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Congenital Heart Defects and Chromosomal Abnormality

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ABSTRACT Chromosomal abnormality is one of the causal factors in the formation of the congenital heart defects. 65 patients (33 male and 32 female) with heart defects were referred for karyotyping and counseling. Chromosomal abnormalities were detected in 27 (41.5%) and 38 had a normal karyotype. Numerical abnormality was found in 21 (77.8%) and structural in 6 (22.2%), numerical was detected in 14 females and 7 males, and structural in 4 female and 2 male patients. Numerical abnormality was one with 47,XX+13; 2 with 45,X and 18 with 47,XX+21 (11) or 47,XY+21(7). Structural abnormality was derivative 9 in 2, deletion 11q, derivative 14, Robertsonian translocation between 14 and 21 and ring 18 mosaicism in one each. Parental origin of the structural abnormality revealed that two were maternal and one was paternal. In the present study, association could be detected between chromosome 21 and the female probands with chromosomal abnormality and heart defects.

INTRODUCTION

Congenital Heart Defects (CHDs) include all structural anomalies of the heart and the intrathoracic great vessels resulting from the errors in morphogenesis during development. The incidence of CHDs among live births is estimated to be 3.7 to 7.7 per 1000 (Ferencz et al. 1985). CHDs are etiologically heterogeneous and could be due to genetic (single gene defects, chromosomal abnormality) and/or environmental (multifactorial, teratogens) or unknown factors (Michels and Ricardi 1990). From literature, it is seen, that six percent of CHDs are due to chromosomal abnormality (Greenwood et al. 1975). Conversely, the reported incidence of CHDs among individuals with chromosomal abnormality is around thirty percent.

Objectives

This paper aims to find the occurrence of the chromosomal abnormality and its association to CHDs in consecutively referred patients to the Division of Human Genetics, St John's Medical College, Bangalore.

MATERIAL AND METHODS

A total of 65 patients with CHDs were referred for karyotyping and counseling, during a period of 5 years. There were 33 male and 32 female patients and their age ranged from neonate to 16 years. The patients' details were recorded in a pro forma.

Chromosomal preparations were using the modified leucocyte micro culture method (Arakaki and Sparkes 1963) followed by Giemsa-Trypsin-Giemsa banding technique (Seabright 1971), automated photography and karyotyping.

RESULTS

Table 1 shows that **c**hromosomal abnormalities were present in 27 cases (41.5%). There were 18 (18/32, 56.2%) female and 9 (9/33, 27.3%) male cases. 22 (81.5%) cases had single CHDs, 3 (11.1%) had undifferentiated congenital heart defects (CHDs) and 2 (7.4%) had complex CHDs. In the 27 cases with chromosomal abnormalities, 9 (33.3%) were male probands (6 single CHDs, 3 undifferentiated) and 18 (66.7%) were female (16 with single CHDs; 2 with complex CHDs). The rest 38 (58.5%) had a normal karyotype (46, XX-14; 46,XY-24);(16 with single CHDs; 12 with complex CHDs; 10 with undifferentiated CHDs).

Table 1: Congenital Heart Defects (CHDs) versus karyotype

S. No.	*CHDs*	*Karyotype*
59	Tetralogy of Fallot, patent ductus arteriosus, pulmonary atresia	46,XY
60	Patent ductus arteriosus	46,XY
61	Atrio ventricular canal defect	46,XY
62	Pulmonary tricuspid stenosis, VSD, patent ductus arteriosus	46,XY
63	Pulmonary atresia,VSD	46,XY
64	Tetralogy of Fallot	46,XX
65	Pan systolic murmur	46,XY

Numerical chromosomal abnormalities were found in 21 (21/27, 77.8%) (14 female; 7 male) and structural chromosomal abnormalities in 6 (6/27, 22.2%) (4 female; 2 male).

CHDs found in numerical chromosomal abnormalities:

1. Female probands: Coarctation of aorta and coarctation of aorta with bicuspid aortic valve in 2 with 45, X; dextrocardia with trisomy 13; in trisomy 21 Down syndrome 3 with ventricular septal defects (VSD); atrial septal defects (ASD) and atrio ventricular septal defects (AVSD) in 2 each; patent ductus arteriosus and VSD, mild trisuspid regurgitation, cleft mitral valve and murmur one in each.
2. Male probands: Trisomy 21 Down's syndrome 3 with VSD; AVSD, ASD, patent foramen ovale and murmur one in each.

The observed 6 structural abnormalities (6/27,22.2%) were derivative 9 in 2 cases (females); deletion in the long arm of 11(male), derivative 14 (female), Robertsonian translocation between chromosome 14 and 21 leading to translocation Down's syndrome (male) and ring 18 in mosaicism (female) in one each. Among them, 2 were male probands and 4 were female probands.

The parental origin of the structural chromosomal anomalies were detected in 3, 2 from the father with the karyotypes 46,XY,t(2;9)(p23;p23) and 46,XYt(3;14)(q25;p10) and one from the mother [(46,XX,t(9;21)(q22;q22)] resulting in derivative 9s in 2 patients and derivative 14 in one.

