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Human Population Cytogenetics: A Review*

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ABSTRACT Population cytogenetics is the study of the incidence of major and minor chromosomal aberrations in a rather random-sample of a population. The main aim of such type of studies had been to estimate the incidence of various chromosomal anomalies, their causation and the selective forces operating on persons with these anomalies. It is also stressed to study of different populations having contracts with environmental chromosome damaging agents, both mutagenic chemicals and irradiation effects (Court-Brown 1967). Quantitative karyotype term was assigned to the type of study in which observations of chromosomal anomalies and variant among normal healthy individuals were reported (Lubs and Ruddle 1970). Studies on human chromosomes had revealed that there was a great deal of polymorphism with certain pairs of complement. The variation in human chromosome can be divided in two parts: (i) Major and cryptic aberrations which are associated with developmental malformation and reproductive wastages and (ii) Variations which seem not have phenotypic disadvantage. In the present study an attempt has been made to review the incidence of both of them investigated in various human populations.

1. INTRODUCTION

Since the development of human cytogenetics and the discovery of different syndromes with chromosomal aberrations, the main emphasis in various cytogenetic laboratories had been to study persons with abnormal karyotypes rather selectively. The major criteria for such studies had to be phenotypic in expression, such as congenital abnormalities, clinical signs of established syndromes and institutionalized patients with lower intelligence quotient. The occurrences of some types of chromosome aberration were common in the population examined, but there is little knowledge of incidence of these in human population. Court-Brown (1967) coined the term 'Population Cytogenetics' for the study of the incidence of major and minor chromosomal aberrations in a rather random-sample of a population. The main aim of such type of studies is to find out their causation and the selective forces operating on persons with these anomalies. Court-Brown (1967) also stressed the study of different populations having contacts with environmental chromosome damaging agents, both mutagenic chemicals and irradiation effects.

Observations of chromosomal anomalies and variants among normal healthy individuals were reported by Lubs and Ruddle (1970) who assigned the term 'Quantitative Karyotype' for this type of study. Since then, several reports have been published providing quantitative data about the variability of human karyotype in normal adult and newborn populations.

The term 'variant' has been recommended for use in situations where deviations from the norm of chromosome morphology are observed (Paris Conference 1971) whereas in a supplement of the Paris Conference (1975) the term 'heteromorphic' has been recommended to describe the chromosomes with variable bands. With the advent of new banding techniques, a more specific and detailed characterization of the already known variants, as well as new variants has become much easier (Caspersson et al. 1971; Craig-Holmes and Shaw 1971; Evans et al. 1971; Schnedl 1971a; Bhasin and Singh 1978; Wyandt and Tonk 2004).

Studies on human chromosomes had revealed that there was a great deals of polymorphism with certain pairs of complement; in particular pairs 1,9 and 16 along with the distal part of the long arm of the Y chromosome and D and G group chromosomes (Cohen et al. 1966; Craig-Holmes and Shaw 1971; Lubs and Ruddle 1971). The five pairs of human acrocentric chromosomes are of interest for at least the following four reasons:

(a) the short arms are involved in association between themselves and with the secondary constriction sites of the nonacrocentric chromosomes of the complement (Ferguson-Smith and Handmaker 1961, 1963; Shaw 1961).

(b) They show heteromorphism for all three arm regions

(i) the short arms proper,

(ii) the satellite stalks, and

*In loving memory of my guide, colleague and friend **Prof. Dr. W. Fuhrmann** (Institute for Human Genetics, der Justus-Liebig-University Giessen, D-35 392, Giessen, Germany)

(iii) the satellites themselves (Paris Conference 1971)

(c) the short arms are the location for the genes coding for 18S and 28S ribosomal RNA, and the human is highly polymorphic with respect to a number of such genes (Henderson et al. 1972; Evans et al. 1974a) and

(d) the proximal regions of acrocentric chromosomes are the sites of breakage and exchange in the formation of Robertsonian translocations, the most frequent structural rearrangement in man (Jacobs et al. 1974a).

Heteromorphic regions consist of constitutive heterochromatin[1] and are known to contain varying amounts of different classes of highly redundant DNA. In view of the repetitious DNA that is present, as well as other characteristics, this constitutive heterochromatin[1] is believed to contain no structural genes. But a possible relationship with the control and functioning of the organization of the nucleolus, the cell's machinery to produce ribosomal DNA, evolutionary change, attracting homologues at meiosis, providing raw material for new genes, acting as gene spacers and loci for recombination and as an 'absorbent' for mutagens, carcinogens, clastogens etc., that constantly bombard the cell, lends significance to the variability of these regions (Walker 1971; Yunis and Yasmineh 1971; Cooper 1975; Hsu 1975).

Reviews by Jacobs (1977 a,b), Lubs (1977), Bhasin et al. (1978), Verma and Dosik (1980), an edited volume by Wyandt and Tonk (2004) and on heteromorphisms have presented their occurrence, distribution, nature, clinical significance and applications. Heteromorphisms have been shown to be very useful for the identification of individual chromosomes, cells and individuals. They have been frequently used in linkage studies for assignment of gene loci, in establishing paternity to distinguish zygosity, as well as maternal and foetal cells in amniotic cultures and in tracing the origin of extra chromosome in trisomies and triploidies. Because of difference in frequencies among populations with respect to heteromorphisms the population studies could help in gaining precise knowledge of the selective forces maintaining these heteromorphisms.

More variations are identified with each new cytogenetic technique, but the sites involved in some of the techniques may essentially be the same. Most commonly, heteromorphisms have been studied by G- and R- banding techniques (Arrighi and Hsu 1971; Casperasson et al. 1971; Drets and Shaw 1971; Verma and Lubs 1975a, b). GAG banding was utilised for differential staining of various pairs of acrocentric chromosomes, thereby giving estimates of variation shown by individual pair of homologues. The same can be studied using QFG (Q-) and RFA (R-) banding procedures also, where, besides size variation, intensity variation, is also observed (Verma et al. 1977a, 1978b).

