SECTION- III

SUMMARY
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1. The study of genetic basis of pediatric disorders has become one of the most active areas in human genetics. Genetic disorders are enormous; millions of people are suffering from inherited diseases. The distressing and disturbing truth in this sad saga is that there is no cure available to these diseases and hence, the prevention of the inheritance of such diseases becomes absolutely essential. A very large population of India with high birth rate and consanguineous marriage favored in many communities, a high prevalence of genetic disorders.

2. The present study has been made to analyse the genetic basis of a few pediatric disorders like Down syndrome which is common cause of mental retardation and sex chromosomal aneuploidy in Mysore population. Though many investigators claim that advanced maternal age is the well established risk factors of causing nondisjunction of the above aneuploidy, there was no systematic study in India. Therefore, the present investigations was undertaken to unravel the etiological and demographic factors for Down syndrome and sex chromosomal aneuploidy in Mysore population.

3. Prevalence of pediatric disorders in Mysore population was studied for five years from 2001-2005 and found 2.06 to 4.45% of abnormal births, of which 0.9 to 2.2 % are with genetic disorders. The common genetic disorders among them are Down syndrome, Turner and Klinefelter syndrome.
4. A total of 190 prospective clinically diagnosed Down syndrome and sex chromosomal aneuploidy were considered for the present study from three major Hospitals of Mysore, K. R. Hospital, C. S. I. Holdsworth Memorial Hospital, J. S. S Hospital and rehabilitation homes. A total of 200 healthy families were also randomly selected from different ethnic backgrounds as controls from different localities of Mysore city, South India.

5. Genetic register was established for 190 patients and 200 controls. Some of the assessed traits were parental and grandparental age, consanguinity, region-wise distribution, exposure to chemicals, educational status of the family, habits of the parents, prenatal diagnosis of the mother and reproductive performance of mother etc.

6. The pedigrees were constructed for all the patients and control families to understand the influence of parental age, maternal grandparental age, inheritance pattern and consanguinity, etc.

7. The phenomics of Down syndrome and sex chromosomal aneuploidy revealed the varied expression of clinical features. Dermatoglyphics features like simian crease were found in about one third of the Down syndrome children. The number of Turner syndrome showing multiple pigmented navi, amenorrhea and prominent whorls in fingers was less and none of the cases encountered severe mental retardation and transverse palmar crease. The number of Klinefelter syndrome showing simian crease, infertility and fifth finger clinodactyly was less and none of the cases encountered severe mental retardation.
8. The cytogenetic analysis reveals the following:

- Of the 190 patients screened for chromosomal anomalies about 150, 16 and 9 of the patients were shown Trisomy 21, X0, and XXY syndromes respectively, and the remaining mentally challenged (~8%) patients did not show any chromosomal anomalies.

- Of all the Down syndrome patients, 97.6% were with Trisomy 21, 1.6% cases with trisomy mosaic and 0.8% with translocation trisomy. About 53% of Down syndrome children were females.

9. For the assessment of the influence of age in causing Down syndrome and sex chromosomal aneuploidy, the age of parents and grandparents were classified into different age groups namely 18-24, 25-29, 30-35, 36-40 and >41 years. The findings revealed the following:

(a) The mothers of control, Down syndrome and sex chromosomal aneuploidy families produced more children in their young age than the advanced age.

(b) The highest number of children born to fathers of Down syndrome in the age range of 30-35 years.

(c) Advanced age maternal grandmother produced more of Down syndrome children and sex chromosomal aneuploidy.

(d) The mean age of mother, father, grandmother and grandfather of Down syndrome and sex chromosomal aneuploidy was higher than the control families.

(e) The highest number of children was born to maternal grandfathers in
control families in the age range of 30-35 years, whereas in Down syndrome and sex chromosomal aneuploidy families in the age range of 36-40 years.

10. The logistic regression analysis of Down syndrome was done at all combinations to establish specific relations of grandmother's age with other variables. The 95% confidence intervals for the effect of the age of mother and age of father were lower than age of maternal grandfather and maternal grandmother. At the four variable levels, the father and grandmother showed significant difference in odds ratio suggesting that the advanced age of father and grandmother are the risk factors. Similar analysis in sex chromosomal aneuploidy families revealed that advanced grandmother age is the risk factor.

