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# Chromosomal Abnormalities: Genetic Disease Burden in India

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**KEYWORDS** Mental Retardation. Congenital Anomalies. Microcephaly. Down Syndrome. Sex Anomalies. Male Infertility

**ABSTRACT** Chromosomal abnormalities are frequent events. Globally, at least 7.6 million children are born annually with severe genetic or congenital malformations. Precise prevalence data are difficult to collect, especially in India, owing to great diversity of conditions and also because many cases remain undiagnosed. Genetic and congenital abnormality is the second most common cause of infant and childhood mortality and occurs with a prevalence of 25-60 per 1000 births. The higher prevalence of genetic diseases in a particular community may, however, be due to some social or cultural factors.

## INTRODUCTION

Globally, at least 7.6 million children are born annually with severe genetic or congenital malformations; 90% of these are born in mid and low income countries. Precise prevalence data are difficult to collect, especially in developing countries, owing to great diversity of conditions and also because many cases remain undiagnosed. The genetic and congenital disorder is the second most common cause of infant and childhood mortality and occurs with a prevalence of 25-60 per 1000 births. The higher prevalence of genetic diseases in a particular community may, however, be due to some social or cultural factors. Such factors include tradition of consanguineous marriage, which results in a higher rate of autosomal recessive conditions including congenital malformations, stillbirths, or mental retardation. Furthermore, maternal age greater than 35 years is associated with higher frequencies of chromosomal abnormalities in the offspring (WHO 2005).

Genetic diseases can vary in severity, from being fatal before birth to requiring continuous management; their onset covers all life stages from infancy to old age. Those presenting at birth are particularly burdensome, and may cause early death or life-long chronic morbidity. This brief review will concentrate on chromosomal abnormalities which form a major part of genetic disease burden in India.

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## 1. MENTAL RETARDATION (MR)

The incomplete development of mental capacities and associated behavioural abnormalities are referred to as mental retardation. It is the single largest neuropsychiatric disorder in every civilised society affecting 2.5-3.0% of the total population. Chromosomal abnormalities are the important cause of mental retardation. Cytogenetic investigations were carried out on mentally challenged individuals that were referred to the Centre for Genetic Disorders, Guru Nanak Dev University, Amritsar, India. During 1996 to 2002, 143 cases were referred mainly as suspected Down syndrome, delayed milestones, mental retardation and others. The age group of the patients ranged from 1 month to 18 years. Interestingly, maximum number of patients that is, 58/143 (40.5%) were the firstborns and the average maternal age was 27.6 years (Kaur et al. 2003).

Cytogenetically invisible unbalanced translocations have been reported to cause mental retardation syndromes. In all these syndromes, phenotypic characteristics in addition to the mental retardation contribute to the recognition of the disorder and to the identification of the deletions. A multicentric study by ICMR was conducted in 1991 among 1314 patients. The chromosomal anomalies were found in 23.7%, metabolic defects in 5.0% and an identifiable genetic syndrome in 11.6% of the patients. In the remaining 59.7% patients, no known genetic cause could be identified. However, 66.5% of these patients had one or more of the following conditions: congenital malformation with or without neurological deficit, history of

consanguinity, positive family history of mental retardation or a positive screening test but without a confirmed diagnosis of metabolic defect suggesting that there may be additional unidentified genetic causes of mental retardation.

Moghe et al. (1981) studied the frequency of karyotype abnormalities in 74 mentally retarded patients selected from a total of 306 cases. Fourteen of these cases had chromosomal abnormalities. Autosomal abnormalities were 46,XX,1q-; 46,XY,2q-; 46,XY,5p-; 46,XY,dup(5p); 45,XX,t(13,14); and 46,XY,17p-.

Velagaleti et al. (2005) studied a total of 18 idiopathic MR patients. Chromosome analysis was carried out on all patients to rule out gross chromosomal abnormalities. Two subtelomeric rearrangements were detected (11.1%). The first case involved a 17-year-old with severe MR, profound deafness and dysmorphic features with reciprocal translocation t(3;7)(q26.2; p15.1). The second case involved a 4.6-year-old with mild developmental delay and a terminal deletion of the long arm of chromosome 2, del(2) (q37.3).

**Down Syndrome (DS)**

The maximum number of children with DS are born due to free trisomy of chromosome 21. However, there are cases of mosaics and inherited DS due to translocation of chromosome 21 to other chromosome. A survey of DS in Hyderabad by Isaac et al. (1985) gave an incidence of 1.17 per 1000 or 1 in 853 live births. In Delhi region, the frequency of DS was 0.81/1000 (Verma et al. 1998). A prospective study of 17,653 consecutive births for two years in Mumbai was undertaken to survey an overall incidence of malformations. The incidence of Trisomy 21 was 1 in 1200 (Patel et al. 2005). In Baroda region a study of malformations and DS on 31,775 babies showed an overall prevalence of 1.04/1000. Also maternal age specific prevalence of DS increased from 0.54/1000 at 15-19 years to 15.6/1000 at >40 years (Modi et al. 1998). Puri et al. (1977) recorded high frequency of DS in younger couples of first cousin marriages, while Stene et al. (1978) on the other hand, found high frequency of DS in uncle-niece unions. Sayee and Thomas (1998) observed that consanguinity does not predispose to Down syndrome on the basis of comprehensive study based on 417 couples.

In our study from March 1991 to March 2005, chromosomal analysis was carried out in 1950 cases referred with genetic disorders (Table 1; Fig. 1). Of these 222 (11.3%) were confirmed Down syndrome cases, 156 were (70.2%) males and 66 (29.7%) female children. The frequency of free trisomy 21 was 90.5% (201 cases), frequency of mosaicism was 3.1% (7 cases), 2.7% (6 cases) for translocations and remaining showed normal constitution. In our previous study (Kaur et al. 2003) chromosomal investigations were carried out on 143 mentally subnormal individuals. In cases with DS abnormal karyotype was seen in 86.3% cases, of which 68.1% were males and 31.8% females. Free Trisomy 21 was seen in 64.3% cases, while translocations were seen in 2.05% cases. These included 45,XY,+t(13;14), t(13;21), t(14;21), karyotypes.

