PROLOGUE

Lysosomes are the subcellular organelles of the human system to keep the cell healthy and functioning. They contain numerous acid hydrolases synthesized in the Golgi apparatus to catabolize proteins, lipids, nucleic acids, sulphatase, phosphatase, and complex carbohydrates. Thus, lysosomal enzymes are the catabolic functionals that keep the cells free from unwanted cell debris. Lysosomal storage disorders (LSDs) are the heterogeneous group of genetic disorders, which results from inadequate intra-lysosomal degradation of intra- and extra- cellular complex substance due to lack of specific enzymes, lack of protein co-factor (activator protein), defect in membrane transport protein (sialic acid) or lysosomal membrane associated enzymes.

LSDs represent a group of nearly 50 genetically distinct, biochemically related, inherited diseases. The cumulative incidence is estimated to be about 1:5000 to 1:7000 live births in some populations, though they seem to be under diagnosed due to overlapping phenotypes, non-availability of investigative facility in majority of the centers and lack of awareness among treating clinicians in India. So far, the available data are mainly case reports, anecdotal study from few centers about the occurrence representing a small community of the country and very few molecular reports. Since LSDs are the fourth most important cause of death after infectious disease, heart disease and cancer, early confirmative diagnosis is very important; for early therapeutic intervention and counseling to the families. But majority of these childrens die early in infancy attributed to the lack of awareness among clinicians, parents and absence of appropriate genetic counseling regarding the risk for subsequent pregnancies. Considering the large population with ethnical diversity in India, LSDs are likely to be more common than thought that puts enormous social trauma and financial burden to the families and loss of important lives where early treatment can save the precious life. It is therefore an urgent need to spread awareness about the importance of definite diagnosis, management of these disorders, by enzyme replacement therapy (ERT) or stem cell transplantation and prevention through prenatal diagnosis in subsequent pregnancies.

The present study proposes to carry out biochemical diagnosis using various enzymes specific substrates followed by molecular study of *HEXA* gene identifying diseases causing allele for TSD. TSD been reported in children of virtually all ethnic and racial groups with prevalence in general population varies between 1:2,00,000 and 1:3,50,000 and more common in Ashkenzi Jewish population (1:3600). Though, TSD is considered to be very rare and not well studied till date in Indian context. It is likely to be the same or may be higher due to genetically heterogeneous population and high rate of consanguineous marriages in many parts of the country. Our recent study demonstrated that TSD is the second most common storage disorder after Gaucher disease. Considering molecular pathology, 170-disease associated alleles have been reported so far and, about 8 to 10 alleles have significant frequencies in various ethnic and demographic groups. However, this information is lacking for Indian TSD patients. Therefore present study proposes to carry β-Hexosaminidase (Hex-A and total-Hex) enzyme studies from leucocytes in clinically suspected children followed by molecular analysis of the gene to identify disease causing alleles in the population.

Molecular characterization of the disease is very important to identify the carrier detection, understand phenotype-genotype correlations for better therapeutic approaches and confirmative prenatal diagnosis where enzyme study is non-informative. Till date, there is a lack of available information on disease frequency, its carrier frequency and molecular mechanism to provide precise genetic counseling to the affected family members. Present study will provide the first line specific diagnosis, elucidate molecular heterogeneity of the TSD in the country and there by its prevention.