Down's Syndrome

In Table 2 is given the observed phenotype and karyotype in the probands with Down's (Figs. 1 and 2). Probands have manifested the typical features.

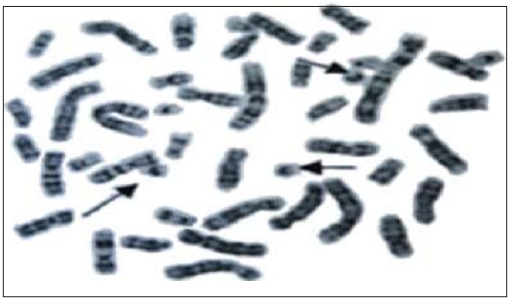

Fig. 1. Metaphase spread. Trisomy 21, Down Syndrome. Arrows indicate the three 21s

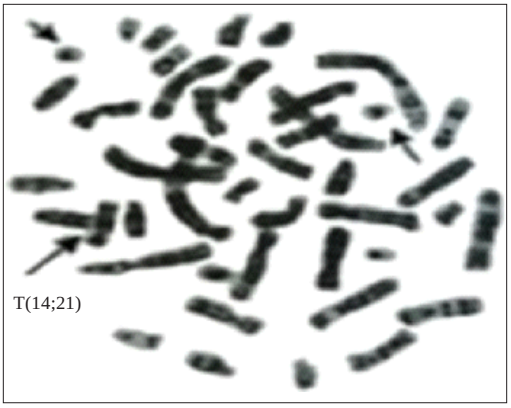

Fig. 2. Metaphase spread. Translocation, Down syndome Arrows indicate the 14:21 and 21s

Trisomy 13: 47,XX+13

A female 3-month-old was born premature to non-consanguinous parents. Features included frontal prominence of skull with bitemporal narrowing, metopic suture, microcephaly, high forehead, micropthalmos, hypertelorism, sparse eyebrows, bilateral coloboma, proptosis, depressed nasal bridge, antiverted nostrils, abnormal helices, low set ears, high arched palate, micrognathia, midfacial hypoplasia, cleft lip/palate, short neck, hypoplastic nipples, bilateral Simian crease, broad big toes, bilateral polydactyly, wide space between 5th and 6th toes, dextrocardia, umbilical hernia, polycystic kidney, anteriorly spaced anus, hypotonia, cerebral atrophy, and sacral dimple. The parents' karyotypes were normal (Fig. 3).

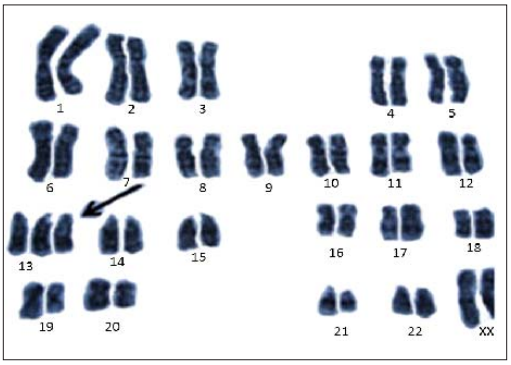

Fig. 3. 47,XX+13. Trisomy 13. Arrow indicates the three 13s

Table 2: Down syndrome: Phenotype: 18 cases

Features	*Serial no. of patients*						
	1	*2*	*3*	*4*	*5*	*6*	*7*
Age	*8 months*	*4 years*	*8 months*	*1 year 10 months*	*15 days*	*7 months*	*9 months*
Sex	*F*	*F*	*F*	*M*	*M*	*F*	*M*
Maternal age	42	19	28	23	29	18	30
Paternal age	52	27	31	32	34	26	33
Age difference	10	8	3	9	5	8	3
Birth order	6	1	4	1	2	1	1
Family history	-	-	-	-	-	-	-
Consanguinity	-	-	-	-	-	-	-
Mental retardation	+	+	+	+	+	+	+
Epicanthic fold	+	-	+	+	+	+	+
Slant	+	+	+	+	+	+	+
Hypertelorism	+	+	+	+	+	+	+
Flat nasal bridege	+	-	+	+	+	+	+
Protruding tongue	+	-	+	-	-	-	-
Low set ears	-	+	-	+	-	+	-
Clinodactyly	-	+	-	+	-	+	+
Simian Crease	+	-	+	+	+	+	-
CHD	VSD/CMV	murmur	VSD	VSD	PFO	PDA	murmur
Karyotype	47,XX+21	47,XX+21	47,XX+21	47,XY+21	47,XY+21	47,XX+21	47,XY+21

Features	*Serial no. of patients*						
	8	*9*	*10*	*11*	*12*	*13*	*14*
Age/Sex	*2 years/F*	*4 months/F*	*1 year/F*	*2 years/M*	*13 days/F*	*3 years/M*	*2 years 6 months/F*
Maternal/ Paternal ages	22/25	35/48	21/30	21.29	23/28	24/32	20/32
Birth order	3	3	1	1	2	1	1
Mental retardation	+	+	+	+	+	+	+
Epicanthic fold	+	+	+	+	+	+	+
Slant	+	+	+	+	+	+	+
Hypertelorism	+	+	+	+	+	+	+
Flat nasal bridge	+	+	+	+	+	+	+
Protruding tongue	-	-	-	+	-	-	-
Low set ears	-	+	-	-	-	-	-
Clinodactyly	-	+	-	-	+	+	+
Simian crease	+	+	+	+	-	+	+
CHD	VSD	AVSD	murmur	AVSD	ASD	VSD	ASD
Karyotype	47,XX+21	47,XX+21	47,XX+21	47,XY+21	47,XX+21	47,XY+21	47,XY+21

