SECTION- I

REVIEW OF LITERATURE ON A FEW PEDIATRIC DISORDERS
Genetics is rooted in the research of Gregor Mendel, a monk who discovered how traits are inherited. The molecular basis of heredity was revealed when James Watson and Francis Crick elucidated the structure of DNA. The human genome project is engaged in the detailed analysis of human DNA (Snustad and Simmons, 2006). Genetics is relevant in many venues outside the research laboratory. Classical genetics has provided physicians with a long list of diseases that are caused by mutant genes. The study of these diseases began shortly after Mendel's work was rediscovered. In 1909 Garrold work on inborn errors of metabolism was seminal. Followed to this a large number of inherited human disorders were identified and cataloged. Earlier reports indicate that 3-5% of all births result in congenital malformations, of these 0.5% of all newborns and 7% of all stillborns have a chromosomal abnormality (Robinson and Linden, 1993) and 20-30% of all infant deaths are due to genetic disorders (Berry et al., 1987). Though individual genetic disorders are rare, collectively they comprise over 15,500 recognized genetic disorders (McKusick, 1994).

Genetic disorders

The genetic diseases fall into four categories: a) Diseases related to single gene mutations of large effect (Mendelian disorders), b) Diseases related to multiple gene mutations of small effect (diseases with multifactorial (polygenic) inheritance), c) Diseases arising in chromosomal aberrations (cytogenetics disorders) numeric or structural changes in chromosomes and d) Non traditional inheritance (www.merck.com/mrkshared/mmanual).
a) *Mendelian disorder:*

The single gene disorder is determined by a single genetic locus and the specific allele(s) on one or both members of a chromosome pair. Single gene defects are often rare, with a frequency of less than 1 in 200 births. Single-gene disorders are characterized by the pattern of transmission in families by pedigree analysis. There are four basic patterns of single gene inheritance: a) Autosomal Single Gene Disorders: examples - Huntington’s Chorea (HC), Alzheimer’s disease, Achondroplasia. b) Autosomal recessive disorders: examples - Sickle cell Anemia, Cystic fibrosis, Phenylketonuria. c) X-linked Single Gene Disorders: examples - Hemophilia, colour blindness. d) X-linked dominant disorders: example - incontinentia pigmenti.

b) *Multifactorial disorders:*

The most common and least understood of the categories of genetic disease are those that result from the interaction of a number of genes and environmental factors. The majority of common disorders such as diabetes mellitus, hypertension, or mental illness as well as common birth defects such as cleft lip and palate, congenital heart disease, spina bifida/anencephaly, pyloric stenosis, scoliosis, dislocated hip, and many isolated malformations such as intestinal atresia are the result of this mechanism.
c) **Non traditional disorders:**

In addition to the above, three more genetic mechanisms like "nontraditional inheritance" - germline mosaicism, uniparental disomy and mitochondrial inheritance will also result in number of genetic diseases. Two newly described phenomena that may modify the traditional notions of inheritance also includes, genomic imprinting and anticipation. In some measure, these phenomena explain the "exceptions to the rules" that have been observed in families that have what otherwise appear to be straightforward genetic disorders with consistent manifestations.

Germline mosaicism is the presence of two or more cell lines with differing genotypes or karyotypes. It is due to a mutation that occurs in a cell of the developing organism some time after fertilization. Depending on the timing and developmental destination of the cell in which the mutation occurs, the adult organism may bear only somatic manifestations of the mutation or the gonads may be affected as well. The reproductive adult, therefore, may produce gametes that have both the normal and abnormal alleles and yet not be affected clinically with the disorder.

Uniparental disomy refers to the situation in which a child possesses two copies of one of one parent's chromosome and no copies of the same chromosome from the other parent. The result is that the child is homozygous for all genes located on that one chromosome. If that chromosome should bear an allele that causes a recessive condition or disease, the child will be affected, even though one parent is not a carrier of the gene. This phenomenon has been
described several times in patients who have cystic fibrosis, an autosomal recessive condition, as well as with the Prader-Willi and Angelman syndromes.