The C-banding technique is the best amongst the banding procedures of study the heteromorphisms of chromosomes 1,9,16 and Y, since it stains most of the heterochromatin[2] dark. Even though other chromosomes of the complement also contain centric heterochromatin and show variation, identification of the specific pairs of chromosomes is not possible with C-banding. Since good quality chromosomal spread with a clear band is a must for evaluation of chromosomal heteromorphisms (Lubs 1977; Jacobs 1977a), sequential staining of G- or Q- and C-banding is not always up to the mark. Cytochemical staining methods are also reported to locate in nucleolus organizing regions (NORs) of metaphase chromosomes viz., N-banding (Matsui and Sasaki 1973) and Silver (Ag-NOR) staining (Goodpastrue and Bloom 1975).

The variations in human chromosome can be subdivided in two parts: (I) Major variations which are associated with developmental malformation and reproductive wastages and (II) Minor variations which do not have any phenotypic disadvantage. This study has been divided into these two categories and the incidences of both to them reported in various human populations have been summarized respectively.

1.1 Major Variations in Human Chromosome Complement

Court-Brown (1967) reported that about one percent of all children born possess chromosomal abnormalities, of which 50 percent have structural rearrangement. Data were cumulated from MacLean et al. (1964) for sex chromosome aneuploidy, Penrose (1963) for Trisomy 21, Marden et al. (1964) for Trisomy 17/18 and Court-Brown et al. (1966) for structural rearrangement. After initiation of the above frequency studies of various major anomalies, a number of large newborn surveys have been done in respect of the genetic, clinical and social significance of chromosomal variation on the human population.

Seven major surveys have been reported on newborns for estimation of frequencies of major and minor variations in various human

populations. These are on 4353 newborns of New Haven (U.S.A.) by Lubs and Ruddle (1970a, b); 2081 Canadian newborns (Ontario) by Sergovich et al. (1969); 13151 Boston (U.S.A.) newborns by Walzer and Gerald (1972); 11680 Edinburgh (U.K.) newborns by Jacobs et al. (1974b), 2500 Russian newborns by Bochkov et al. (1974); 11148 Danish newborns by Nielsen and Sillesen (1975) and 13939 Canadian newborns by Hamerton et al. (1975). The incidence and percentages of various chromosomal abnormalities from the above seven surveys have been compiled in Table 1 & 2. Nielsen and Wohlert (1991) reported chromosome abnormalities found among 17872 boys liveborn and 17038 newborn girls (34910 newborn children), this study included 11148 newborns reported earlier listed in the Tables 1, 2 (Nielsen and Sillesen 1975).

Table 1: Frequencies of chromosomal anomalies in various newborn populations

Chromosome anomalies	*Population and Authors*															
	New Heaven Lubs & Ruddle (1970) Total = 4353		*Conadian Sergovich et al. (1969) Total = 2081*		*Boston, Walzer & Gerald (1977) Total = 13751*		*Edinburgh Jacobs et al. (1974) Total = 11680*		*Danish Nielsen & Sillesen (1975) Total = 11148**		*Canadian Hamerton et al. (1975) Total = 13939*		*Canadian Lin et al. (1976) Total = 930*		*Russian Bochkov et al. (1974) Total = 2500*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Sex Chromosme Anomalies																
Males																
XYY	3	0.14	4	0.37	11	0.03	10	0.13	5	0.087	4	0.06	2	0.4	-	-
XXY	4	0.18	1	0.09	39	0.7	9	0.71	8	0.14	6	0.09	1	0.2	1	0.08
Others	-	-	-	-	-	0.09	5[b]	0.06	5	0.087	2	0.02[f]	-	-	6	0.18
Females																
XO	1	0.05	-	-	-	-	-	-	3	0.056	-	-	-	-	-	-
XXX	3	0.14	-	-	-	-	5	0.13	8	0.15	5	0.07	-	-	-	-
Others	-	-	-	-	-	-	2[e]	0.05	-	-	2	0.03	-	-	-	-
Autosomal Aneuploidy																
+ D 1	0.02	-	-	-	-	-	-	1	0.01	1	0.01	-	-	-	-	
+ E 1	0.02	-	-	-	-	2	0.02	1	0.01	3	0.02	-	-	-	-	
+ G 3	0.07	2	0.10		0.08	17	0.15	16	0.14	14	0.10	-	-	4	0.16	
Others	-	-	-	-	-	-	1[d]	0.01	6	0.05	-	-	-	-	2	0.68
Structural Rearrangements																
Balanced																
D/D	2	0.05	1	0.05	5	0.06	6	0.05	15	0.135	12	0.09	-	-	-	-
D/E	1	0.02	-	-	3	0.02	4	0.03	2	0.02	1	0.01	-	-	1	0.04
Reciprocal and Insertional Translocations	3	0.07	-	-	12	0.06	10	0.09	15	0.135	11	0.08	1	0.2	2	0.08
Inversions	-	-	-	-	7	0.02	2	0.02	-	-	1	0.01	-	-	-	-
Unbalanced																
Robertsonian translocations	-	-	1	0.05	-	-	1	0.01	-	-	-	-	-	-	-	-
Reciprocal translocations	-	-	1	0.05	-	-	1	0.01	6	0.05	1	0.01	-	-	-	-
Inversons	-	-	-	-	-	-	1	0.01	1	0.001	-	-	1	0.2	2	0.08
Deletions	-	-	1	0.05	2		-	-	1	0.001	-	-	-	-	1	0.04
Supernumery	-	-	-	-	5	0.04	1	0.01	-	-	-	-	-	-	-	-
Others	-	-	-	-	-	-	2[e]	0.02	-	-	2	0.01[g]	-	-	-	-
Total 22	0.50	10	0.48	84	0.46	78	0.67	93	0.834	65	0.46	5	0.54	19	0.76	

(a) 46,XY/47,XXY,46,XY(2) 46, XX 47, XXp- Y, 46, Xinv (Y) (6) Cases 46, XYq-
(b) 46,XX 46, XY/47,XYY, 45,X/46,XY/47,XYY,46 XY/47 XXY (c) 45, X/46, 45,X/46, XY
(d) 69, XXY (e) 46, XX/47, XX, +r, 46, XY/46, XY, 16q+
(f) 46, XY/47, XXX 45, X/46, XY/47, XYY (g) 46, XX/47,XX, + mar. 46, XX/47, XX, + mar