Features	*Serial no. of patients*				
	15	*16*	*17*	*18*	*19*
Age/Sex	*2months20days/F*	*9months/F*	*45days/M*	*9months/M*	*6months/M*
Maternal/ Paternal ages	31/37	18/27	31/39	18/24	18/27
Birth order	2	1	2	1	1
Mental retardation	+	+	+	+	+
Epicanthic fold	+	+	-	-+	-
Upward slanteyes	+	+	+	+	+
Hypertelorism	+	+	+	+	+
Flat nasal bridge	+	+	+	+	+
Protruding tongue	-	-	-	-	-
Low set ears	+	-	-	-	-
Clinodactyly	-	+	-	+	+
Simian crease	-	+	-	+	-
Distance between 1st and 2nd toes	+	-	-	-	-
CHD	AVSD	VSD	VSD	ASD	AVSD
Karyotype	47,XX+21	47,XX+21	47,XY+21	47,XY+21	46.XY.t(14;21)

Turner Syndrome

In Table 3 is given the observed phenotype and karyotype in the probands with Turner (Fig. 4) syndrome. Probands have manifested the typical features.

Table 3: Turner syndrome: Phenotype: 2 cases

Features	*Serial no.*	
	1	*2*
Age	6months	8 1/2 years
Birth order	1	1
Consanguinity	+	+
Presenting complaint	Short stature	Short stature
Lymphadema at birth	No	Yes
Webbed neck	-	+
CHD	CoA and bicuspid aortic valve	CoA
Cubitus valgus	-	+
Digital abnormalities	-	Clinodactyly
External genitalia	Normal	Normal
Karyotype	45,X	45,X

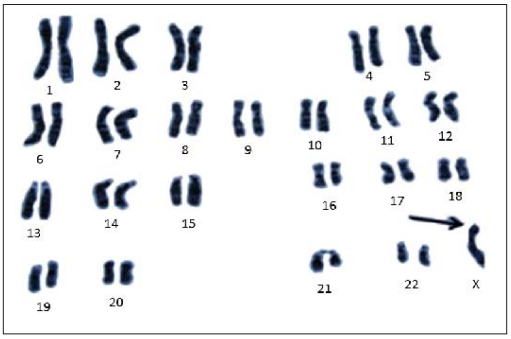

Fig. 4. 45, X. Arrow indicates the single X

Derivative 9: 46,XX,der(9)(9qter->9p23::2p22->2pter)

A proband, female, 10-month-old was born to non-consanguinous parents and had respiratory distress at birth and was kept in an incubator for 7 days. Features included metopic suture, high forehead, hypertelorism, dacrocystitis, strabismus, depressed nasal bridge, antiverted nostrils, tethered tip, open mouth, protruding tongue, high arched palate, mictognathia, wide set hypoplastic nipples, bilateral post axial polydactyly, bilateral Simian crease, long toes, patent ductus arteriosus, hepatosplenomegaly, clitoris and labia minora absent, hypotonia, 3 episodes of unconsciousness with loss of body tone, poorly defined parietal seizures, reduced T4 hormone levels, and mental retardation. The mother's and paternal grandparents' karyotypes were normal. The father and the elder sister were translocation carriers for 2 and 9: 46,XY,t(2;9)(p22;p23). (Fig. 5).

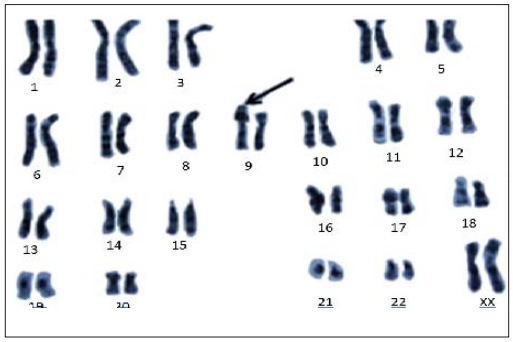

Fig. 5. 46, XX, der (9). Arrow indicates the der (9) (9 qter →9q23::2p22 →2 pter). Paternal in origin

Derivative 14:46,XX,der(14)(14qter->14p10::3q25-> 3qter)

A 4-month-old female baby, the 3rd child, was born to non-consanguinous parents. Features included bitemporal narrowing, slight frontal bossing, metopic suture, trigonocephaly, triangular face, micropthalmia of right eye, megalocornea of left eye, continuous watering, thick and convergent eyebrows, small nose, broad and depressed nasal bridge, antiverted nostrils, carp shaped mouth, cleft soft palate, micrognathia, smaller right ear, barrel chest, widely spaced hypoplastic nipples, bilateral clinodacytly, bilateral Simian crease, slight spasticity, rocker bottom feet, frequent respiratory tract infections, VSD, anteriorly placed anus, sacral dimple, hypoplastic genitalia, hypotonia, head control not attained, and reduced T4 hormone levels. The mother's and the brother's karyotypes were normal. The father was a translocation carrier for 3 and 14:46,XY,t(13;14)(q25;p10) (Fig. 6).