In addition to the 22 pairs of autosomes, two sex chromosomes were present in each nucleated cell, a 25th chromosome is contained in each mitochondrion within the cytoplasm of the cell. Each cell contains many mitochondria and, therefore, many copies of the mt DNA. Because only the ovum carries a mitochondria into fertilization, mt DNA is maternal in origin. Therefore, a disease that is caused totally or in part by a mutation of the mitochondrial genome will be maternally inherited. Organs that are highly dependent on energy production will be the most severely affected by mutations of mt DNA. The organ systems affected most commonly are the central nervous system, muscle, and heart (www.merck.com/mrkshared/mmanual).

d) Chromosomal based inheritable disorders and syndrome:

Majority of chromosomal anomalies causes mental retardation. It is due to the influence of a variety of genetic and environmental factors, characterized by significantly below average intellectual functions existing concurrently with related impaired limitations in two or more of the following applicable adaptive skills areas: communication, self care, home living, social skills, community use, self direction, health and safety, functional academics, leisure and work, manifest before the age of 18 years (Kaur et al., 2003). The causes of mental retardation vary with the severity of the disorder, which are thought to be multifactorial in origin.
The genetic cause of mental retardation found to be 36%, the most common being Down syndrome (Dave et al., 2005), which occurs in at least 4% of all recognized pregnancies and is the leading known cause of pregnancy loss and the leading genetic cause of mental retardation (Hassold et al., 1996). Even homocysteinemia, hyperglycinemia, Phenylketonuria, hypothyroidism and Glucose 6 phosphate dehydrogenase deficiency were also found to cause mental retardation (Devi et al., 2004). It is estimated that 5-10% of all the cases of idiopathic mental retardation may have a small subtelomeric rearrangement (Slavotinek et al., 1999). Cytogenetically invisible unbalanced translocations have been reported to cause mental retardation. In all these syndromes, phenotypic characteristics, in addition to the mental retardation contribute to the recognition of the disorders and to the identification of the deletion (Holinski-Feder et al., 2000). The early diagnosis of mental retardation is essential for child healthcare, medical treatment, and facilitation for evaluation of prognosis and for the estimation of risk of recurrence (Kaur et al., 2003).

Until 1956, the number of chromosomes in the normal human cell was considered to be 48. Due to improvements in techniques it was discovered that the correct number is 46 by Tjio and Levan (1956). In order to draw conclusion 2n=46, they analysed 265 preparations from 22 different cell cultures made from the lung tissues of four different legally aborted embryos. Following this, further technological improvement allowed the identification of individual chromosomes and the association of specific genetic disorders with specific chromosomes. Chromosomal aberrations occur in approximately 1 in 150 live newborns. At least
60% of spontaneously aborted fetuses have a chromosome abnormality, as do 5% to 10% of stillbirths. Chromosomal aberrations may be either numerical or structural. Numerical abnormalities include aneuploidy in which there are either one or three or more copies of a single chromosome instead of the normal diploid number of two. These include trisomy 21 (Down syndrome), 18 (Edward syndrome), and 13 (Patau syndrome). The most common aneuploidy involving the sex chromosomes are Turner syndrome (45, X) and Klinefelter syndrome (47, XXY). Other aneuploidies have been reported but are quite rare, and some have never been observed in a live born child (Lewis, 2001).

Structural abnormalities include deletions or duplications of small amounts of chromosome material, inversions of chromosome material within the same chromosome, and translocations of chromosome material from one chromosome to another (Lewis, 2001). Chromosome translocations may be balanced or unbalanced. For example, 1 to 2% of children who have Down syndrome are found to have the extra number 21 chromosome attached at the centromere to either another number 21 chromosome or to one of the D group chromosomes which is a Robertsonian translocation. Such translocation may have arisen de novo or it may have been inherited from one of the parents who are a carrier of a balanced translocation (Lewis, 2001). Even though catalogues of chromosome abnormalities exist, it is extremely difficult to compare cytogenetic abnormalities from patient to patient accurately. Apparently similar aberrations may have slightly different breakpoints involved in the rearrangement.
Some of the classical chromosomal disorders are as follows:

i) **Down syndrome:**

Down syndrome is named after the nineteenth century physician John Langdon Down who worked at an asylum in Surrey, England and who in 1866 was the first to describe the condition. It was first shown to be due to an extra chromosome number 21 by the French physician Lejeune (1959). The presence of three copies of a chromosome is known as trisomy, hence Down syndrome also known as trisomy 21 (Lejeune, 1959). Down syndrome occurs in all races and a similar condition can even occur in chimpanzees and some other primates.