In a similar study on 645 DS cases from Delhi, Verma et al. (1991) found 600 cases (93%) with free trisomy, translocations in 26 (4%), and 17 (2.6%) with mosaicism. Thomas et al. (1992) examined chromosomal constitution of 1343 mentally challenged children and discovered that 365 (27.1%) were DS, of which 86.5% had free trisomy, 7.6% had translocation and 5.75% were mosaics. Similarly Jyothy et al. (2000) recorded

**Table 1: Cytogenetic studies in 1950 cases during March 1991 - March 2005 (Centre for Genetic Disorders)**

| *Indications* | *No.* | *%* |
|---|---|---|
| Recurrent abortions/Missed abortions/Bad obstetric history | 440 | 22.5 |
| Down syndrome | 222 | 11.4 |
| Mental retardation/microcephaly/fragile-X | 182 | 9.3 |
| Ambiguous genitalia/hypogonadism | 78 | 3.9 |
| Primary amenorrhea | 66 | 3.3 |
| Turner syndrome | 46 | 2.3 |
| Chronic Myeloid Leukemia | 31 | 1.5 |
| Muscular dystrophies | 16 | 0.8 |
| Neural tube defects | 16 | 0.8 |
| Azoospermia/oligoazoospermia/infertility | 7 | 0.3 |
| Cleft Lip and Plate (CL±P) | 3 | 0.1 |
| Miscellaneous (syndromes/metabolic/Congenital/others) | 843 | 43.2 |

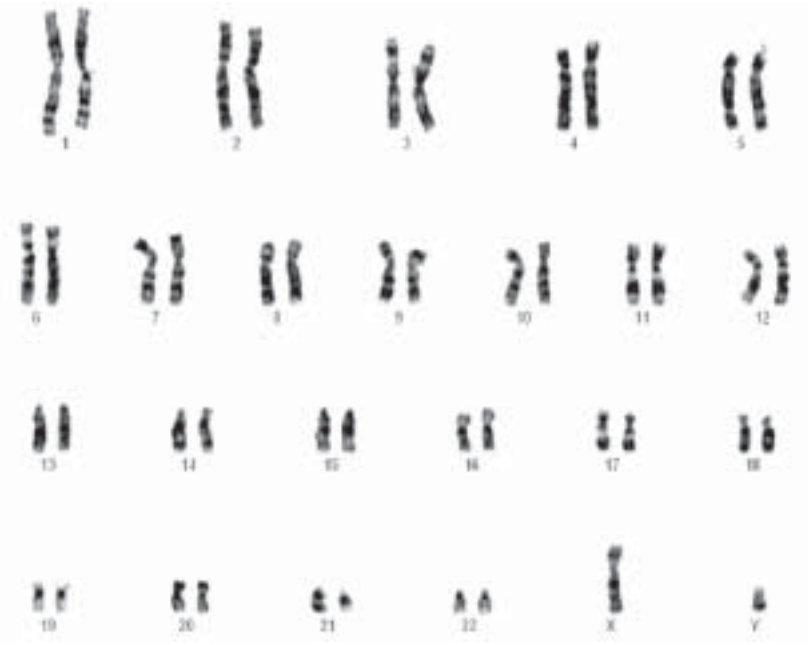

**Fig. 1. Robertsonian translocation in a male child with Down syndrome 46,XY,+t(21;21)**

cytogenetic data obtained from 1001 patients of DS and their parents over a period of 20 years (January 1979-January 1999). The frequency of pure trisomy, mosaicism and translocation was 880 (87.92%), 77 (7.69%) and 44 (4.39%) subjects respectively. The origin of the extra chromosome 21 due to meiotic non-disjunction was 79.24% maternal and 20.76% paternal. Birth order of DS showed a higher number of first and second-born. The mean maternal age was found to be 30.34 years and mean paternal age was 31.04 years. Lakshminarayana (1990) karyotyped 500 DS children. Translocations were seen in 15 and of these 9 were the cases of *de novo* translocations, while 6 cases were inherited from parents.

In sands of Kerala, natural radiation dose ranges from 1.0 to over 35.0 mGy per year. To assess the health effects of this naturally occurring high-level natural radiation on human populations, Kochupillai et al. (1976) demonstrated a significantly high frequency of mental retardation and DS in the region. Rajangam et al. (1997) reported the associated malformations and the clinical findings that were observed in 417 cytogenetically confirmed DS patients. Among them congenital heart defects occurred more frequently (75; 17.98%) than osteoarticular malformations (23; 5.52%), eye anomalies (22; 5.27%) and gastroenterological malformations (n=16; 3.84%). Congenital heart disease was present in 18.3% of cases with ventricular septal defect being the most common type of defect. Kava et al. (2004) studied cases of DS (524) over a period of 7.5 years (303 males and 221 females; M:F ratio 1.37:1). Average age at presentation was 19.4 months and average maternal age at birth of the affected child was 26.8 years. Craniofacial features noted were mongoloid slant (83.9%), ear abnormalities (66.9%), epicanthic folds (56.9%), and flat facial profile (50.9%). A total of 76.3% cases had hypotonia. Congenital heart disease was clinically diagnosed in 96 cases (18.3%). Apart from these sandle sign (46.2%), unilateral or bilateral simian crease (33.2%), clinodactyly (36.1%), brachydactyly (11.1%), hypertelorism (33.9%), nystagmus (3.2%), Brushfield spots (3.2%), squint (2.7%) and cataract (1.9%) were also noted.