Deletion 11q: 46,XY,del(11)(pter->q23)(del 11q23->qter)

A 7-month-old male proband was born to non-consanguinous parents with breech presentation and LSCS delivery. Features included trigonocephaly, shallow orbits, temporal flattening, flat maxilla, divergent squint, broad nasal bridge, antiverted nostrils, bow shaped upper lip jutting out and overlapping the lower lip, microg-

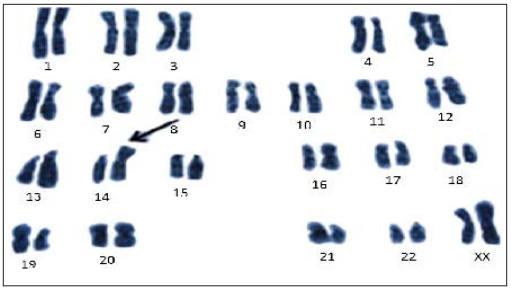

Fig. 6. 46, XX, der (14). Arrow indicates the der (14) (14 qter →14p10::3q25 →3 qter). Paternal in origin

nathia, dysplatic low set ears, left ear lobe folded up, short neck, widely spaced nipples, bilateral Simian crease, conical fingers, right hand middle finger camptodactyly at 1st interphalangeal joint, left hand middle/ring/little fingers camptodactyly, contracture of 3rd and 4th fingers, ulnar deviation, bilateral long 1st toe and 2nd/3rd/4th toes all same length, ASD. The parents' karyotypes were normal (Fig. 7).

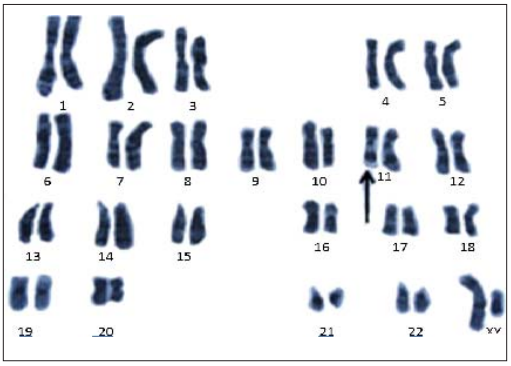

Fig. 7. 46, XX, der (11q). Arrow indicates the del (11) (11 q23 →11qter)

Ring 18:46,XX,r(18)(56%)/46,XX(44%)

A proband 3-year-old female was born to non-consanguinous parents. Features included bitemporal narrowing, frontal prominence, small forehead, microcephaly, epicanthic folds, hypertelorism, nystagmus, broad nasal bridge, antiverted nostrils, short philtrum, absent columella, slight clefting at angles of the mouth, micrognathia, mid facial hypoplasia, posteriorly rotated low set ears, upper lobe of helix folded, antihelix plain, short webbed neck, widely spaced hypoplastic nipples, conical fingers, bilateral clinodactyly, and hypotonia, ASD. The parents' and two siblings' karyotypes were normal (Fig. 8).

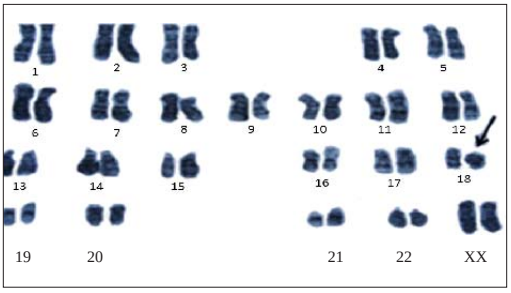

Fig. 8. 46, XX, r (18). Arrow indicates ring 18

Derivative 9: 46,XX,-21,+der (9)(9pter->9q22::21q22->21qter)

An 11-month-old female baby, the 1st child, was born to non-consanguinous parents. Features included p remature at birth, intra uterine growth disorder, oligohydramnios, respiratory distress, neonatal septicemia, small foregead, bitemporal narrowing, small face, microcephaly, right eye samller, epicanthic folds, depressed broad nasal bridge, antiverted nostrils, small mouth, thin lips, high arched narrow palate, micrognathia, posteriorly rotated low set ears, hypoplastic nipples, bilateral Simian crease, contracture at birth elbow/wrist/fingers/knee, bilateral small toes, 2nd and 3rd toes syndactyly, hypoplastic genitalia, anteriorly placed anus, cervical kyphosis, congenital displacement of hip, sacral dimple, ASD, hypertonia, and bihemispheric slow wave disturbance with rare left frontal sharp discharge. The mother was the carrier for the translocation between 9 and 21 (46,XX,t(9;21)(q22;q22) and the father's karyotype was normal (Fig. 9).

