

G2MC Young Investigators Project proposal (2021)

Title:

Clinical, biochemical and molecular characterizations of lysosomal storage disorders (LSDs) in India: The initiative to implement NGS based screening for LSDs.

Young Investigator contact information:

Dr. Mehul Mistri (Ph.D-Biochemistry)

Email: mistrimehul@yahoo.co.in

Mob. No: +91-9913345194

Introduction:

Lysosomal storage diseases are rare genetic disorders because of the defects in either a lysosomal enzyme, transport, or membrane protein. To date, nearly 50 such enzyme deficiencies are responsible for around 40 known storage diseases that have been identified. The cumulative incidence is estimated to be about 1:5000 to 1:7000 live births in western country they are likely to be higher or equal for India. So far, the available data are mainly case reports, anecdotal study from few centres 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 counselling to the families. But majority of these children's die early in infancy attributed to the lack of awareness among clinicians, parents and absence of appropriate genetic counselling 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.

Therefore present study proposes to provide precise diagnosis for various LSDs in clinically suspected patients followed by enzyme study which is further confirmed 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.

Vision:

Overall vision of project is to establish the first center of excellence for lysosomal storage disorders (LSDs) in India. In nutshell the advance centre for LSDs will be of its kind in the country where all clinical, screening, biochemical analysis, molecular analysis and therapeutic options if available and training of students and clinicians will be the main focus. Also, persuade application of molecular NGS-based testing (either in the form of WES or targeted gene panels) in this perspective represents a real and valuable aid to provide timely and correct diagnosis, detect carriership status, and ensure genetic counseling for family planning, thus improving the overall standards of care for patients and families.

Aims:

- To know the burden and demographic distribution of various LSDs among population, study the mutational spectrum of commonly prevalent LSDs in Indian patients and elucidate the pathogenic effect of novel and/or founder variants via functional characterizations.
- To understand influence of genotype on phenotype development.
- To provide genetic counselling to affected families, prevent the disease through prenatal diagnosis and increase medical awareness for various LSDs.

Impact:

- The advanced genetic diagnostic centers, specific counseling and therapeutic options to the affected families is the key to minimize the burden of genetic disorders.
- The molecular profiling and genomic sequencing information may prompt the design of novel therapeutic drugs targeting specific mutations.
- The development of more effective treatments will open the possibility for new clinical trials that address stratified patient subclasses and will pave the way to personalized medicine.

Executive Plan: Project plan outlining goals and activities in quarterly format G2MC

Partners: G2MC members (individual/country affiliation).

Children suspected of having different types of LSDs will be referred to us from pediatrician or clinical geneticist. The selection criteria include those with clinical signed symptoms like

regression of milestone, neuroregression, organomegaly, skeletal abnormality, dysmorphic faces, cherry red spot in macula etc. After confirmative enzyme study, those who are affected with different selective LSD's will be selected for molecular analysis. Prenatal diagnosis would be offered to the affected families. An informed consent will be obtained from each family and institutional ethical committee approval will be obtained before initiating the study.

As a project plan, enzymatic assay for various LSDs will be carried out and of these nearly 100 clinically or enzymatically confirmed cases will be enrolled for molecular diagnosis via whole-exome sequencing (WES). Per quarter, we will try to enrol ~25 new cases diagnosed with various LSDs for molecular diagnosis via WES and to performed functional characterizations for novel or founder mutations. In cases of a confirmed diagnosis, genetic counselling will be provided to the family about the recurrence risk, prenatal diagnosis and possible therapeutic intervention. We will also train students in advanced biochemical and molecular techniques for the diagnosis of various lysosomal storage disorders.

Other Organizations: Non-G2MC collaborators (individuals/industry/NGOs, etc)

- Not applicable.

Future funding: Plans for follow-on funding for continued support.

If future funding will be available, then the ultimate aim will be to continue the project by enrolling more patients to understand the molecular heterogeneity for various LSDs in Indian subjects and generate a mutational database for the most prevalent LSDs. This database can be used as a tool for carrier screening of a larger Indian population. In addition to this, our aim is to set up and validate of targeted Next-Generation Sequencing approach for the diagnosis of LSDs to aid carrier screening and prenatal diagnosis. Moreover, our aim is to maintain the DNA Biobank of affected patients and try to create a large cohort that will be useful to promote the development of the DNA chips and therapeutic model development.

Budget with brief budget justification (projects will be funded for a maximum of 12 months)

	Budget justifications	Budget
Personnel	This is requested for salary+HRA	\$16,150 (USD)
Materials and supplies	This is requested for purchase of various reagents for biochemical and molecular study and other	\$30,282 (USD)

	material	
Support for local/country involvement	This is requested to set logistic services	\$2020 (USD)
Travel and meeting support (if needed)	This is requested for attending and participating in national/international conferences or workshop on LSDs	\$1500 (USD)
	Total	\$49952 (USD)