## Microcephaly

Microcephaly is characterized by a reduced brain volume and small skull associated with

mental retardation, convulsions and other neurological symptoms. While some cases are due to monogenic abnormalities, the others may have been due to injuries during delivery or infections like Rubella, Cytomegalovirus or Toxoplasmosis during early stage of pregnancy. Microcephaly can also be seen as one of the symptoms in several rare syndromes with monogenic background and in certain chromosomal anomalies (Gustavson 1996). Microcephaly may also be a part of a well recognized syndrome like cri-du-chat, Dubowitz syndrome, Rett syndrome, Cohen syndrome and others. Cytogenetic investigations of microcephalic individuals reveal various aberrations at chromosomal level. Cases with apparently normal chromosomal complement may have some monogenic abnormality or complex structural rearrangements that are beyond the detection limit of G-banded chromosome analysis. It is estimated that 5-10% of all the cases of idiopathic mental retardation have a small subtelomeric rearrangement (Slavotinek et al. 1999) but the number of patients that are identified with this etiology remains small. The incidence of microcephaly is not known in India. However, it is higher in Karnataka where 33% of the marriages are consanguineous (Kumar et al. 2004). The phenotypic features like microcephaly, micrognathia, developmental delay, growth retardation are commonly associated with mosaic variegated aneuploidy (Lane et al. 2002).

In our previous study (Kaur et al. 2003), phenotypic and clinical examination of 143 cases with MR showed microcephaly in 13 cases (9.0%). In this study 33 cases (23.0%) were referred as having mental retardation, delayed milestones, congenital anomalies and fragile-X and others. Two of these patients had abnormal karyotype that is 47,XY,+21 and 46,XY, del (18). In another study carried out on 11 institutionalised individuals with microcephaly, three cases showed chromosomal aberrations like 2p deletion (Fig. 2), 18p deletion and ring chromosome 7 (Kaur et al. 2008).

It is important to ascertain the cause of mental retardation, so that recurrence risk can be reduced. When standard cytogenetics fails to identify the presence of unbalanced chromosomal aberrations, the Comparative Genome Hybridisation (CGH) and Fluorescent *in situ* Hybridization (FISH) can provide rapid and comprehensive identification. M-FISH is able to detect cryptic translocations in supposedly normal metaphase spreads (Uhrig et al. 1999) and the screening of subtle structural anomalies can be done by using telomere specific FISH probes.

**Fig. 2. Mental retardation in female showing 46,XX, del (2)(p25-p22)**

**Fragile-X**

Fragile-X usually results from amplification of the CGG repeat in the 5' untranslated region of the FMR1 gene. Fragile-X syndrome is the commonest form of inherited mental retardation.

In our study of 1950 cases, cytogenetic investigations were carried out in 182 cases with mental retardation. Five males (2.7%) were referred with fragile-X syndrome. The fragile site at Xq27 was seen in one case only. Elango and Verma (1996) screened 1,111 patients for fragile-X syndrome. Twenty patients were diagnosed to have the fragile-X syndrome. The prevalence of fragile-X syndrome was 1.8% among patients of both sexes and 2.8% in males only. Jain et al. (1998) screened 1206 children with mental retardation. Twenty three (6.38%) of them were found to be positive for fragile-X syndrome using cytogenetic techniques. Molecular confirmation in 21 affected boys showed full mutation in 19 (5.27%). This frequency (5.27%) of fragile-X patients, among children with non-specific mental retardation is comparable to the results of studies in the west. Similarly, Sharma et al. (2001) reported 7.7% frequency of fragile-X in an institutionalized sample population of 130 in New Delhi. In a study, Pandey et al. (2002) found 3/118 males having the FMR1 full mutation. None of the patients tested were positive for the FMR2 full mutation. The Fragile-X prevalence was 2.5% among males, which is lower than previously reported in Indian mentally retarded patients. To assess the extent of variation of the CGG repeat in the population from the eastern region of India, Saha (2001) studied 98 mentally retarded individuals living in and around Kolkata and identified 21 distinct alleles ranging in size from 8 to 44 CGG repeats. A repeat size of 28 was the most frequent; this value is different from the most frequent repeat size found in other studies indicating a racial or ethnic variation.

## 2. SEX ANOMALIES

The genetic sex of the embryo is established at fertilization, the phenotypic sex determining process is set in motion during the period of organogenesis when the gonads develop. Apart from sex specific genes present on X and Y chromosomes and some autosomal genes also play a role in sex determination (Damiani et al. 1997). Any alteration in the genes, gene dosage or the sex chromosomes lead to abnormalities of sexual development, ranging from complete sex reversal to hermaphroditism.

In our cytogenetic investigations of 1950 cases with genetic disorders, from March 1991 to March 2005, 190 (9.7%) cases were presented with sex anomalies. Ambiguous genitalia and hypogonadism constituted 4% cases, primary amenorrhea in 3.3% and Turner syndrome constituted 2.3% of the cases (Table 1). The total frequency of sex anomalies was 9.7%. Earlier we investigated 156 cases with varied abnormalities of sexual development during 1991 to 2001 (Kaur et al. 2004). Among these, 88 were raised as females (56.4%) and 68 were raised as males (43.6%). The age of females ranged from 26 days to 44 years and that of males from 3 days to 30 years. A total of 40 cases (25.6%) showed abnormal karyotypes. These included 10 cases (25%) with mosacism, of which 7 cases (7.5%) were with 45,X/46,XX chromosomal complement, 2 cases (5%) with marker chromosome, that is, 45,X/46,X,+mar and 1 case (2.5%) with 46,XY/47,XXY constitution. Of the 88 phenotypic females, 55 females had primary ammenorrhea of which 11 showed 46,XY karyotype and 4 cases (10%) had pure monosomy. In one case (HK-459) with 45,X/46,X,+mar constitution, Southern analysis of the proband and her parents was carried out. Primers DYZ3 and DYS1 representing centromeric heterochromatic and euchromatic region in the long arm of Y chromosome detected Y-specific signals in the proband and her mother confirming that the Y-derived marker chromo-some was of maternal origin (Bashamboo et al. 2003; Fig. 3).