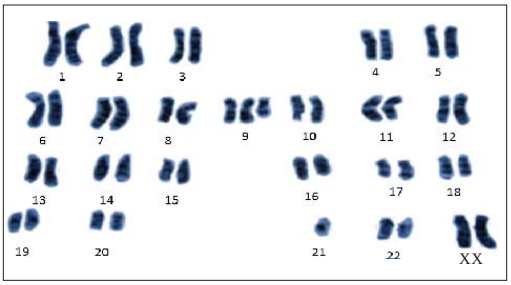

Fig. 9. 47, XX, +der (9). Arrow indicates der (9) (9 pter →9q22::21q22 →21 qter). Maternal in origin

DISCUSSION

CHDs are among the most common anomalies associated with chromosomal abnormality. These two issues could be often a part of the recognizable syndromes like Patau syndrome (trisomy 13), Down's syndrome (trisomy 21), and Turner syndrome (X monosomy). Chromosomal abnormality could be numerical or structural. Numerical abnormality includes aneuploidy, which refers to monosomy or trisomy of the sex chromosomes and the autosomes. The commonly observed autosomal trisomies in CHDs are the trisomy 13, 18 and 21 (Paladini et al. 1993). It is estimated that ten percent of Turner syndrome patients may have clinically evident heart defects. Included in the structural abnormality is the break/exchange/rejoin phenomenon resulting in genetic balance as in translocation or genetic imbalance as in deletion and duplication, resulting in partial trisomy or monosomy for the involved chromosomes. The extensively studied one is the deletion in the long arm of chromosome 22 (22qdel) and its prevalence in CHDs. Moreover, the well known association of atrioventricular defects in Down's syndrome and coarctation of aorta in Turner syndrome indicate that there may be specific genes on chromosomes such as 21, 22 and X predisposing to particular types of CHDs.

In literature, it is reported that the incidence of the chromosomal abnormality in CHDs ranges from 5.51 to 12.9 percent (Ferencz et al. 1985) (Table 1). In CHDs, it is the numerical chromosomal abnormalities, which constitute the majority of the chromosomal abnormality. In the present study, 41.5 percent (n 27/65) had chromosomal abnormalities. Twenty-one cases had (21/27, 77.8%) numerical abnormality, out of which 2 (9.5%) were X monosomy, one (4.7%) was trisomy 13 and 18 (85.8%) were trisomy 21.

It is reported that autosomal trisomy is the most common abnormality in CHDs (Nora et al. 1991) and in the present paper, similar findings (trisomy 21 in 18, trisomy 13 in one) (19/21, 90.5%) have been observed.

From the review, it is seen that the incidence of CHDs is similar for all major ethnic groups (Mitchell et al. 1971) and for males and females (Richards et al. 1955), although a differential sex ratio for certain types of CHDs may exist. In this paper, the prevalence is seen for female probands (18/27, 66.6%) with chromosomal abnormality. Out of which, numerical was seen in 14 female probands with 47,XX,+21 (n11), 47, XX+13 (n1, female) and 45,X (n 2) karyotypes and structural in 4 (derivative 9 in 2; derivative 14 in one, ring 18 mosaicism in one).

The reasons may be because of the types of CHDs and the trisomy 21 condition, where in female conceptions might have survived.

Patau Syndrome

Nearly eighty percent may have CHDs. In the present paper, except for the prosencephaly, the female proband has manifested most of the features cited in the literature and the CHD was dextrocardia (Table 4).

Table 4 : Review-Trisomy 13

Trisomy 13 Features	*Jones 1997*	*Present study 2003*
Microcephaly	>50%	+
Holoprosencephaly	>50%	?
Deafness	>50%	+
Micropthalmos	>50%	+
Colobomata	>50%	+
Cleft lip/palate	60-80%	+
Abnormal helices	>50%	+
Low set ears	>50%	+
Simian crease	>50%	+
Polydactyly	+	+
CHD	80%	Dextrocardia
Umbilical hernia	>50%	+
Polycystic kidney	31%	+

Down's Syndrome

Down's syndrome is known as the most common numerical autosomal chromosomal abnormality in live births. Based on the karyotype, Down's syndrome is classified as free trisomy 21, translocation and mosaicism. It is reported that five percent of CHDs are accounted by trisomy 21 and forty percent of Down's syndrome may have CHDs, out of which fifty percent may have AVSD (Holtzmen and Epstein 1992). It is stated that in Down's syndrome, the frequently seen CHDs are AVSD, isolated VSD, secundum ASD and patent ductus arteriosus (Tolmie 2002). It is also reported that the commonly observed CHDs in Down's syndrome are the VSD followed by ASD and AVSD. It is reported that although fifty-six percent of Down's syndrome infants may have AVSD, only thirteen percent of those over

one year have an AVSD, and it is due to a high mortality in the 1st year of life in Down's syndrome (Shaher et al. 1972).

In the present paper, Down's syndrome karyotype was detected in 19 patients (90.55), out of which 18 were trisomy 21 and one was translocation Down's syndrome. These individuals had the typical phenotype in addition to the CHDs. All probands have manifested the typical phenotype. VSD was detected in 7 (7/19) (4 female and 3 male), followed by ASD (4/19, 2 female and 2 male), AVSD (4/19, 2 female and 2 male), systolic murmur (3/19, 2 female and one male), patent foramen ovale in one male and patent ductus arteriosus in one female. Three patients with AVSD were under one year, while one was over one year of age.