*Nielsen and Wohlert (1991): Liveborn boys = 17872 and liveborn girls = 17038 Total = 34910; Sex Chromosome abnormalities: *Klinefelter's syndrome*=30; *XYY syndrome*=20; *Triple X syndrome*=17; Turner's syndrome=8; other=3; Total=78 and *Autosome Chromosome Abnormalities:* +13=2;+18=7; +21=51; +8=1; +mar=24;+ring=1; Deletions=3; Duplications=3; 13/14=34; 14/21=7; 15/21=1; 15/22=1; Reciprocal translocation=50; inv (2)=8; inv (6)=3; inv (11)=1; fra (X)=1; Total=198 Sex Chromosomal and autosomal abnormalities=276).

Table 2: Number and percent of chromosome abnormalities in six newborn studies

Type of Abnormality	*Edinburgh[1] (U.K.)*	*Arhus[2,3] (Denmark)*	*London[4] (U.K.)*	*Winnipeg[5] (Canada)*	*Boston[6] (U.S.A.)*	*New Haven[7] (U.S.A.)*	*Total*
Sex chromosome-Males							
47,XYY	10(0.13)	3(0.05)	4(0.37)	4(0.06)	11(0.08)	3(0.14)	35(0.093)*
47,XXY	9(0.11)	6(0.10)	1(0.09)	6(0.09)	9(0.07)	4(0.18)	35(0.093)*
Others	5(0.06)[a]	9(0.16)[b]	-	2(0.02)[c]	12(0.09)[d]	-	28(0.074)*
*Sex chromosome—Females**							
45,X	-	1(.02)	-	-	-	1(0.05)	2(0.010)*
47,XXX	5(0.13)	7(0.13)	-	5(0.07)	-	3(0.14)	20(0.104)*
Other	2(0.05)[e]	3(0.06)[f]	-	2(0.03)[g]	-	-	7(0.037)*
Autosomal trisomies							
+D	-	1(0.01)	-	1(0.01)	-	1(0.02)	3(0.005)
+E	2(0.02)	1(0.01)	-	3(0.02)	-	1(0.02)	7(0.012)
+G	17(0.15)	16(0.14)	2(0.10)	14(0.10)	19(0.14)	3(0.07)	7(0.125)
Other	1(0.01)[h]	-	-	-	-	-	1(0.002)
Structural Rearrangements – Balanced							
Robertsonian translocations							
t(DqDq)	6(0.05)	14(0.13)	1(0.05)	12(0.09)	5(0.04)	2(0.05)	40(0.072)
t(DqGq)	4(0.03)	2(0.02)	-	1(0.01)	3(0.02)	1(0.02)	11(0.019)
Reciprocal and insertional translocations	10(0.09)	15(0.13)	-	11(0.08)	12(0.09)	3(0.07)	51(0.090)
Inversions	20(0.02)	1(0.01)	-	1(0.01)[u]	4(0.03)	-	8(0.014)
Structural Rearrangements – Unbalanced							
Robertsonian translocations	(1.01)	-	1(0.01)	-	2(0.01)	-	4(0.007)
Reciprocal and insertional translocations	-	6(0.05)[n]	-	1(0.01)[r]	-	-	7(0.012)
Inversions	1(0.01)[o]	-	-	-	-	-	1(0.002)
Deletions	-	2(0.02)[p]	1(0.01)[q]	-	2(0.01)[r]	-	5(0.009)
Supernumerary	1(0.01)	4(0.04)	-	-	5(0.04)	-	10(0.018)
Other	2(0.02)[j]	2(0.02)[k]	-	2(0.02)[m]	-	-	7(0.012)
Total abnormalities	78(0.67)	93(0.84)	10(0.48)	66(0.4)[v]	84(0.61)	22(0.50)	353(0.620)
Total newborns	11,680	11,148	2,081	13,939	13,751	4,353	56,952
Males	7,849	5,761	1,066	7,176	13,751	2,176	37,779
Females	3,831	5,387	1,015	6,763	—	2,177	19,173

*The rates for the sex chromosome abnormalities apply only to the affected sex, not the total studied.
[a]46XX, 46,XY/47,XYY. 45.X/46,XY/47XYY, 46XY/47,XXY, 46,XY/47/XXY [b]45,X/46,XY/47,XYY. 46,XY/47,XYY. 46,XY/47,XXY, 46,XY/47,XXY, 46,X,inv(Y). 46,X,inv(Y). 46,X,inv(Y). 46,X,inv(Y), [c]46,XY/47,XYY. 45,X/46,XY/47,XYY. [d]46XY/47,XYY. 46,XX 46,XY/47,XYY (2cases). 46,X,inv(Y) 6 cases, 46,XYq-. 47,XXp-Y. [e]45,X/46,XY. [f]45,X/47,XXX, 45,X/46YX. 45,X/46,XX. [g]45,X/46,XYq-. 45,X/46,XX/47,XXX. [h]69,XXY. [i]includes one 47.XY,+2 inv (19) also scored as an inversion [j]46,XX,47,XX+r. 46,XY/46,XY,16q+. [k]46XX/47,XX,+mar. 46,XY/47,XY,+mar. [m]46,XX/47,XX,+mar. 46XX/47.XX.+mar. 46.XY/47+mar. [n]46,XY,15p+=Yq. 46,XX,22p=Yq. 46,XY,15p+,?t(15p+;Yq-)mat. 46,XY, 15p+, t(15p+Yq) pat. 46,XX, 15p+?t(15p;Yq-)mat. 46,XX, 15p+,?t (15p+Yq-)pat [o]47,XX,inv(18)p11q21)+rec(18)dup p. [p]46,XY/46XY/46,XY,5p-.46,XY.12p-. [q]46,XX.Bp- (cri du chat). [r]46,XX,-18+der(18)ins (11:18) (p 15:q11q21). [s]46XY,-Dt(DqDq). 46XY,-G,+t(GqGq).t (46,XY,Bp-. 46,XY5p-[u]Same case as in i above. [v]I mosaic with marker detected since ref. 5 appeared. (Modified and updated from "A cytogenetic Survey of 14.069 Newborn Infants" by Hamerton et al., Clinical Genetics, Vol. 8 pp. 223-245. 1975.)