In our study of 68 phenotypic males (43.6%), referred with conditions like ambiguous genitalia, intersex, hypospadias, suspected Klinefelter's syndrome, undescended testis and gynaecomastia revealed 4 (5.9%) with 47,XXY karyotype; one (1.5%) showed 46,XY/47,XXY chromosomal constitution. In cases with ambiguous genitalia, 46,XX karyotype was seen in 2 cases (2.9%). In the cases of hypogonadism, 30.9% had 46,XY chromosomal complement while in 8 cases (11.8%) of hermaphroditism, 2 cases showed 46,XX karyotype. The 4 cases (5.9%) with undescended testis had 46,XY karyotype; in 5 cases of hypospadias, three showed 46,XY, one (1.5%) each had 46,XX and 47,XY,+21 constitution respectively. Amongst 2 cases (2.9%) of gynaecomastia, one (1.5%) had 46,XY,+15q karyotype (Kaur et al. 2004).

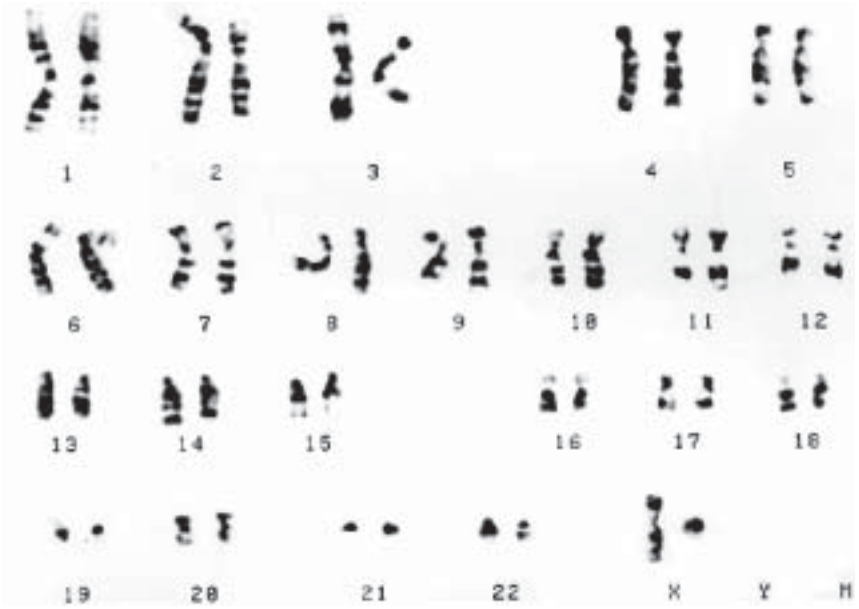


**Fig. 3. Female with Turner stigmata showing marker chromosome 46,X,+mar**

Ganguly and Sahni (2003) studied 280 adolescent girls and reported that 29% of them had some chromosomal anomaly. Amongst those with sex chromosomal anomalies, 34% had 46,XY karyotype while 51% were 45,X or mosaic with normal XX or other aberrations in X. Their study also indicated the involvement of autosomes in causing improper sex development and further reported that only 1% of the pure line 45,X conceptions are viable, indicating the necessity of mosaicism with X or Y chromosome. Verma et al. (1998) found the incidence of hypogonadism to be 5.6/10,000 births and 1.6/10,000 births in case of intersex/cryptoorchidism (Table 2).

Rajendran and Hariharan (1995) studied thirty five children with ambiguous genitalia from January 1986 to December 1991. Eighteen cases were assigned female sex. Parents prefer the intersex children to be reared as male possibly because of the less social stigma attached to an impotent male than to sterile female, and because males are socially independent.

Gender identity is a complex process of differentiation that is affected by numerous variables. Several social, cultural and religious factors related to the area influence the gender assignment of intersex patients. Timely intervention in cases with sex abnormalities is essential for proper genetic counseling and their normal development. The classical cytogenetics combined with FISH and molecular techniques can help these cases to get the proper hormonal, surgical and psychological management.

## Male Infertility

Complete deletions of the AZFc region in distal Yq are the most frequent molecular genetic cause of severe male infertility. They are caused by intrachromosomal homologous recombination between amplicons large, nearly identical repeats and are found in 5–10% of cases of azoospermia and severe oligozoospermia. Homologous recombination may also generate different partial deletions of AZFc, but their contribution to spermatogenic impairment has not been confirmed (Ferlin et al. 2005).

Rao et al. (2004) analysed metaphase chromosomes of 251 infertile men with varicocele and unexplained infertility using Giemsa-Trypsin-Giemsa banding and FISH. The frequencies of chromosomal defects in varicocele and idiopathic infertility were 19.3% and 8.76% respectively, whereas Y chromosome microdeletions were

5.26% and 3.60% respectively. Overall rate of incidence of chromosomal anomalies and microdeletions in 251 infertile men were 11.5% and 3.98% respectively, indicating a very significant higher association of genetic defects with varicocele than idiopathic male infertility. The microdeletions in 6 genes and 18 sequence-tagged-sites in the Yq region were screened using polymerase chain reaction (PCR) techniques. Genetic defects were observed in 38 (15.13%) infertile individuals, including 14 (24.56%) men with varicocele and 24 (12.37%) men with idiopathic infertility.