Down syndrome is the most frequent genetic cause of mild to moderate mental retardation and occurs in one out of 600-800 live births (Antonarakis, 1993; Stoll *et al.*, 1998). Three genetic mechanisms which are free trisomy 21 (92-95%), mosaic trisomy 21 (2-4%) and (3-4%) translocation trisomy 21 causes Down syndrome. Scientists have medical evidence that Down syndrome, while sterile in males, can be fertile in females. It has also been known that one third of all babies born to Down syndrome mothers have Down syndrome, thus increasing the risk dramatically in females with Down syndrome. Recently, it has been suggested that children with Down syndrome might benefit from medical intervention that includes amino acid supplements and a drug known as Piracetam which is a psychoactive drug that some believe may improve cognitive function. Affected children are characteristically very friendly, cheerful and often greatly enjoy music (Fowkes *et al.*, 1997)
Two parallel hypotheses have been proposed to explain the etiology of Down syndrome. According to the developmental instability hypothesis, loss of chromosomal balance causes Down syndrome, on the other hand gene dosage hypothesis tends to correlate gene overexpression with Down syndrome etiology (Reeves et al., 2001). The chromosome 21 contains 350 genes, some of which located at the Down syndrome critical region (DSCR) are thought to contribute to the pathogenesis of Down syndrome, although function of most of the encoded proteins still remains unknown (Roper and Reeves, 2006).

ii) **Klinefelter syndrome:**

Klinefelter (1942) studied nine male patients who could best be described as feminized males. The person with Klinefelter Syndrome is a male who has a hormone imbalance, hypogonadism, small penis, gynecomastia, infertility, abnormally long legs, lack of secondary male sexual characteristics and somewhat lower IQ but not mental retardation. Postnatal diagnosis is unlikely to be made in the first decade of life, and many individuals with Klinefelter syndrome may not be diagnosed at all (Nielsen, 1984; Abramsky and Chapple, 1997).

The chromosomal basis for the syndrome was not reported until 1956 and the exact chromosomal abnormality until 1959 (Arens et al., 1988). Klinefelter Syndrome, XXY male is a common genetic abnormality and affect one in every 500 to 1000 newborn boys. A Danish study by Bojesen et al., (2003) indicated that Klinfelter syndrome was present in 153 per 100,000 babies tested prenatally. Elevated second-trimester maternal serum levels of alpha-fetoprotein (Fejgin et
Al. et al., 1990) and HCG (Ben-Neriah et al., 1991; Barnes-Kedar et al., 1993) have been associated with fetuses with Klinefelter syndrome. In addition, fetuses with Klinefelter syndrome typically do not have abnormal ultrasound.

The benefit of knowing early that a baby or child has Klinefelter syndrome is that parents can be alert for signals that a child may need medical or developmental intervention. Most symptoms are treatable and early intervention can prevent developmental and educational difficulties. Children often have some degree of language impairment, which can lead to difficulty in reading and writing. A body may require testosterone injections in adolescence (Visootsak and Graham, 2003).

iii) Turner syndrome:

Turner syndrome, also known as Ullrich-Turner syndrome was first described by Turner (1938). It occurs 1 in 3000 female newborns. The clinical features are hypogonadism in phenotypic female, primary amenorrhea, infantile genitalia, under developed breast and pubic hair, short stature, webbing of the neck, failure to develop secondary sex characteristics. It is a gonadal dysgenesis affecting girls in which one of the two X chromosomes is partially or completely missing. In 1959, Turner syndrome was shown to be due to a missing X chromosome. Turner syndrome can arise as a result of nondisjunction during meiosis and that it represents the ‘flip-side’ of Klinefelter syndrome. In theory, equal numbers of Klinefelter and Turner syndrome individuals should be born. In reality, Turner's syndrome is significantly rarer. This is because Turner syndrome is far more likely to be fatal early in pregnancy. It is estimated that only about 2-
3% of Turner syndrome conceptions survive to birth. Interestingly, Turner syndrome also seems to be responsible for a relatively high proportion of miscarriages, perhaps as great as 20%. Although Turner syndrome is generally considered to affect only females, a Y chromosome may also be present (karyotype 45, X/46, XY). However, the 45, X/46, XY karyotype can result in a variety of different phenotypes besides Turner syndrome, including normal male (Wheeler et al., 1988; Chang et al., 1990).

Approximately 50-70% of Turner syndrome cases are due to 45, X (Hook and Warburton, 1983; Gotzsche et al., 1994; Gravolt et al., 1996; Jacobs et al., 1997; Ruiz et al., 1999; Savendahl and Davenport, 2000; Huang et al., 2002) The karyotype 45, X/46, XX accounts for roughly 15% of Turner syndrome cases, and the other karyotypes contribute to Turner syndrome cases to a lesser degree (Hook and Warburton, 1983; Gravholt et al., 1996).