1.1.1 Sex Chromosomal Abnormalities

In sex chromosome abnormalities, the incidence of the XYY syndrome among 34379 males examined cytogenetically in seven surveys is approximately 0.102 percent. Though not showing a consistency in different studies. It ranges from nil in Russian newborn series (Bochkov et al. 1974) to 0.37 percent among Canadian newborns (Ontario) (Sergovich et al. 1969). XXY (Klinefelter's syndrome) also shows an incidence of 0.113 percent in 34379 males examined and ranges from 0.07 percent in Boston newborns (Walzer and Gerald, c.f. Jacobs et al. 1974) to 0.18 percent in New Haven (U.S.A.) newborns (Lubs and Ruddle 1970). Other types of sex chromosome anomalies in males are approximately 0.0359 in the total male sample.

The incidence of 45, XO male or 46, XX male has been estimated to be 1 per 15000 to 20000 boys.

Of the 20370 female newborns studied, only 8 are of XO (Turner's syndrome) constitution and an incidence of 0.04 percent in the total sample has been given, while XXX (Trisomy X) shows a high incidence 0.12 percent.

Gardner and Sutherland (2004) estimated from a non-banded data and moderate level non-banding data of newborns studies for sex chromosome aneuploidy among male (XXY-0.12 percent, XYY-0.12 percent and other 0.015 percent) and female (45, X and X/XX-0.03 percent and XXX-0.11 percent).

1.1.2 Autosomal Chromosomal Abnormalities

Among autosomal trisomies, +D or + 13 (Patau's syndrome) and +E or + 18 (Edwards' syndrome) show a low incidence; only 3 cases of the former out of 54,749 infants studied are giving an incidence 0.005 percent of 8 instances of the latter, which comes to 0.015 percent. A total of 63 individuals has been found with +G or + 21 trisomy (incidence 0.115 percent) and show a range from 0.07 percent in the New Haven study (Lubs and Ruddle 1970a) to 0.16 percent in Russian newborns (Bochkov et al. 1974). Other extra autosomal marker chromosomes are found in 0.03 percent cases. Gardner and Sutherland (2004) estimated automal trisomy –13 (0.008), -18 (0.015) and 21 (0.12 percent) among newborns, from non-banded data and moderate level banding data.

1. Structural Rearrangements: Balanced Type: In structural rearrangements of the balanced type D/D translocations show an incidence of 0.08 percent and which range from 0.05 percent in New haven newborns (Lubs and Ruddle 1970) to 0.13 percent in Danish newborns (Nielsen and Sillesen 1975). D/G translocation shows 0.02 percent in the total sample. Reciprocal trans-locations also showed a frequency of 0.085 percent in the total sample, whereas inversions shows an incidence of 0.013 percent. Gardner and Sutherland (2004) estimated structural rearrangement, balanced 1 in 120 reciprocal translocations – 0.25 percent, Robertsorian translocations – 0.10 percent and inversions pericentric–0.08 percent.

2. Structural Rearrangements-Unbalanced Type: In structural rearrangements of an unbalanced nature Y autosomal translocations show an incidence of 0.01 percent and deletion an incidence of 0.009 percent. The total genome mutation has been found to be 0.57 percent and ranges from 0.32 percent in Winnepeg newborns (Hamerton et al. 1972) to 0.76 percent in Russian newborns (Bochkov et al. 1974). Gardner and Sutherland (2004) estimated structural rearrangement, unbalanced form newborns studies as 1 in 250.

Some more studies, though not as large as described earlier, have conducted for cytogenetic evaluation of newborn infants. Conen et al. (1970) reported in a male survey of 1080 newborns, 4 abnormal cases, one with XYY, one with XXY, one male with 45, XO constitution with no evidence of a Y chromosome or translocation and one with +G chromosomal complement. Cohen et al. (1975) in a survey of 500 Jerusalem newborn infants did not find any numerical anomaly though six inherited structural rearrangements (four inversions and two deletions) were observed in the sample. Lin et al. (1976) has reported from chromosomal analysis of 930 Canadian newborns with the help of Q-banding technique the incidence of major chromosome aberrations to be 0.54 percent. The incidence of XYY was 0.4 percent and that of XXY 0.2 percent. One male was found to have translocation involving chromosomes 10 and 21 and one female was with inversion in chromosome 5.

It can be concluded from the various reports that there is a wide range of distribution of chromosomal aberrations frequency in different populations. The main emphasis of the study is to procure the incidence of chromosomal aberrations in human populations. The etiological reasons are still unknown and precise knowledge of the selective forces also not yet explored. The selection for a trait may occur from zygote level and therefore newborn surveys are more important as correct (though not exact) incidence could be ascertained. Further data could be more informative if the spontaneous abortion surveys are also included in a study. Still we cannot detect chromosome aberrations in zygotes of a few weeks age as only those abortuses can be studied which survive long enough to give rise to a clinically recognizable size. There is no information on conspectuses which are losing early in pregnancy. The frequencies of common chromosomal aberrations reported from various newborn surveys have been therefore regarded

as minimal estimates as they refer only to those abnormalities which are detectable in mitotic cells and which are compatible with a recognizable pregnancy (Jacobs 1972).

Further studies of a large number of newborns and spontaneous abortion cases from different populations would reveal more information on etiological factors and selective forces operating on these chromosomal variations, especially with the help of banding techniques.

Miller and Therman (2001) estimated incidence of numerical and structural chromosome abnormalities in spontaneous abortuses and still birth and reported that almost half (47.9%) of all spontaneous abortuses are chromosomally abnormal with 9.8 percent polyploid (mostly triploid) 8.6 percent 45, X, and 26.8 percent trisomic for one or another chromosome and added that virtually all trisomies have been seen in abortuses. Nearly 6 percent of still births are chromosomally abnormal, with 0.6 percent polyploid, 0.25 percent 45, X and 38 percent trisomic.