Turner Syndrome

Both female patients had coarctation of the aorta, the frequently reported CHD in Turner syndrome (Van der Hauwart et al. 1978). A parent of origin effect has been reported between Turner syndrome and CHDs and patients with maternally derived X are more likely to have CHD.

Structural Chromosomal Abnormalities

These have been detected in 0.4 percent of cases with CHDs (Roskes et al. 1990) and the chromosomes involved may be 1, 3, 7, 8, 9, 10, 11, 15 and 18. Investigations have also reported the involvement of chromosomes 2, 4, 6, 8, 12, 13, 14, 15, 21, 22 and Y (Johnson et al. 1997). From literature, it is seen that the involved chromosomal regions in CHDs may be 1q, 3p, 3q, 4p, 4q, 6p, 7q, 8p, 8q, 10q, 11q, 17p, 22p and 22q (Van Karneebeek and Hennekam 1999). In the present study, the structural chromosomal abnormality has occurred in 6 cases with CHDs (9.23%). The involved chromosomes in the present study are 2, 3, 9, 11, 14, 18 and 21 as reported in literature and the chromosomal regions involved are 2p, 3q, 9p, 9q, 11q, 14p, 18p, 18q and 21q. In the paper, the chromosomal regions differed for 2 (2p), 9(9p,9q), 14(14p), 18 (ring between 18p and 18q) and 21 (21q).

Derivative 9

1st Case: More than 50 cases with trisomy 2 have been reported (Lurie 1995) with the majority resulting from family rearrangements. The 2p trisomy arrangements involving other chromosomes include 3, 4, 5, 6, 7, 11, 14, 15, 16, 17, 18, 21 and X. But in the paper, the involved chromosome with 2 was 9 and the partial trisomy for the short arm of 2 (2p) and the monosomy for the short arm of 9 (9p) are due to the inheritance from the father who had the balanced translocation rearrangement between 2 and 9. The proband has manifested most of the phenotype described in literature for the partial trisomy in the short arm of 2 (2p) or the monosomy in 9p. The presence of the bilateral postaxial polydactyly in the patient has been described only once as an unusual finding (Hahm et al. 1999). Hepatosplenomegaly observed in the proband has not been noted either for the partial trisomy 2p or monosomy 9p. Likewise, the trisomy for the 2p regions 2p22->pter in association with 9 has not been reported nor the paternal translocation 2 and 9 in these breakpoints (Table 5).

Table 5: Review- Derivative 9: 1st case

Derivative 9: Partial Trisomy 2p23->pter features	*de Grouchy and Turleau 1984*	*Present study 2003*	*Partial monosomy 9p23->pter features*	*de Grouchy and Turleau 1984*	*Present study 2003*
Metopic suture	+	+	-	-	-
Hypertelorism	+	+	-	-	-
Flat nasal bridge with antiverted nostrils	+	+	Flat nasal bridge with antiverted nostrils	+	+
Prominent nasal tip	+	+	-	-	-
Strabismus	+	-	-	-	-
Eye anomalies	+	+	-	-	-
Long toes	+	+	Long toes	+	+
Genital hypoplasia	+	+	Genital hypoplasia	+	+
Hypotonia	+	+	-	-	-
Mental retardation	+	+	Mental retardation	+	+
Hepatosplenomegaly	-	+	Hepatosplenomegaly	-	+
CHD	+	PDA	CHD	+	PDA

Derivative 14

In the present study, the proband showed partial trisomy for the long arm of 3 (3q25 -> qter) and she has manifested the characteristic clinical appearance of the partial trisomy 3q. The phenotype is similar to Cornelia de Lange syndrome, which has been localized to 3q26.1 (Ireland et al. 1991) and hence overlaps the trisomy 3q region. For the 3q duplication, the region considered as essential is 3q26.3 -> q27.3 (Aqua et al. 1995). The segment lost in the partial monosomy in 14p10->pter is not that significant in the phenotype, since it is involved only in nucleolar organizing regions. In the proband, the critical region is present in 3 copies. In those cases with partial trisomy 3q, seventy five percent are due to parental rearrangement of the chromosomes. In the present study, the partial trisomy 3q is paternal in origin because the father had the translocation 3; 14 (Table 6).

Table 6: Review- Derivative 14

Derivative 14: Partial trisomy 3q25-qpter features	*de Grouchy and Turleau 1984*	*Present study 2003*
Abnormal shape of skull	+	+
Thick and convergent eyebrows	+	+
Hypertelorism	+	-
Depressed nasal bridge and anteverted nostrils	+	+
Down turned mouth with thin upper lip	+	+
Retromicrognathia	+	+
Cleft palate	+	+
Clinodactyly	+	+
CHD	+	VSD
Genitalia	No ovaries Bifid vagina	Hypoplastic
Spine	Coccygean dimple	Sacral dimple

Deletion 11q

Several articles have reported 11q deletion in CHD. Deletion is usually from 11q13->qter including the critical region at 11q24, which is involved in 11q deletion syndrome. Moreover, the 11q deletion syndrome is observed to be prevalent in females. 11q deletion was observed in the male proband who had manifested nearly sixty percent of the phenotype of the 11q deletion (Table 7).

