CHAPTER – 5

SUMMARY AND CONCLUSIONS

Oral clefts are the second most common birth defects among the newborn. Although oral clefts are usually not a major cause of mortality in developed countries, it can leads to disturb the functions such as feeding, digestion, speech, middle-ear ventilation and hearing, respiration and facial and dental development[231]. In most cleft cases the exact cause of the cleft is unknown and no single factor can be identified as the cause.

NSCLP caused by genetic predisposition and certain environment factors that may or may not be specifically identified. It has been hypothesized that the biological mechanisms associated with clefts are only modestly affected by a single SNP but greatly influenced by an SNP in combination with additional SNPs in genes derived from either identical or distinct biological pathways. Over the last decade, numerous linkage and association studies have been performed to identify the genes that predispose to NSCLP. In view of the complex and heterogeneous nature of NSCLP, the relative contribution of individual susceptibility genes varies across different populations, thereby accentuating the need for replication of association studies in different populations. The purpose of the present study was to investigate the role of transcription factors gene polymorphisms in the pathogenesis of NSCLP in south Indian population.
**Summary and Conclusion**

*IRF6* rs223571 and rs223575 SNPs showed significant differences in genotype or allele frequencies between controls and cases with NSCLP and are associated with increased risk of NSCLP. *TFAP2A* polymorphisms were not associated with NSCLP. The distribution of genotypic frequencies for *MAFB* rs13041247 and rs11696257 and were similar and acted as surrogates in both cases and controls. Both SNPs were significantly associated with a reduced risk of NSCLP. The *ABCA4* variants are not found to be associated with NSCLP. *MSX1* gene rs11726039 variant significantly associated with a reduced risk of NSCLP. Significant association of *TBX2* 2rs7055763 and rs41307258 with NSCLP were found only in women. Both polymorphisms increased the risk for NSCLP but it is not significant. Both SNPs are not associated with risk for NSCLP in men. The mutations in *SATB2* exon 6 (rs137853127 and rs200074373) were monomorphic and the intronic variant (rs1992950) was polymorphic and the genotype distribution is not statistically significant between NSCLP and controls. No linkage disequilibrium (LD) was found between variants of *IRF6*, *TFAP2A*, *ABCA4*, *MSX1* and *SATB2* genes. The MAFB variants are in strong LD. Pair-wise linkage disequilibrium between *TBX2* gene rs7055763 and rs41307258 is strong and significant. None of the haplotypes examined were significantly associated with NSCLP. Genotype-genotype interaction analysis showed significant synergetic interaction between *SATB2* rs1992950 and *IRF6* rs2235375 SNPs in the pathogenesis of NSCLP.
Summary and Conclusions

The present study demonstrated a role for transcription factor gene variants in the etiology of NSCLP and expanded knowledge of craniofacial development. In the future, the combination of deep phenotyping and exome or whole genome sequencing will give us insights into the etiology of the full spectrum of clefting phenotypes, including subclinical defects. Ultimately, this work can benefit to identify the susceptible genes to increase the risk of NSCLP.