Videbech and Nielsen (1984) studied chromosome abnormalities and the season of birth and they observed significant seasonal variation in birth for males with Klinefelter's syndrome born before 1946, but not for those born later and not for any other sex chromosome abnormality. Further, no significant monthly variations was found for any autosomal abnormality, except a significant increase in the frequency of conceptions for Down's syndrome during the first 4 months of the year. Kallen and Masback (1988) studied seasonality and parity effects in Down's syndrome and observed that high observed/expected values are January-March.

Nielsen et al. (1982) studied the etiological aspects of chromosomal abnormalities in newborn children and found no indication of any environmental etiological factor for the different chromosome abnormalities by recording the residence area, social status, maternal occupation and marital status. Parental social status is evaluated from the status of the father and it is interesting that fathers of boys with enlarged Y chromosome, who also would be expected to have an enlarged Y chromosome themselves are found more frequently among the lower social classes (77 percent) compared with 59 percent for parents of children with normal karyotypes; however, statistically the differences are not significant. The only significant increase in maternal age is found for the mothers of children with aneuploid or unbalanced autosomal abnormalities.

Studies are available on associations between paternal and maternal age and trisomies. Early studies in births demonstrated strong association with increasing maternal age, but most studies (Jenkins 1933; Penrose 1933; Sigler et al. 1965; Milham and Gittlesohn 1965), if not all (Mantel and Stark 1966; Lilienfield 1969), detected no independent contribution of advancing paternal age. Nonetheless the hypothesis that paternal age might also have an influence is reviewed in light of cytogenetic evidence suggesting that in about one-fifth of trisomy 21 births the extra chromosome is paternal (Wagenbichler et al. 1976; Hanson and Mikkelsen 1978; Mikkelsen et al. 1980; del Mazo et al. 1982; Juberg and Mowrey 1983); the proportion of paternally derived cases is lower according to molecular analysis (Chakravarti et al. 1989). Subsequent research in both liveborns and foetuses diagnosed prenatally has, with few exceptions (Stene et al. 1977, 1981, 1987a, b; Mastsunaga et al. 1978; Erickson and Bjerkedal 1981), continued to find no association between advanced paternal age and trisomy 21 (Cohen et al. 1977; Erickson 1978, 1979; Regal et al. 1980; Hook et al. 1981, 1990; Hook and Cross 1982; Roecker and Heuther 1982; Ferguson-Smith and Yates 1984; Cross and Hook 1987). Hatch et al. (1990) studied paternal age and trisomy among spontaneous abortions and concluded that neither on statistical nor biological grounds do the data provide compelling evidence of paternal age effects on the trisomies found among spontaneous abortions, or on chromosomally normal losses. Schwanitz and Eggermann (1999) observed that despite the high frequency of trisomies, their aetiology remains imperfectly understood and further added that there is consensus regarding a causative role of any of the many factors that have been investigated with the single important exception of maternal age.

Low oestriol concentrations are found in 7 percent of the mothers of the 93 children with chromosome abnormalities, compared to 2.1 percent of the mothers of the 4,895 children with normal karyotypes and the difference is significant. Sterility problems in parents with a balanced translocation or inversion are found in

20 percent which is significantly higher than the 6 percent among parents of children with normal karyotypes. An increased frequency of abortions and neonatal death is found for the carriers of autosomal reciprocal translocations. There is also an increased frequency of abortions in mothers of boys with an enlarged Y. The frequency of twin birth is significantly higher among boys with an enlarged Y. Oestrogengestagens given 2 to 6 months before pregnancy are taken by 15 percent of the mothers of children with all types of aneuploid chromosome abnormalities and by 20 percent of mothers of children with sex-chromosome abnormalities. These frequencies are significantly higher than among mothers of children with normal karyotypes and AB Rhesus negative blood type is found to a significantly higher degree in children with chromosome abnormalities compared with children with normal karyotypes. This indicates the need for studies of the association between non-disjunction, *de novo* structural chromosome aberrations and certain blood types.

Patil et al. (1977b) reported a chromosomal study of 4342 seven-eight year old children and observed an over all frequency of chromosome abnormalities of 0.48 percent which is less than that found in newborn infant studies (0.62 percent). Twenty one chromosomally abnormal children are ascertained. They observed lower frequency of autosomal trisomies, absence of XXX girls and the frequency of XYY males. The autosomal rearrangements are similar to that found in newborn surveys [(a) Sex Chromosomes: males 47, XYY (Three); 46, XY/47, XXY: (one); 46, X inv (Y) (p11q11): one; female structural rearrangements: four; (b) Autosomal trisomies: 47, XY +21: two; (c) Balanced reciprocal translocations: three (d) Robertsonian translocations: three and inversions: one].

Some reports are available on the incidence of Down's syndrome where the overall incidence at birth varies from 0.098 percent (Japan 1970-1993 by Kuroki et al. 1977) to 0.132 percent (Sweden 1968-1970 by Lindsjö 1970). The other studies available are from Western Australia (0.114 percent 1966-1975 by Mulcahy 1979); Copenhagen area (0.115 percent 1960-1971 by Mikkelsen et al. 1976); Manitoba (0.108 percent 1965-1968 by Uchida1970); British Columbia (0.128 percent, 1952-1973 by Lowry et al. 1976); Wallonia, South Belgium (0.123 percent, 1971-1978 by Kouischer and Gillerot 1980).

The frequency of 0.95 percent of standard trisomy 21 is usually accepted (Mulcahy 1979). The frequency of translocation is about 3 percent (varies from 2.61 percent reported from Wallonia to 6.2 percent observed in Copenhagen). Hook and Hamerton (1977) tabulated newborn chromosome studies and observed 72 Down 's syndrome patients (0.126 percent), in which only (1.38 percent) is an unbalanced translocation carrier.