Rao et al. (2005) observed a strong and statistically significant association (OR=1.89; P=0.0235) of chromosomal abnormalities and sex chromosome abnormalities (OR=4.29; P=0.001) in azoospermics when compared to oligoasthenoteratozoospermics (OAT). The authors analysed metaphase chromosomes of 744 infertile men, including 272 men with azoospermia and 472 men with OAT, using trypsin-Giemsa banding and FISH. Chromosomal abnormalities were observed in 59 (7.9%) individuals of the total studied population. Among these, 30 out of 272 (11.0%) azoospermic men and 29 out of 472 (6.1%) infertile men with OAT showed chromosomal abnormalities. In addition, six autosomal abnormalities associated with azoospermia and two abnormalities involving Y chromosome, which include a novel karyotype (mos 46,XY/51, XYYYYYY) in OAT individuals, were detected.

We carried out cytogenetic investigations in twenty males with severely compromised semen parameters. These cases were selected from Centre for Human Reproduction, Jalandhar and fifteen healthy individuals were taken as control. Out of 20 cases, 6 were oligozoospermic males and 14 were azoospermics and their age group ranged between 31-45 years. Most of them were farmers or from rural background and were exposed to pesticides and fertilizers. The six oligozoospermic males showed normal 46,XY male karyotype. In one case (AZK-4), the testosterone levels were found to be low, whereas leutinizing hormone, prolactin and follicle stimulating hormone were within the normal range. Among 14 azoospermic males, 13 showed 46,XY male karyotype, whereas one case (AZK-9) revealed 46,XX chromosomal constitution. His testosterone levels were found to be low, whereas levels of leutinizing hormone and follicle stimulating hormone were elevated. FISH analysis was carried out in this case (AZK-9) and presence of SRY was confirmed (Kaur et al. 2007; Fig. 4)

In a similar study, Ramanujam et al. (2000) studied 145 infertile men. Their age group ranged

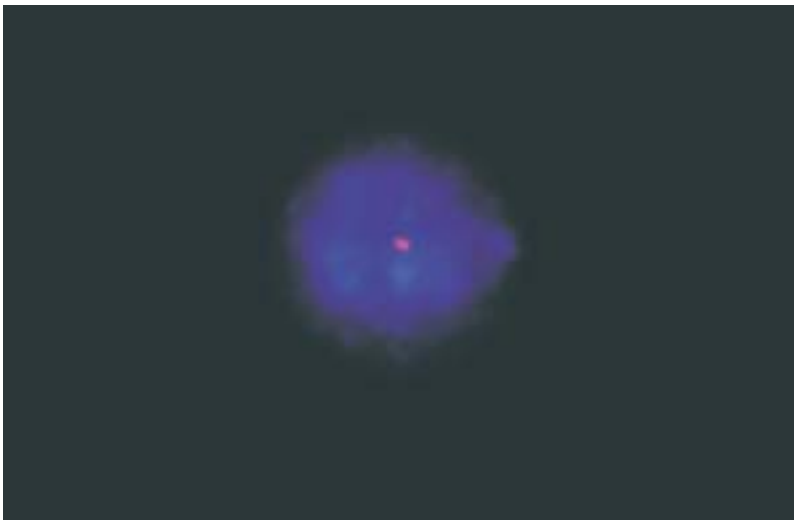

**Fig. 4. 46,XX, male with SRY positive signal (Kaur et al. 2007)**

from 24-65 years. The plasma leutinizing hormone, follicle stimulating hormone and testosterone levels were elevated in patients with sperm counts less than $10X10^6$/ml. The males with 46,XX karyotype are sterile males. The incidence varies from 1 in 9000 (de la Chapella 1972) to 1 in 20000 (Nielsen and Sillesen 1975). The majority of the cases are due to interchange of a fragment of the short arm of the Y chromosome containing region that encodes the testes determining factor with X chromosome (Muller et al. 1986). SRY is the candidate gene for the testes determination. It resides within 35 kilobase region of the Y chromosome immediately proximal to the pseudo-autosomal region. When SRY gene is present, testes are formed and in its absence gonads develop into ovaries.

In a similar study, Nagvenkar et al. (2005) studied 88 infertile men of which 42 were azoospermics and 46 oligozoospermics. Chromosomal aberrations were seen in only 9 cases. PCR analysis for the detection of AZF microdeletions showed the deletion of AZFc region along with deletion of the heterochromatin in only one male with normal karyotype 46,XY. Similarly, Tuzun et al. (1996) studied 50 infertile men of which only 4 cases showed chromosome anomalies. Pandiyan and Jequir (1996) studied 1210 infertile men showing chromosome aberrations in 44 patients. Ali et al. (2005) studied 109 cases of male infertility from Bangalore showing various chromosome abnormalities in 3 cases. PCR based microdeletion analysis showed deletion in AZFc region of 6 patients with normal male karyotype.

However, as standard cytogenetic analysis using G banded technique is not sensitive enough to detect subtle chromosomal rearrangements, so all these cases should be considered for FISH. Molecular analysis should also be done for the detection of microdeletions on Y chromosome regarding region AZF, DAZ, CDY1, RBM, SRY in infertile men showing 46,XY karyotype. It is expected that such studies would be very useful for genetic counseling as well as for isolation of genes that are important for normal sperm development.

## 3. CONGENITAL ANOMALIES

An incidence of 14.64 per 1000 births with congenital anomalies is reported in a survey of over 4000 births (Mishra and Baveja 1989). Major malformations were seen in 1.1% and minor in 0.4% births. The pattern of congenital anomalies included multiple anomalies (37.68%), anomalies of central nervous system (13.33%) and anomalies of skin and appendages (13.33%). Another large survey consisting of 9000 babies indicated major anomalies in 1.6% of live births compared to 16.4% in stillbirths (Aggarwal et al. 1991). Table 2 and 3 show the prevalence of some common congenital abnormalities in India.