Table 7: Review-Deletion 11q

Deletion 11q features	*de Grouchy and Turleau 1984*	*Present study 2003*
IUGR	76%	-
Mental retardation	100%	+
Hypotonia	+	-
Trigonocephaly	90%	+
Microcephaly	40%	-
Epicanthic folds	60%	+
Hypertelorism	70%	-
Ptosis	67%	-
Strabismus	75%	?
Flat nasal bridge	93%	?
Large carp mouth	78%	+
Micrognathia	77.7%	+
Low set malformed ears	85%	+
Contracture of joints	65%	+
CHD	60%	ASD

Ring 18

It is mostly de novo in origin and in 1/10th of the cases mosaicism for the ring formation in 18 seems to be present. The ring formation is between the short and long arms of 18 resulting in loss in both its arms. In the proband, ring 18 was in mosaic status and the features expressed correlated with that of 18q deletion (Thesis et al. 1998) (Table 8).

Table 8: Review-ring 18 mosaicism

ring 18 features	*de Grouchy and Turleau 1984*	*Present study 2003*
Microcephaly	2/3	+
Facial dysmorphism	+	+
Carp like mouth	+	+
Hypertelorism	+	+
Epicanthic folds	+	+
Ocular malformation	25-33%	nystagmus
Micropthalmos	+	+
Folded ears	++	+
High arched palate	+	-
Short neck	+	+
Pterigium coli	+	+
Micromelia	+	+
Clinodactyly	+	-
Abnormal external genitalia	+	+
CHD	20%	ASD
Mosaic status of ring 18	10%	+
De novo status of ring 18	mostly	+

Derivative 9: 2nd Case

Mother of the proband is a translocation carrier with balanced genotype and normal phe-

notype. On review it was seen that patients with a complete or near complete trisomy 9 exhibited a pattern of malformation more severe than those seen in patients with trisomy 9p syndrome. The proband has expressed the features of partial trisomy 9 as well as that of monosomy 21 (Table 9).

The observed differences may be because of the sample size or sample selection or mortality (population, all births, live births, stillbirths, abortions) since in the present study, the patients with CHDs only have been selected, which has led to the ascertainment bias.

Interpretation

The meiotic mechanism behind the formation of the monosomy and trisomy are because of the non-disjunction phenomenon at the time of the parental gametogeneis. The process involves either loss or gain of the chromosomes, due to the irregularity in the separation of the paired parental chromosomes, during gametogenesis. The other mechanism is the anaphase lag of the chromosomes, which occurs after the formation of the normal zygote and in the early cleavage stages of the normal zygote. In eighty percent of Turner syndrome patients, the X monosomy is because of the anaphase lag of the paternal X before implantation. Whatever are the mechanisms, the loss or gain of the chromosomal segments and the genes and their transcribed products from the chromosomes are directly or indirectly associated to the CHDs.

In Down's syndrome, the critical region is located to the long arm of chromosome 21 at 21q22. The genes responsible for AVSD or CHDs may be in the 6.63 Mb segment of DNA in 21q and in that Col6A1 gene is attracting the research interest, since the contribution from the disjoining parent may be a determinant of the CHDs in Down's syndrome. In Turner syndrome, the loss of the paternal X suggests that the genes on paternal X may be important in the normal development of the aorta. In Patau syndrome, the 3 copies of the 13s may be involved in expressing the CHDs. Whether trisomy 13 or 21, the genetic products become 1.5 times greater and in X monosomy, it is 0.5 times lesser than the normal diploid cells with 46 chromosomes.

Derivative 9

It is detected in two female patients. In the 1st case, in the female proband, the karyotype was 46,XX,der(9)(9qter-> 9p23::2p22->2pter). The

Table 9: Review- Derivative 9: 2nd case

Partial trisomy 9 features	*Present study 2003*
Microcephaly	+
Retromicrognathia	Micrognathia
Low set and protuberant ears	Low set ears
Osteoarticular anomalies	+
Dislocation of the hips	+
Deformities of the spine	Cervical kyphosis
CHD	ASD
Cerebral anomalies	Abnormal EEG
Mental retardation	+
Simian crease	+
and	