Kleczkowska et al. (1988) reported 569 male patients with X-chromosome polysomies out of 77,000 persons karyotypes in the Leuven Cytogenetic Center between the years 1966 and 1987. They found classic 47, XXY karyotypes in 522 patients: different variants of this 47, XXY constitution i.e., mosaicism and/or autosomal rearrangements in 22 males and in the rest of the 25 patients they detected other types of X-chromosome polysomy with cell-lines including a 48, XXXY and/or 49, XXXXY chromosome constitution. Based on nuclear sexing surveys of newborn babies, the incidence of the 47, XXY karyotype is found to be 1.01 per 1000 (Buckton 1983). In the same surveys the incidence of 46, XY/47, XXY mosaicism is much higher (7 mosaics with a 47, XXY cell line versus 43 males with the classic 47, XXY karyotype in a total of 42602 male newborns) than has been found in the Leuven study: 15 mosaic patients versus 522 males with 47, XXY karyotype giving a ratio of 1 to 35 compared to the 1 to 6 ratio in the newborn studies. The constitutional presence in the human complement of an additional ("supernumerary") small chromosome, which is not directly equivalent to any of the normal chromosome, has been reported (Soudek and Sroka 1977; Steinbach et al. 1983). Such an "accessory" chromosome of unknown origin is referred to as a marker chromosome (mar) using the standardised human chromosome nomenclature (Paris Conference 1971) and they comprise a mixed collection of structurally rearranged chro-mosome regions. Buckton et al. (1985) observed that Mar Chromosomes are largely, but by no means exclusively heterochromatic. Mar probands are relatively rare in the general population with prevalence of less than 1 in 1000. They are found more frequently among various abnormal individuals with a high prevalence rate of 3.27 per 1000 in patients in mental subnormality hospitals.

1.1.3 An Analysis of Chromosome Aberrations in Human Sperms

A few reports on chromosomal analysis of spermatozoa from normal men are available which show the frequency of chromosomal abnormal sperms varied among different studies (Rudak et al. 1978; Martin et al. 1982, 1983, 1987; Brandriff et al. 1984, 1985, 1988; Kamiguchi and Mikamo 1986., Jenderny and Roehrborn 1987; Martin and Rademaker 1990; Estop et al. 1991, 1995; Pellestor 1991; Rosenbusch et al. 1991; Benet et al. 1992; Jenderny et al. 1992; Benkhalifa et al. 1994; Templado et al. 1996). It has been observed that the frequency of structural abnormalities is higher (varies from 6.2 to 13.0 percent) as compared with numerical chromosome abnormalities (about 2 percent) except in the study of Martin et al. (1983) where reverse relationship has been observed i.e. higher aneuploidy rate (5.2 percent) versus a lower rate of structural chromosomal abnormalities (3.3 percent). The main types of structural chromosomal abnormalities in all studies are particularly chromosome-type breaks followed by chromosome-type fragments. The most likely explanations for different frequencies of numerical chromosome abnormalities seem to be interring individual variability among the different donors. The different results between the frequencies of structural chromosome abnormalities in difference the various investigations could be additionally ascribed to the different scorings of chromosomal abnormalities among the laboratories and different culture conditions. In human sperm metaphases reciprocal chromosome translocations, inversions and small deletions are the most important types of chromosomal aberrations. These types may originate from induced chromatid or chromosome type aberrations in spermatogonial stem cells, because they have the chance of being transmitted to mature sperm cells (Jenderny and Roehrborn 1987). For review on chromosome abnormalities on sperm see Guttenbach et al. (1997).

1.1.4 Cytogenetic Abnormalities Detected by Amniocentesis

Systematic studies of women at prenatal stage provide the best relatively unbiased source of data on the frequency of chromosomal abnormalities. A number of reports are available on cytogenetic findings in prenatal diagnosis from a large single center (Squire et al. 1982) and large scale collaborative studies (Simoni et al. 1982; Hook et al. 1984; Ferguson-Smith and Yates 1984; Hook and Cross 1987a). These studies have reported the frequencies of various chromosomal abnormalities and their association with parental (maternal and paternal) age, and the analysis of rates of inherited and mutant structural abnormalities.

1. Cytogenetic Abnormalities: Schreinmachers et al. (1982) have analyzed the results of 19675 prenatal cytogenetic diagnosis reported on women aged 35 years or over in whom there is no known cytogenetic risk of a chromosome abnormality except parental age. It is observed that the frequency of trisomies of sex chromosomes (XXX and XXY) is almost identical whereas the frequency of XYY shows an increase in live births. They observed an increase in maternal age-specific rates of 47, +21 conspectuses. The frequencies of autosomal trisomies shows a decrease in the live births as compared to the fetuses studied prenatally. It appears possible that spontaneous fetal death accounts for the differences.

Ferguson-Smith and Yates (1984) have analysed a larges scale European study of 52965 prenatal cytogenetic diagnosis carried out at multiple centers in Europe from 1970 to 1981 which indicated that after increasing exponentially from age 35 years the proportions of the autosomal trisomies reached a peak at specific age and then leveled off or declined in at the upper end of the age range; whereas Hook et al. (1984)[3] analyzing North American data on 56075 fetuses studied because of no known cytogenetic risk factor (aside from maternal age) observed that for 47, +21 the data from amniocentesis studies provided no evidence for any drop in the rate of change of proportion with maternal age up to 49 years. For 47, +18 the data from prenatal diagnosis are more consistent with an exponential increase up to age 43 years and a level proportion of rate[3] after that Table 3.

For 47, +13 no case is observed above age 42 years, consistent with the drop in proportion of affected above this age observed in European series. Hook et al. (1984) emphasised the possible effect of sampling fluctuation and reporting error upon those apparent trends.