Children between 0-6 years of age from six villages of Ambala District were screened for congenital malformations (Kumar et al. 1994). Of 1371 children, malformations were observed in 30 (prevalence 22/1000). Twenty children had major malformations and six had multiple anomalies. Cardiovascular malformations were the commonest (37%) followed by musculoskeletal (30%), gastrointestinal (23%), central nervous system (13%) and genitourinary anomalies (6.6%).

A prospective study of 17,653 consecutive births during two years at Mumbai, was undertaken by Patel and Adhia (2005) to asses overall incidence of malformations: 294 (1.6%) had a major malformation, 1400 (7.92%) had a minor malformation, 328 (1.85%) were still births and out of these 52 (15.8%) were malformed. The incidence of congenital malformation in still births was higher than the live babies. Analysis of an overall distribution of malformations showed that central nervous system was most frequently involved. Consanguinity was found in 8.1% cases. The polygenic malformations

**Table 2: Prevalence of common malformations in India**

| *Malformations* | *Cases per 10,000* | *Estimated births* |
|---|---|---|
| Neural tube defects | 36.3 | 88,532 |
| Talipes | 14.5 | 35,364 |
| Polydactyly | 11.6 | 28,364 |
| Hydrocephalus | 9.5 | 23,169 |
| Cleft lip and/or palate | 9.3 | 22,681 |
| Congenital heart disease | 7.1 | 17,316 |
| Hypogonadism | 5.6 | 12,194 |
| Tracheo-oesophageal fistula | 3.7 | 9,023 |
| Diaphragmatic hernia | 2.6 | 6,341 |
| Anorectal atresia/stenosis | 2.4 | 5,853 |
| Microcephaly | 2.2 | 5,365 |
| Cleft palate alone | 1.7 | 4,146 |
| Intersex and cryptorhidism | 1.6 | 3,902 |
| Intestinal atresia/stenosis | 1.2 | 2,926 |
| Anophthalmia/microphthalmia | 1.0 | 2,438 |

Verma et al. 1998

**Table 3: Rate of incidence of congenital malformations in Indian sample studies**

| *Area* | *Authors* | *N* | *Rate/1000 births* |
|---|---|---|---|
| Ajmer | Gupta et al. 1971 | 2145 | 19.1 |
| Bombay | Kolah et al. 1975 | 29550 | 14.1 |
| Bombay | Purandare 1966 | 39458 | 8.6 |
| Calcutta | Mitra 1966 | 19191 | 3.1 |
| Calcutta | Ghoshal 2004 | 301595 | 8.12 |
| Calcutta | Banerjee and Hati 1993 | 171117 | 5.58 |
| Calcutta | Guha and Mukherjee 1980 | 41256 | 3.0 |
| Calcutta | Choudhary et al. 1984 | 21016 | 2.9 |
| Calicut | Nair and Mittal 1964 | 19191 | 3.1 |
| Chandigarh | Saifulla et al.1967 | 3721 | 13.4 |
| Delhi | Ghosh and Bali 1971 | 1000 | 36.0 |
| Delhi | Singh and Sharma 1980 | 4150 | 34.0 |
| Hyderabad | Mathur et al. 1975 | 6274 | 27.0 |
| Hyderabad | Rao et al. 1988 | 1060 | 14.0 |
| Hubli | Garavalingappa et al. 1979 | 2398 | 31.3 |
| Jaipur | Hemrajani et al. 1971 | 28511 | 21.3 |
| Kanpur | Mittal and Grewal 1969 | 4150 | 22.3 |
| Lucknow | Sharma et al. 1972 | 2851 | 14.3 |
| Madras | Raju and Ramakrishna 1976 | 23000 | 18.9 |
| Madras | Chandra and Harial 1977 | 24192 | 17.9 |
| Madurai | Kamla et al. 1978 | 11619 | 11.1 |
| Mysore | Dash and Sharma 1970 | 5554 | 2.5 |
| Mysore | Veena and Prasad 1967 | 3879 | 27.5 |
| Patna | Khanna and Prasad 1967 | 5376 | 14.0 |
| Pondicherry | Datta et al. 1968 | 11056 | 10.5 |
| Pondicherry | Puri et al. 1979 | 10767 | 37.9 |
| Trivandrum | Sagunbai 1982 | 7167 | 10.4 |
| Varanasi | Chandra and Singh 1982 | 1774 | 20.8 |

Modified from Verma 1984; Ghoshal 2004

accounted for 45.25%. Sporadic malformations which occur separately, singly and in non-epidemic form accounted for 20.9%. Deformations were found in 4.76%. Chromosomal abnormalities were found in 4.08% whereas in autosomal recessive traits were in 4% cases. In 1400 (7.92%) cases minor malformation were seen. There were 149 twin pregnancies, one triplet and the remaining singleton pregnancies. Amongst 17,653 births, 328 (1.85%) were still births out of which 52 (15.8%) were malformed and led to early death in 40 (13.6%) cases. The incidence of congenital anomalies was higher amongst still born than among live babies.

Congenital malformations occur all over the world and are responsible for about 15% of the perinatal mortality in India (Merchant 1989; Datta and Chaturvedi 2000). In a study conducted in Maharashtra from 1998 to 1999, a total of 2968 births (live and still) were screened for congenital malformations soon after birth or within the first week of life. The babies with congenital malformations diagnosed at birth were 37(1.24%). Out of these 26 (70.3%) babies had 34 major anomalies and 11 babies (29.4%) had 14 minor anomalies. Congenital anomalies were more significant in still births as compared to live births. Central nervous system defect was main cause in still born. Anorectal malformations (ARM) are complex group of malformations diagnosed at the time of birth because of absence or an ectopic location of anus. The incidence is approximately 1:5000 live births and they are more often seen in boys than in girls.

