CONCLUSION, SUMMARY AND FUTURE PROSPECTS

7 Conclusion, Summary and Future Prospects

7.1 Conclusion

- Based on clinical presentation the most common type-I GD was found in 43 of 50 (86%) patients suggesting its dominance in Indian patients.

- L444P (c.1448T>C) was the most common mutant allele in 50% of patient with GD in India and this can be used as the first line of molecular screening and carrier detection in the population. In 10 patients, rare mutations (20%) were observed mostly in exons 6-9 of the *GBA* gene.

- Our study has identified four novel missense mutations A100P (c.415 G>C), G250A (c.866 G>C), L354V (c.1177 C>G), and I427S (c .1397T>G) in exons 4, 7, 8 and 10 mostly stabilizing enzyme structure by affecting α or β helicle structure.

- Study also demonstrates that exon 8 and 10 are the hotspot region of the *GBA* gene accounting 59% of the mutant allele. Remaining mutation in exon 4, 6, 7, 9 and 11 accounting for 41% of mutations.

- This overall study provides the insights into the molecular basis of the disease demonstrating that Indian GD patients are presented with phenotype of type I GD showing L444P (c.1448T>C) as the mutant allele and are likely to have a higher risk of progressing to type III GD at a later stage which can be confirmed only by longer follow up study. This is the first study from India identifying mutational spectrum for GD that can be of help in offering precise genetic counseling, treatment and prevention of the disease.

7.2 Summary and Future prospects

- From the pool of 747 patients,LSD affected patients were 313 and normal patients were 434. From affected LSDs patients, 53 patients found to have hepatosplenomegaly, 15 hepatomegaly and 5 splenomegaly. From these 50 were confirmed to have GD.
- All 50 patients had shown significantly reduced activity of β-Glucosidase in the range of 8.0-32.0 nmol/hr/mg protein with mean of 13-29% activity as compared to normal subjects.
- 42 (84%) patients were found to have marked increase of chitotriosidase and suggest its utility as a screening test followed by prognostic value in therapeutic monitoring.
- In present study, 50 unrelated patients were enrolled. From these 6 were carrier parents in which index case was not available. All these patients were further enrolled for molecular study.
- Screening of common mutations showed L444P (c.1448T>C) as the most common mutations in exon 10 in 25 of 50 (50%) patients from which 22 (44%) were homozygous, 1(2%) was heterozygous/ unknown and 2 (4%) patient had shown compound heterozygosity for L444P (c.1448T>C) / R496C (c.1603 C>T) in exon10/11 and L444P (c.1448T>C) / R329C (c.1102 C>T) in exon10/8 respectively.
- The sequencing analysis of *GBA* gene revealed 13 mutations in 14 patients, 4 of which were novel missense mutation, and remaining 9 were missense homozygous mutations. R395C (c.1300C>T) in exon 9, R359Q (c.1193G>A), G355D (c.1181G>A), V352M (c.1171G>A) and S356F (c.1184C>T) in exon 8 were identified one in each patient (10%). E326K (c.1093G>A) mutation in exon 8 was observed in two Srilankan siblings (4%) in homozygous state. G202R (c.721 G>A) and F213I (c.754 T>A) in exon 6 were identified in one (4%) patient each in homozygous state. In carrier parents, L444P (c.1448T>C) found in exon 10 in 4 patients and in 1 patient Y220C (c.766 A>G) mutations in exon 7 found.

- Novel missense mutations were identified by *GBA* gene bidirectional sequencing. Four novel missense mutations I427S (c .1397T>G), L354V (c.1177 C>G), G250A (c.866 G>C) and A100P (c.415 G>C) found in Exon 10, 8, 7 and 4 respectively in 4 (8%) patients each.
- In nearly 25(50%) of patients, L444P (c.1448T>C) was the most common mutant allele found in India. This can be used as the first line of molecular screening and carrier detection in the population.
- Study also demonstrates that nearly 59% of mutations are found in exon 8 and 10 and that can be used as a hot spot region for sequencing in absence of common mutations.
- Identified mutation spectrum in Indian GD patients that will be helpful in offering precise genetic counseling and prenatal diagnosis. Additionally, identification of novel mutations provides further insight to the molecular understanding of the *GBA* gene in Indian subjects.
- We have also demonstrated that all *GBA* mutation for Indian patients is associated with mild to severe phenotypes
- This database can be used as a tool fordeveloping the DNA chips as a simple cost effective molecular screening for the most frequent mutations in Indian patients. Therapeutic decisions and its prognostications can also be improved with this information.