Monosomy 21 features (Huret et al. 1995)	*Partial/Complete monosomy*	*Present study 2003*
Mental delay	93%/100%	+
Hypertonia	88.9%/57%	+
Forehead	High/narrow/receding	narrow
Micropthalmos	33%/42.8%	+
Epicanthus	50%/75%	+
Anteverted nostrils	50%/66%	+
Microretrognathia	100%	=
Low set ears	62.5%/89%	+
Simian crease	83.3%/50%	+
Arthrogryposis	100%	+
Ambiguous genitalia	50%/100%	+
CHD	77.8%/71/5%	ASD

father of the proband had the translocation 2; 9 with break, exchange and rejoin without any obvious genetic or phenotypic imbalance and the break has occurred in chromosomal regions at 2p22 and at 9p23. For the father, the translocation seemed to have occurred 'de novo' in status. In the proband, the chromosomes 2's are normally derived one each from the mother and the father, but the chromosome 9 derived from the father is the translocation 9 with chromosome 2. In the proband, the derivative 9 had chromosome 9's regions from the tip of its long arm (9qter) to region 23 in its short arm (9p23), thereafter it was chromosome 2 from its short arm region 2p22 to the tip of its short arm 2pter. Proband, hence had partial trisomy for the short arm of 2 (p22->pter) and monosomy for the short arm of 9 (9p23 to 9pter). Here, trisomy for the genes on the short arm of 2 for the regions 2p22 to 2pter may have given rise to more genetic products from 2 and less products for the chromosome 9's short arm of 9p23 to 9pter.

In the 2nd case, in the female proband, the karyotpye is 46,XX,der(9)(9pter -> 9q22::21q22-> 21qter). The mother was found to be the translocation carrier 9; 21 with break, exchange and rejoin without any obvious imbalance in her genotype and phenotype. Chromosome 9 is present as 3 copies and 21 as one copy. Chromosome 21 and one of the normal 9s have come from the father. Another normal 9 and the derivative 9 have come from the mother. Derivative 9 is present from it 9pter region to 9q22 regions followed by 21 from 21q22 region to 21qter, resulting in partial trisomy for the 9 and monosomy for the 21.

Derivative 14

It had the karyotype in the female proband as 46,XX,der(14)(14qter -> 14p10::3p25 -3pter) and it was because of the paternal transmission who had balanced translocation 3;14 between the regions 3q25 and 14p10 without any obvious abnormality in phenotype. The proband had 2 normal chromosomes, 3 derived normally from both the parents and one normal 14 from the mother. The derivative 14 is present from 14qter to 14 p10 and continued with 3q25 to 3qter. Because of which proband has partial trisomy for the long arm of 3 and monosomy for the short arm of 14. Proband has expressed trisomy 3q features since the genes in the 14 p are involved in the formation of nucleoli.

11q Deletion

The female proband with deletion 11 in 'de novo' status had loss of the regions between its long arm 11q23 to 11qter and the karyotype was 46,XY,del(11)(q23). Parents had normal karyotype.

Ring 18

It was in mosaicism status with the karyotype 46,XX,r(18)(56%)/ 46,XX (44%). The ring formation occurred 'de novo' in the proband with break and joint between its long and short arms. The genes near the terminal regions of the short and long arms are supposed to be very active in the expression of the genetic products. The proband has partial monosomy for the 18p and 18q regions. She has manifested with 18q deletion features.

In those cases with parental origin, the recurrence risk becomes high because of the meiotic mechanisms. For example, in the mother and father with translocation, at the time of parental gametogenesis, they could give rise to normal gamete with normal chromosomes or gamete with translocation chromosome or to gametes with unbalanced chromosomes. The first category gives rise to normal zygote, the 2nd category to zygote with translocation as in the parents and the 3rd category to zygotes with unbalanced chromosomal segments resulting in monosomy or trisomy status and if born as live births with congenital malformations including CHDs.

The exact relationship between chromosomal abnormality and the formation of CHDs is not yet known. However, the complex critical steps in the development of the heart and the great vessels suggest that numerous genes may be involved. Understanding the pathogenesis of CHDs will continue to evolve as recurrence risks in relatives are redefined and chromosomal abnormalities associated with CHDs become mapped and understood better at the DNA level.

In the present study, it may be noted that the involved chromosomes (2, 3, 9, 11, 14, 18, 21) especially chromosome 21 (20 times; trisomy 21 in 18, translocation 21 and as part of derivative 9 one in each) that may be considered for the as-

sociation between the genes/chromosomes and CHDs. Moreover, female probands (18/27, 66.7%) were associated with chromosome abnormalities and CHDs.

Genetic Counseling

Genetic counseling is a communication process extending from a period of a few hours to years. The messages conveyed to the families with affected individuals are the diagnosis and prognosis and management. The patients' families were referred to Cardiology for appropriate medical management and treatment. At the Division of Human Genetics, the families were counseled regarding the recurrence risk of the chromosomal abnormality especially to the parents with translocation carrier status and information on prenatal diagnosis,

CONCLUSION

Sixty-five patients with CHDs were referred for karyotyping and counseling. There were 33 male and 32 female probands. Chromosomal abnormalities were detected in 27 (41.5%) and 38 had a normal karyotype. Numerical chromosomal abnormality was found in 21 (77.8%) and the structural in 6 (22.2%). Numerical chromosomal abnormality was seen in 14 female and 7 male and the structural in 4 female and 2 male probands. Karyotype was normal in the rest of the 24 male and 14 female probands.

It was found that chromosomal abnormality was associated with CHDs and the association could be found between the female probands and chromosome 21 and CHDs.

RECOMMENDATION AND FUTURE RESEARCH STUDY

Molecular analysis may highlight the localized genes especially in those cases with chromosomal abnormality.

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