To find the prevalence of associated anomalies in children with ARM, Mittal et al. (2004) studied one hundred and forty patients (80 males and 60 females) to detect associated anomalies and to find their prevalence. High and low type of ARM was seen in 52.14% and 47.86% of patients respectively. Associated anomalies were more common with high type of ARM (78.08%) than in patients with low type of ARM (37.31%). 58.57% patients had associated anomalies which included those of urinary system (37.14%), vertebral system (34.28%), skeletal system other than vertebral (15.17%), genital system (14.29%), cardiovascular system (12.14%), gastrointestinal tract (10.7%) and spinal cord (10%).

Congenital malformations were studied over

a period of five years in 10,100 consecutive births in Shimla by Grover (2004). Out of these, 180 babies had one or the other congenital malformations and the overall incidence was 1.78%. Amongst the 311 still born babies, 47 had congenital malformations indicating that the incidence of congenital malformations was much higher in still born babies (15.1%) as compared to the live born babies (1.3%). The malformations involving the central nervous system were the commonest (40%) followed by musculoskeletal system (23.8%), while genitourinary system malformations were the least common and accounted for 3.8% of the cases. Incidence of congenital malformations was the highest in babies born to mothers over 35 years of age and gravida four and more. The incidence was 2.8% in both the groups; the incidence of congenital malformation was more in babies weighing < 2500gms was 2.6%.

Verma et al. (2003) provided genetic counseling to 3500 subjects. Among these 28.7% were for prenatal diagnosis, 13.7% for mental retardation with/without malformations, 11.5% for thalassaemia, hemophilia and leukemia, 8.5% for neural tube defects, 8% for muscle dystrophy and spinal muscle atrophy. Chromosomal studies in blood (n=5459) were carried out for recurrent abortions (57.8%), delayed milestones (14.7%), malformations (11%), infertility and ammenorrhea (10.2%). Amniotic fluid studies were conducted (n=835) due to advanced maternal age (35.7%), high risk result on triple test (21.3%), previous child with trisomy 21 (21.3%) and abnormalities seen on ultrasound (11.1%). Molecular studies were mostly for thalassemia (843, 24.3%), Duchenne muscular dystrophy (443, 12.5%), fragile X syndrome (367, 10.3%), spinal muscular atrophy (315, 8.9%), thrombophilia profile (233, 6.6%), Friedreich ataxia (162, 4.6%), cystic fibrosis (140, 3.9%) and mitochondrial disorders (101, 2.9%).

Ronya et al. (2002) investigated a total of 3000 consecutive births over a 9-month period and showed the frequency of congenital malformations to be 21.1 per 1000 births. Stillbirths were associated with a higher incidence of malformations (14.5%) as compared to live births (1.8%). The commonest systems affected were the gastro-intestinal tract and the genito-urinary tract (20.4% each) followed by the central nervous system (17.3%). Among the various possible risk factors studied, a higher incidence of congenital malformations was associated with increased maternal age (> 35 years), higher gravida mothers (> G4), parental consanguineous marriages, previous history of abortions, maternal hypertension and others.

Congenital malformations were studied prospectively from September 1989 to December 1992 covering 12,797 consecutive deliveries by Bhat and Babu (1998). The incidence of malformations was 3.7% and it was 3.2% among live births and 15.7% among still births. Three hundred and ninety seven birth defects were observed among 308 live births and 72 among 45 still births. The incidence of malformation was significantly higher among male babies ($p < 0.001$), still births ($p < 0.001$), low birth weights ($p < 0.001$) and preterm babies ($p < 0.001$). Consanguinity among parents of malformed babies was more common ($p < 0.001$). Musculo-skeletal malformations were the commonest (9.69 per 1000) followed by cutaneous (6.33 per 1000), genitourinary (5.47 per 1000), gastrointestinal (5.47 per 1000), central nervous system (3.99 per 1000) and cardiac anomalies (2.03 per 1000). In another study of 1371 children, from North, malformations were observed in 30 (prevalence 22/1000). Twenty children had major malformations and six had multiple anomalies. Cardiovascular malformations were the commonest that is, 37% followed by musculoskeletal in 30%, gastrointestinal in 23%, central nervous system in 13% and genitourinary anomalies in 6.6% cases (Kumar et al. 1994).

In our study of cases from 1996 to 2005, various congenital malformations were seen (Table 4; Figs. 5, 6). Genitourinary malformations were seen in 62 (53.9%) cases, musculoskeletal abnormalities in 22 (19.1%), craniofacial in 14 (12.1%), sensory in 10 (8.6%), cardiovascular in 4 (3.4%) and cleft lip/cleft palate were observed in 3 (2.6%) cases.

**Table 4: Types of congenital malformations seen during 1996-2005 in Centre for Genetic Disorders**

| *Type of malformation* | *Number of cases* |
|---|---|
| Genitourinary malformations | 62 (53.9%) |
| Musculoskeletal Disorders | 22 (19.1%) |
| Craniofacial | 14 (12.1%) |
| Sensory (deaf/dumb/blind) | 10 (8.6%) |
| Cardiovascular | 4 (3.4%) |
| Cleft lip/cleft palate | 3 (2.6%) |
| Total cases | 115 |

