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Genotype-Phenotype Corelation of Various GNE Mutations-Understanding GNE Myopathy

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GNE myopathy is a rare autosomal recessive neuromuscular disorder caused due to biallelic mutations in GNE (UDP-GlcNAc 2-epimerase/ManNAc kinase), a bifunctional enzyme (N-terminal epimerase and C-terminal Kinase domain) that catalyses the rate limiting step in sialic acid biosynthesis. There is no absolute cure for the disease as lack of clear understanding about disease pathomechanisms at molecular and cellular levels limits the identification of effective therapeutic target options. Currently, more than 200 mutations have been identified worldwide but a detailed understanding of genotype to phenotype co-relation that determines the pathological outcome of the disease is missing. We aim to clone, express and purify wild type and mutant GNE proteins of Indian origin (R193C, I618T & V727M) from E. coli followed by functional activity determination using epimerase and kinase assays. Both epimerase (D207V & R193C) and kinase (V603L, V727M & I618T) mutants showed significant reduction in epimerase activity indicating mutation in one domain affects activity of other domain. Among kinase mutants V603L mutant showed significant reduction in kinase activity suggesting alternate pathway for kinase function in the cell. The CD spectroscopy studies revealed increased alpha helicity in D20V GNE mutant but not in other GNE mutant proteins, suggesting a mutation specific response. With an aim to identify small effector molecule rescuing GNE function, an anti-diabetic molecule, Metformin, was shown to increase the kinase activity of V603L GNE mutant. Our study provide insights towards genotype to phenotype co-relation of various GNE mutations and offer potential therapeutic molecule identification.

Biography

Shweta sharma is a final year Ph.D. student at Jawaharlal Nehru University, School of Biotechnology Department. She received a bachelor's degree in science from Government Nagarjuna Post Graduate College of Science and a master's degree in biotechnology from Pt.Ravishankar Shukla University in Raipur, Chhattisgarh. Her research is based on understanding the pathomehanism of a rare nuromuscular disorder "GNE Myopathy". She is currently investigating the status of Endoplasmic reticulum Calcium dynamics of GNE deficient cells. She has excellent skills in animal tissue culture handling, molecular biology techniques and well trained in the area recombinant protein expression and purification.