2. Structural Cytogenetic Abnormalities Detected by Amniocentesis: Structural chromo-

Table 3: Frequency of chromosome abnormalities in fetuses studied prenatally

Type of abnormality	*U.S.A. Schreinemachers et al. (1982)*	*European Ferguson-Smith and Yates (1984)*	*North Americans Hook et al. (1984)*
Sex Chromosomes			
XXX	20(0.10)	65(0.12)	-
XXY	25(0.13)	87(0.16)	-
XYY	10(0.05)	18(0.03)	-
Autosomal Trisomies			
+21	179(0.91)	613(1.16)	473(0.84)
+18	49(0.25)	121(0.23)	120(0.21)
+13	12(0.06)	39(0.07)	32(0.06)
All Other	67(0.34)	257(0.49	
Total Abnormalities	362(1.84)	1200 (2.26)	
Total Fetuses	19672	52965	56075
Maternal Age Range at Amniocentesis	35-49 years	35-52 years	35-49 years

some abnormalities while less frequent than numerical abnormalities, still have an important effect upon human morbidity and mortality Table 4. Hook and Cross (1987a) reported data on diagnosis made on amniotic fluid specimens from 1977 to 1984 which are reported to the New York State Chromosome Registry. They observed rates of mutant and inherited structural cytogenetic abnormalities in about 63000 fetuses and found that the rate of all *de novo* (presumed mutant) abnormalities is about 2 per 1000 in about 61,000 fetuses in which results are unlikely to be biased by the reason for amniocentesis (except from maternal age). This includes about 0.5 per 1000 *de novo* markers, about 0.5 per 1000 other *de novo* unbalanced, and about 1.0 per 1000 *de novo* balanced rearrangements. In about 55,000 foetuses in which rates of inherited abnormalities could be evaluated without apparent bias, the rate of all inherited rearrangements was about 2.9 per 1000. This includes about 0.3 per 1000 inherited markers, about 0.2 per 1000 other inherited unbalanced rearrangements and about 2.4 per 1000 inherited balanced abnormalities. They observed a clear association of mutant markers with maternal age (37.6 ± 2.7 in 24 cases

Table 4: Comparison of frequencies of *de novo* and inherited structural abnormalities among those studied with no known selective factor for any structural abnormality*

Structural abnormalities	*de novo*	*Not known*	*Inherited*			*Proportion inherited among those of known origin*	*Proportion mutant among those of known origin*
			Maternal	*Paternal*	*Total*		
Unbalanced							
Robertsonian	3	2	1	0	6	0.25	0.75
Deletion	11	4	1	0	16	0.08	0.92
Derived aberration	0	0	2	2	4	1.00	0
Markers	21	6	8	4	39	0.36	0.64
Rings	2	2	0	0	4	0.00	1.00
Other	6	3	2	0	11	0.25	0.75
All (excluding markers)	22	11	6	2	41	0.27	0.73
All unbalanced	43	17	14	6	80	0.32	0.68
Balanced							
Robertsonian	15	2	12	9	38	0.58	0.42
Inversions	7	83	23	28	61	0.88	0.42
Reciprocal	29	5	19	32	85	0.64	0.36
All balanced	51	10	54	69	184	0.71	0.29
All Robertsonian	18	4	13	9	44	0.55	0.45
All (excluding markers)	73	21	60	71	225	0.64	0.36
Total	94	27	68	75	264	0.60	0.40

*Includes only those detected in RFS groups G and H listed in Tables, a total of 54806 (after Hook and Cross 1987a)

v. 35.8 ± 3.6 in controls) which was not exhibited in inherited markers (35.8 ± 2.0 in 12 cases v. 36.4 ± 2.8 in controls). Paternal age does not appear to account for the association. Among abnormalities of known origin, the ratio of mutant of inherited cases is for markers 64: 36; for other unbalanced rearrangements 73: 27 and for all balanced abnormalities 29: 71. In a sub-group of about 55,000 foetuses of 263 total abnormalities there are 8 instances of apparent true somatic mosaics (5 mutant and 3 of unknown origin). There are also 20 instances of markers in which presumptive somatic loss has resulted in mosaicism (10 mutant, 6 of unknown origin and 4 inherited) and 13 other instances of mosaicism associated with apparent somatic loss (9 mutant, 3 of unknown origin and 1 inherited). The sex ratio (Y to non-Y karyotypes) for all abnormalities detected is 228: 210 (1.09), not different from controls. Only deletions (5: 14) and 'other' unbalanced rearrangements (5: 13) exhibited a suggestive deviation from this trend. Among foetuses studied because of maternal exposure to putative mutagens there is a non-significant excess of mutants (2.9-5.7) per 1000 v. 1.7-2.2 per 1000) and a borderline significant excess of inherited rearrangements (8.6-11.5 per 1000 v. 2.6-3.1 per 1000). The latter effect, if not due to chance, may be de to effects on segregation.

The comparison between the studies of Ferguson-Smith and Yates (1984) and Hook and Cross (1987a) for structural abnormalities show that for all unbalanced Robertsonian translocations there are 0.13 per 1000 cases in the European series compared with 0.10 per 1000 in the New York series. For balanced Robertsonian translocations the rates are 0.76 per 1000 in Europe and about 0.73 per 1000 in New York. For extra markers the rate is 0.5 per 1000 in the European study compared with about 0.64 per 1000 in the New York study (4 cases for the New York series are excluded as those are not 'extra'). But for non-marker non-Robertsonian unbalanced rearrangements, the rate is 0.43 per 1000 in the European series and 0.75 per 1000 in the New York one and for non-Robertsonian balanced rearrangements the rates are 1.76 per 1000 and 2.67 per 1000, respectively. Hook and Cross (1987a) observed that the reasons for the differences in the latter two comparisons are not readily apparent but they do result in lower rates of all unbalanced, all balanced and total abnormalities in the European series than in the New York series. The comparisons are respectively 1.15 per 1000 v. 1.46 per 1000, 2.51 per 1000 v. 3.39 per 1000 and 3.66 per 1000 v. 4.86 per 1000. There is no ready explanation for these differences. Hook and Cross (1987a) further added that why the New York and European series found roughly equal rates of total Robertsonian rearrangements but disparate rates of all non-Robertsonian abnormalities remains unexplained. The European data do not allow inferences as to whether these differences are in *de novo* of inherited groups.

