Genotype-Phenotype Corelaton of Various GNE Mutatons-Understanding GNE Myopathy

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GNE myopathy is a rare autosomal recessive neuromuscular disorder caused due to biallelic mutatons in GNE (UDP-GlcNAc 2-epimerase/ManNAc kinase), a bifunctonal enzyme (N-terminal epimerase and C-terminal Kinase domain) that catalyses the rate limitng 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 identfcaton of efectve therapeutc target optons. Currently, more than 200 mutatons have been identfed worldwide but a detailed understanding of genotype to phenotype co-relaton 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 functonal actvity determinaton using epimerase and kinase assays. Both epimerase (D207V & R193C) and kinase (V603L, V727M & I618T) mutants showed signifcant reducton in epimerase actvity indicatng mutaton in one domain afects actvity of other domain. Among kinase mutants V603L mutant showed signifcant reducton in kinase actvity suggestng alternate pathway for kinase functon in the cell. The CD spectroscopy studies revealed increased alpha helicity in D20V GNE mutant but not in other GNE mutant proteins, suggestng a mutaton specifc response. With an aim to identfy small efector molecue rescuing GNE functon, an ant-diabetc molecule, Metormin, was shown to increase the kinase actvity of V603L GNE mutant. Our study provide insights towards genotype to phenotype co-relaton of various GNE mutatons and offer potental therapeutc molecule identfcaton.

Biography

Shweta sharma is a fnal 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, Chhatsgarh. Her research is based on understanding the pathomehanism of a rare nuromuscular disorder "GNE Myopathy". She is currently investgatng the status of Endoplasmic retculum Calcium dynamics of GNE defcient cells. She has excellent skills in animal tssue culture handling, molecular biology techniques and well trained in the area recombinant protein expression and purifcaton.