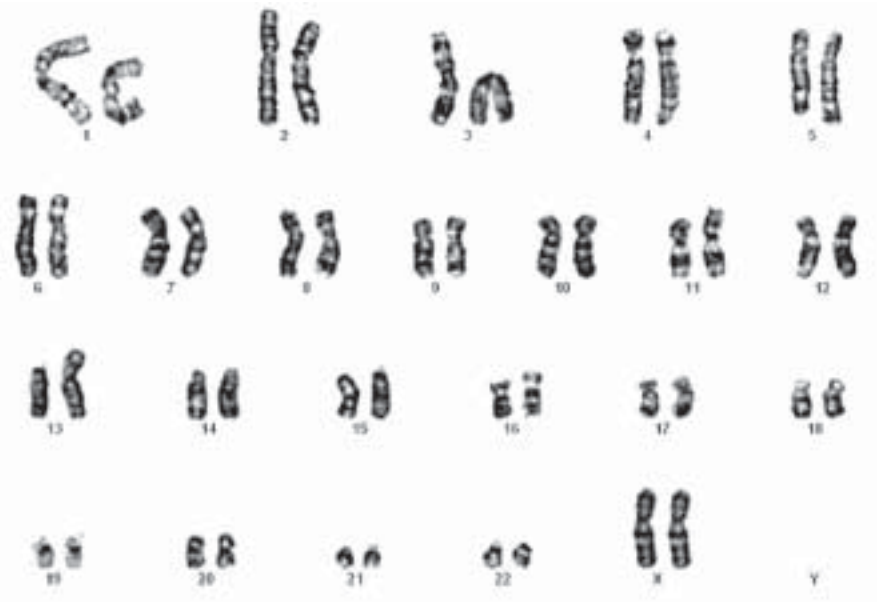

**Fig. 5. Congenital anomalies in a female child showing 46,XX,+t(13;21)**

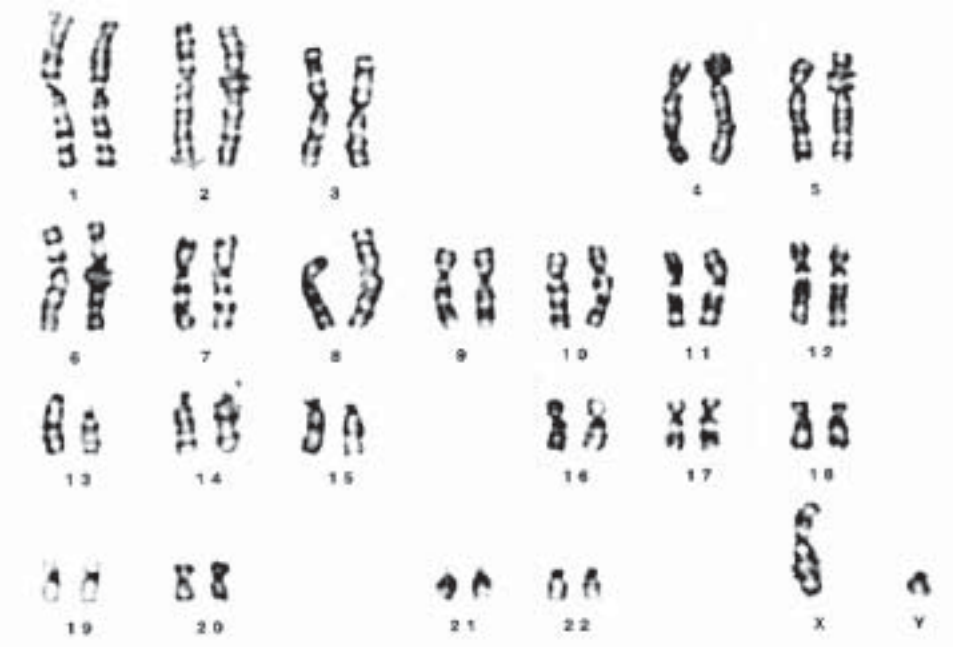

**Fig. 6. Translocation 46,XY,+t(8p;13q) seen in the father of a stillborn child**

## CONCLUSIONS

The control of genetic diseases/chromosomal disorders should be based on an integrated and comprehensive strategy combining best possible treatment and prevention through community education, population screening, genetic counseling and the availability of early diagnosis.

A noninvasive procedure like ultrasound is for imaging certain obvious structural birth defects. It can evaluate gestational age, as well as identify twins, fetal position, placental location, fetal growth, development and movement and any structural birth defects. It also can assess amniotic fluid volume. Many fetal organ systems and anatomical lesions, including some genitourinary, gastrointestinal, skeletal and central nervous system abnormalities can be visualized by ultrasound between 16-20 weeks' gestation. The radiography from 10 weeks' gestation onward can be used for the diagnosis of inherited skeletal dysplasias, particularly osteochondrodysplasia in the second and third trimesters.

Certain markers in the blood indicate the presence of chromosomal abnormality in the fetus. The blood sample is taken between 16 and 18 weeks of pregnancy.

Chromosomal aberrations, like deletions, duplications, translocations, and inversions diagnosed in affected parents or siblings can be detected prenatally or postnatally by cytogenetic and FISH analysis. Chorionic villus sampling and amniocentesis between 8 to 14 weeks gestation can detect chromosomal abnormality. Amniocentesis enables doctors to measure the alpha-fetoprotein level in the amniotic fluid.

Polymerase chain reaction is used to identify affected babies or carrier individuals accurately and quickly. The DNA material can be obtained by chorionic villus sampling.

Folic acid (through diet and supplementation) has been proven to decrease or minimize specific birth defects including neural tube defects, congenital heart disease, urinary tract anomalies, oral facial clefts, limb defects and pyloric stenosis. Preconceptional folic acid supplementation should be recommended to women who may become pregnant. The dose of folic acid supplementation should be adjusted according to the patient's history and needs (Wilson 2003).

The expanded newborn screening can be adopted as a non-mandatory nationwide screening for inherited metabolic diseases in a country like India. The importance of genetic counseling is increasing with the advancement in the field of genetics. The genetic counseling can help families to cope with emotional, psychological and medical consequences of genetic diseases. There are insufficient data currently available on the epidemiology of genetic disorders, the demand for genetic services and the quality, use and outcomes of genetic services in India. The efficient registries, databases and continued investment in genetic research are key to successful public health interventions.

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