11. Consanguineous marriages were classified into four categories, namely, marriage between first-cousin, uncle-niece, second cousin and far relatives. Among all four types of consanguineous marriages, uncle - niece marriage was more frequent both in control and Down syndrome families in Mysore population. However, the marriage between the sibs was not recorded in the present study. The analysis revealed that consanguinity was more prevalent in the Down syndrome families than the control families. The odds ratios were significant for uncle-niece and second-cousin marriage when all the four variables were used one at a time revealing that the marriages between uncle-niece as well as second-cousins are the risk factors. Similar logistic
regression analysis performed for sex chromosomal aneuploidy revealed the nonsignificant effect of consanguineous marriage.

12. The analysis revealed that more Down syndrome and sex chromosomal aneuploidy families were seen in the rural areas than the urban region. The logistic regression analysis was done at two combinations like urban and rural regions to establish a specific relationship of region-wise distribution with other variables. The 95% confidence intervals for the effect of the region-wise distribution for urban area were lower than the rural area. The odds ratio was significant for rural area when the variables were used one at a time. This analysis indicates that the region-wise distribution is an important demographic factor to cause Down syndrome and sex chromosomal aneuploidy.

13. None of the mothers and fathers of control, Down syndrome and sex chromosomal aneuploidy families were exposed to toxic chemicals, but ~5% of mothers, ~13% of fathers in Down syndrome, ~8% of mothers and ~20% of fathers in sex chromosomal aneuploidy families were exposed to drugs used for convolution, diabetes and blood pressure. The analysis of parents of Down syndrome and sex chromosomal aneuploidy families who have exposed to chemicals revealed that the exposure to chemicals by fathers and both the parents are the risk factors.

14. When the educational status of the parents was considered, 25% of mothers and 18% of fathers were uneducated in Down syndrome families. While, in sex chromosomal aneuploidy families, 60% of mothers and 44% of fathers
were uneducated. The analysis revealed that Down syndrome and sex chromosomal aneuploidy babies were born to more of illiterate fathers and mothers than the families which are educated. The odds ratios of logistic regression analysis were significant for all the variables like uneducated father, mother and both the parents when all the variables were used one at a time. This analysis suggests that the parental education is important to have better awareness about pregnancy maintenance.

15. The three common habits of the father observed in controls, Down syndrome and sex chromosomal aneuploidy families were smoking, alcohol consumption and both the habits like smoking and alcoholic. Mothers were no smokers and no alcoholic in India. The number of smokers, alcoholics and fathers with both the habits were high in Down syndrome and sex chromosomal families compared to controls. The odds ratios of logistic regression analysis were significant for smoking and both the habits like alcoholic and smoking of fathers indicating the habits of father could influence the cause of Down syndrome. Similarly, the odds ratio was significant for father having both the habits together when all of them used one at a time for the cause of sex chromosomal aneuploidy.

16. The mothers who had undergone for prenatal scanning were more in Down syndrome and sex chromosomal aneuploidy families than controls. The odds ratio was significant for mother not undergone prenatal diagnosis when it was subjected for regression analysis.
17. The control mothers showed more number of abortions than the mothers of Down syndrome and sex chromosomal aneuploidy families. The still births were high in Down syndrome and sex chromosomal aneuploidy families compared to controls. This suggests that spontaneous abortions will reduce the risk for chromosomal nondisjunction.

18. The data revealed that more abortions were recorded in the control families than Down syndrome families. Down syndrome mothers showed more still births than the control mothers. The odds ratios of the logistic regression analysis were significant for abortions and still births. Similarly, mothers in sex chromosomal aneuploidy families showed more still births than control mothers. The logistic regression analysis revealed that the odds ratio was significant for both abortions and still births. The analysis suggests that the spontaneous abortion will be responsible to reduce the abnormal births.

19. Counseling will help to have better knowledge about preparation for pregnancy, pregnancy maintenance, prenatal diagnosis and maintenance of genetic disorders like the commonly occurring Down syndrome and sex chromosomal aneuploidy.

20. The ultimate goal of research in genetic disorders should be to improve the lives of people with abnormalities and their families. The best way to reduce the frequencies of any particular genetic abnormality in the population is to reduce the rate of reproduction by those individual capable of having affected offspring.
It can be surmised as Patterson and Costa (2005) put it “because of the unprecedented experimental and theoretical tools that are available today, it is not unreasonable to speculate that even the complicated cognitive disabilities that are associated with these aneuploidy might be amenable to therapeutic interventions designed to help people with Down syndrome and sex chromosomal aneuploidy to maximize their potential”.

Thus, to prevent births of unwanted children with anomalies comprehensive maternity care services must be available to all pregnant women regardless of socio-economic status. Therefore, the new born screening and counseling for inheritable diseases in India should be established as a preventive public health programme on a priority basis as immunization program.