by cross-correlation analysis of protein motions in this region. Correlated motions between anticodon binding regions in monomers of G41R mutant are higher in comparison with wild-type protein. A novel *β*-sheet formation was observed in K147-E157 region of G41R mutant for 20-100 ns time interval. It was found the h-bond formations between K147-E157 region and S225 of catalytic KMSSS-loop residue in mutant form trajectory which accompanying with lower values of solvent accessible surface area observation for active site of mutant protein in the catalytic domain.

It may be concluded that the dispersion of CMT-causing mutations in human TyrRS could be understood in terms of long-range structural effects on the enzyme dimer interface.

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