There are many reports of other syndrome showing chromosomal abnormalities such as deletion syndromes and translocation syndromes.

Causes of chromosomal aneuploidy

Human trisomy is attributable to many different mechanisms and the relative importance of each mechanism is highly chromosome specific.

i) **Meiotic nondisjunction:**

Chromosome number abnormalities are remarkably common in human reproduction. Most are caused by chromosomal nondisjunction and premature chromatids separation in oocytes meiosis I. Meiotic nondisjunction is the major
mechanism which largely explains the occurrence of the majority of aneuploidy in early embryos (Pellestor et al., 2005). Chromosomal abnormalities account for the majority of pre- and post-implantation embryo wastage in humans. Most of these abnormalities result from maternal meiotic errors, which preferentially occur during the first meiotic division (Pellestor et al., 2005). Numerical chromosome aberrations constitute the vast majority of chromosomal imbalance in human, both in live-borne and in spontaneous abortions. Molecular studies have confirmed the overwhelming contribution of maternal meiotic nondisjunction to autosomal trisomy and sex chromosomal hyperdiploidy. Exceptions include 47, XYY, 47, XXY and 48, XXYY. However, it has been shown that the impact of nondisjunction goes beyond the aneuploidy of whole chromosomes (Schinzel, 1997). The reason for the occurrence of nondisjunction is currently unknown, although it does seem to be related to maternal age (80%) (Hook, 1992; Antonarakis, 1993), nondisjunction can also be of paternal origin (Murdoch and Ogston, 1984). Nondisjunction leading to autosomal trisomy or sex chromosome aneuploidy constitutes the major cause of chromosomal aberrations, both in live-born and even more, in spontaneous abortions (Schinzel et al., 1997).

Down syndrome involving total trisomy 21 results from nondisjunction, usually in the formation of the eggs or sperm, where a gamete ends up with an extra chromosome 21. Nondisjunction may occur in the first meiotic stage (MI) or the second meiotic stage (MII). The extra chromosome 21 is of maternal origin in 80-93% of the cases and of paternal origin in 7-20% of the cases. Among trisomy 21 cases of maternal origin, approximately 75% result from nondisjunction in MI
and 25% in MI while 40% of trisomy 21 cases of paternal origin occur from nondisjunction in MI and 60% from nondisjunction in MII (Magenis et al., 1977; Mattei et al., 1979; Jyothy et al., 2001; Buraczynska et al., 1989; Antonarakis et al., 1992; Yoon et al., 1996; Savage et al., 1998; Antonarakis, 1998; Muller et al., 2000). There is no maternal age difference between maternal MI and MII nondisjunction (Antonarakis, 1993; Sherman et al., 1994).

Turner syndrome karyotype, 45, X occurs as a result of nondisjunction at either stage of meiosis (meiosis I or meiosis II), resulting in the absence of one sex chromosome after fertilization. The nondisjunction may involve either the maternal or paternal gametes. Since only one sex chromosome is present in 45, X, the parental source of the nondisjunction must be inferred by identifying which parent contributed the X chromosome that is present. The nondisjunction will have occurred in the parent whose sex chromosome is absent. Moreover, since 45, X results from the absence of a chromosome, the exact meiotic division (I or II) where the nondisjunction occurred cannot be determined (Jacobs and Hassold, 1995).

ii) Recombination:

Recombination is the normal process by which chromosomes exchange genetic material with each other during meiosis. Alteration in the placement of the recombination event in both maternal MI and MII errors of chromosome 21 has been observed (Lamb et al., 1996). Among normal females meiotic events, recombination is relatively uniform along the length of the chromosome. In
contrast, among maternal MI errors, the recombinant event is usually telomeric, whereas among maternal MII errors, the event is pericentromeric. The unexpected finding of an association between MII errors and altered recombination suggested that, at least in females, essentially all meiotic errors are initiated during Meiosis I. However, the possibility of a true MII nondisjunction has not been ruled out, and such an error cannot be distinguished from an MI-derived Meiosis II case (MI/MII) (Lamb et al., 1997). Nondisjunction in maternal meiosis I is associated with reduced recombination between the nondisjoined chromosome 21 (Warren et al., 1987; Sherman et al., 1991), suggesting an important role for pairing/recombination failure or reduced recombination in the etiology of trisomy 21. Studies also indicate that nondisjunction may require a second event, or "hit," involving the degradation of a meiotic process (a protein integral to the meiotic event). This "hit" could occur in MI or MII. If there is an environmental risk to DS, this is where it could have influence.

Several studies have reported the maternal X chromosome nondisjunction, to determine whether the effects of recombination are unique to the X chromosome or similar to any of the autosomes thus far studied. Absent recombination is an important factor for X chromosome nondisjunction. However, similar to trisomy 15 and unlike trisomy 21, researchers observed a significant increase in the mean maternal age of transitional MI errors compared with nulltransitional cases. These findings profoundly affect our understanding of the etiology of trisomy 21 and may explain why both maternal meiosis I and II errors are associated with increased maternal age (Lamb et al., 1996).
iii) Maternal age:

Parental age is the important etiological factor in trisomy formation in humans. Trisomy data suggest that most aneuploidy is generated during meiosis I of oogenesis and is maternal age dependent. The only well established risk factor for Down syndrome is advanced maternal age (Mikkelsen, 1985; Hecht and Hook, 1996). The increased risk of Down syndrome with increased maternal age may be related to the physiological status of the ovaries or the eggs (Hassold and Jacobs, 1984; Freeman et al., 2000). Other potential explanations for the association between Down syndrome risk and advanced maternal age include delayed fertilization, changing hormone levels, and “relaxed selection” (Hassold and Jacobs, 1984). The increase risk of maternal age could be explained by the length of time between the beginning of MI and the completion of MI, possibly due to age-dependent degradation of meiosis-specific proteins (Hassold and Sherman, 2000).

What particular aspect of ovarian ageing may be relevant to inducing meiotic chromosome nondisjunction? There are two studies in which the morphology of the meiotic spindles in human oocytes at the second meiotic division (metaphase MII) was compared between young and old women provide valuable insights (Battaglia et al., 1996; Volarcik et al., 1998). Oocytes from young women formed regular bipolar spindles during the MII division, with the chromosomes being tightly arranged on the meiotic spindle equator, while the meiotic spindles of oocytes from older women were much diffuse, frequently showed lack of bipolarity and the chromosomes were irregularly and loosely
attached to the spindle at many different locations. These observations strongly suggested that the process of subsequent chromosome division and segregation will be under much poorer control in the oocytes of older than young women (Volarcik et al., 1998).

Various studies have reported either decreased risk of Turner syndrome with increasing maternal age or no association with maternal age (Hassold and Chiu, 1985; Mathur et al., 1991; Lorda-Sanchez et al., 1992; Gravholt et al., 1996; Ranke and Saenger, 2001). Increased maternal age has been associated with maternal origin of the extra X chromosome in nondisjunction in MII but not MI (Harvey et al., 1990; Lorda-Sanchez et al., 1992; Lanfranco et al., 2004;,) and also the risk of Klinefelter syndrome increases with increasing maternal age was reported (Carothers et al., 1978; Hook 1981; Hook et al., 1983; Ferguson-Smith and Yates, 1984; Carothers and Filippi, 1988).

Li et al., (2005) have reported that one in five oocytes that failed to fertilize after in vitro insemination was abnormal when analysed by conventional cytogenetics. Preconception genetic diagnosis, carried out on the first and second polar bodies by FISH, using 5 chromosome-specific probes (13, 16, 18, 21 and 22), showed that the rate of aneuploidy is higher in women aged 35 or over (52.1%). The possibility that abnormal separation of two or more chromosomes may occur simultaneously in oogonia and that this phenomenon may increase in relation to the increase in age of women (Li et al., 2005).
iv) **Paternal age:**

In humans, the relationship between advanced maternal age and the incidence of trisomy has been long established, but the possible effect of increased age of the father remains controversial. There are reports that there was no obvious relationship between increasing age and disomy 18, but the incidence of XY, YY and XX disomy all were significantly elevated among older men. This suggests that older men, like older women, have an increased likelihood of producing aneuploidy offspring by comparison with their younger counterparts (Griffin et al., 1995). It has been observed that the high proportion of paternal errors resulting in Turner syndrome may result from the absence of pairing along most of the X and Y chromosomes during meiosis I in the father, which may make the sex chromosomes susceptible to both nondisjunction and structural errors (Jacobs et al., 1997).

Several studies have indicated that paternal age has not been reported to influence the paternal origin of Klinefelter syndrome (Jacobs et al., 1988; Harvey et al., 1990; MacDonald et al., 1994). However, it has been shown that older men produce more sperm with aneuploidy (Lowe et al., 2001; Lanfranco et al., 2004). In the exception, increased paternal age was associated with paternal origin of the X chromosome (Lorda-Sanchez et al., 1992).

v) **Other factors:**

The relation of advanced maternal age to an increased risk of Down syndrome has been established, but the effects of other risk factors have not
been confirmed (Bishop et al., 1997; Hassold and Sherman, 2000). However, perusal of the literature indicates that Down syndrome is also associated with lower birth weight, prematurity, and intrauterine growth retardation but not plurality (Khoury et al., 1988; Ramos-Arroyo, 1991; Doyle et al., 1991; Kallen et al., 1996; Riley et al., 1998; Rasmussen et al., 2001; Lapunzina et al., 2002). Down syndrome has been reported among infants conceived by intracytoplasmic sperm injection (ICSI) (Aboulghar et al., 2001). Some evidence suggests that thyroid disorders in the mother may increase risk of bearing a Down syndrome child (Hook, 1984; Fialkow et al., 1971). Ionizing radiation is one of the known lifestyle/environmental agents to induce nondisjunction in experimental animals (Hook, 1984). Studies have reported that women who had infants or fetuses with Down syndrome were more likely to have abnormal folate metabolism and mutations in the methylenetetrahydrofolate reductase (MTHFR) and methionine synthase reductase (MTRR) genes (James et al., 1999; Hobbs et al., 2000; Hassold and Hunt, 2001; O'Leary et al., 2002). This suggests that periconceptional folic acid supplementation or fortification may reduce Down syndrome risk. However, a study that examined co-trimoxazole, a combination of trimethoprim and sulfamethoxazole that is a folic acid antagonist, failed to find any association between the medication and Down syndrome (Czeizel, 1990). Over the last several decades, women carrying a fetus with Down syndrome have been found to have low maternal serum levels of alpha-fetoprotein and estriol and elevated levels of human chorionic gonadotropin (Canick and Saller,
There are no convincing reports about others risk factors for sex chromosomal aneuploidy, apart from the advanced parental ages.

**Genetic disorders in Indian scenario:**

According to WHO 140 million children were born every year and five million die in the first month of life in developing countries. In India 4% of the population is mentally challenged and 5-15% of sick newborns have a metabolic problems (Anil, 2000). India, like other developing countries, is facing an accelerating demographic switch to non-communicable diseases. With a very large population and high birth rate, and consanguineous marriage favored in many communities, a high prevalence of genetic disorders (Verma and Bijarnia, 2002). In the major cities like Mumbai, Delhi and Baroda etc, congenital malformations and genetic disorders are important causes of morbidity and mortality. The major disorders were recorded as repeated abortions (12.4%), identifiable syndromes (12.1%), chromosomal disorders (11.3%) and mental retardation (11%). The estimation of the births showed that 4,95,000 infants with congenital malformations, 3,90,000 with G6PD deficiency, 21,400 with Down syndrome, 9,000 with thalassaemia, 5,200 with sickle cell disease, and 9,760 with amino acid disorders are born each year (Verma and Bijarnia, 2002). The prevalence of late-onset of multifactorial disorders is also large.

Genetic testing place an important role in the investigation of almost every child whose presence with one of the many common inherited disorders make a major contribution to pediatric morbidity and mortality throughout the world. The
rate of progress is so fast that it is difficult for keep abreast of development and to appreciate both the significance and the relevance of some of the major discoveries of recent years. Advances in molecular genetics are providing new ways of detecting mutant genes in individuals. Diagnostic test based on the analysis of DNA are now readily available. With the recombinant DNA technology a new set of tools became available to the study of origin and mechanism of chromosomal abnormalities using DNA polymorphism analysis. Molecular genetics is providing new ways to treat the genetic diseases. Thus, the population screening and investigation of etiological factors for genetic defects will be useful to prevent disability and death by early intervention, follow up and counseling.

In view of this, in the present study, author has made an attempt to analyse the Down syndrome and sex chromosomal aneuploidy in Mysore population addressing the following questions:

1. What is the prevalence of Down syndrome and sex chromosomal aneuploidy in Mysore population?
2. Why more of young age mother giving birth to Down syndrome and Sex chromosomal aneuploidy children?
3. Is the advanced parental and maternal grandparental age, cause the Down syndrome and sex chromosomal aneuploidy?
4. Is there any role of parental consanguinity for the onset of Down syndrome and Sex chromosomal aneuploidy?
5. Are there any other factors involved in meiotic chromosomal nondisjunction?