3. Extra Structurally Abnormal Chromosomes (ESAC) Detected by Amniocentesis: Hook and Cross (1987a) analyzed rates of extra structurally abnormal chromosomes (ESAC) which are detected in prenatal cytogenetic diagnosis of amniotic fluid. These karyotypes include both Extra *Unidentified* Structurally Abnormal Chromosomes (EUSAC) often denoted as "makers" and/or "Supernumerary" and Extra *Identified* Structurally Abnormal Chromosomes (EISAC). They observed the rate of all EUSAC is 0.64/1.000 (0.32-0.40/1000 mutant and 0.23-0.32/1000 inherited), and that of all EISAC is 0.11/1000 (0.07/1000 mutant and 0.04/1000 inherited). The rate of all ESAC is ~ 0.8/1000 (0.4-0.5/1000 mutant and 0.3-0.4/1000 inherited). They reported the mean maternal age of mutant cases 37.5 ± 2.9 which is significantly greater than the value of 35.8 years in controls. Since ESAC include heterogeneous group of abnormalities, the maternal age and paternal age trend, if not the result of statistical fluctuation or undetected biases, may involve different types of events. In the literature, it is reported that chromosomes with *de novo* duplicated inversion of 15p have strong maternal age effect (but little paternal age effect). Such chromosomes, however do not account for the active maternal age trends seen in the study of Hook and Cross (1987b). Inherited ESAC exhibited no such trends.

Eggerman et al. (2002) observed that supernumerary marker chromosomes (SMC) transmission inheritance is almost equal from both the parents.

1.2 Minor Variants in Human Chromosome Complement

There has been a trend in human cytogenetics to attribute the questionable anomalies

to any change seen in the morphology of any of given chromosome. However, human chromosome complements do show variants with normal phenotype. These variants are seen quite frequently and are maintained in the population without precise knowledge of the selective forces favouring them or not.

According the Paris Conference 1971, the term 'variant' (whereas in supplement of the Paris Conference (1975) the term 'Heteromorphic' has been recommended to describe the chromosomes with variable bands) is recommended for use in situations where deviations from the norm of chromosome morphology are observed. These minor variations have been considered polymorphic on the basis of their high frequency in the population with normal phenotype and inheritance by most of them from one generation to another. It is well known that the genomes of higher eukaryotes are divided into two functionally different parts; eu- and hetero-chromatin. Heterochromatin is formed by tandemly organized highly repeated sequences (satellite DNA) that do not encode proteins. Larger amount of heterochromatin are usually associated with the pericentromeric regions of chromosomes. The function of satellite and heterochromatin in general are not known.

A number of cytological techniques have been developed to demonstrate heterochromatic regions in chromosomes (for review see Bhasin and Singh 1978). The heterochromatic regions are recognised on most juxtacentromeric regions either through several treatments or through directly stained slides (Verma 1988). Each technique reveals characteristic staining patterns, a result that demonstrates constitutional differences in heterochromatin; that is, heteromorphisms identified by one technique may not reveal similar variants when another technique is used (Olson et al. 1986). This implies that the adjacent fraction of heterochromatic segments may contain cytochemically distinct chromatin and may stain differently (Babu and Verma 1987). The heteromorphisms of C-band regions of human chromosomes are evaluated by means of restriction endonucleases *Alu* I, *Dde* I, *Mbo* I, *Rsa* I. (Babu et al. 1988).

Initiation of such type of studies has been done by Lubs and Ruddle (1970a, b) who termed, them as 'quantitative karyotype' studies and chromosome variants were identified with the help of conventional staining techniques (Orcein or Giemsa). But with the development of new banding techniques which help in identifying each and every chromosome of a set, some of the variants not recognized with conventional staining procedures could be visualized, like with C-banding procedure (Arrighi and Hsu 1971). C-band heterochromatic regions in each chromosome stain rather selectively and variants found in secondary constriction regions, short arm and satellites of acrocentric chromosomes and distal part of chromosomes are highly polymorphic, whereas Q-banding produces a new class of polymorphic variants in terms of intensity and length of brilliant fluorescent regions of chromosomes 3 and 4 (in the region adjacent to the centromere on the short arm) and in the short arm region of acrocentric chromosome. Various techniques have been described to investigate human chromosome polymorphisms like densitometric measurements (Erdtmann et al. 1981) scanning electron microscopy (Harrison et al. 1985) and flow cytometry (Trask et al., 1989a).

The biological significance of these variants, or heteromorphisms, is still poorly understood. Yet their use as genetic markers is a powerful tool in clinical diagnosis (Verma 1990; Kalz and Schwanitz 2004), paternity exclusion (Olson et al. 1986) and population genetics (Podugolnikova and Korosteler 1980; Erdtmann et al. 1981; Ibraimov et al. 1982). In general heteromorphisms are individually stable (Hoehn et al. 1977), have a low mutation rate (Baliček et al. 1978) follow Mendelian inheritance (Magenis et al. 1977) and provide proof of parentage and determination of zygocity in sets of twins and triplets (Kalz and Schwanitz 2004). The heterochromatin is highly complex and heterogeneous (Verma 1988) and consequently there is no necessary or direct relationship among various types of chromosomal heteromorphisms.

Thus with these developments human chromosome polymorphic variants can be studied in three forms as follows:

1. Heteromorphisms shown by short-arm regions of D- and G- Group chromosomes.
2. Heteromorphisms shown by paracentric long arm regions of chromosomes 1, 9 and 16
3. Variation in the length of the Y chromosome.

1.2.1 Heteromorphisms Shown by Short Arm Regions of D- and G- Group Chromosomes

The first autosomal heteromorphisms to be commonly recognized in the human karyotype

involved the short arm regions of the acrocentric chromosomes[4]. Since 1961, it has been known that the short arm of all five acrocentric chromosomes of both D-chromosomes and G-chromosomes groups are satellited and these regions namely (i) satellite (ii) stalk and (iii) short arm proper vary greatly in size and morphology in the form of (i) enlargement of the short arm (ph+) (ii) absence of short arm (ph-) (iii) enlargement of satellites (ps+) (iv) tandem satellites (pss+) and (v) some very rare variants like (a) streak or multiple satellites and (b) split satellites (Soudek 1973; Niikawa and Kajii 1975; Hayata et al. 1977; Verma et al. 1977b; Schnedl 1978; Mikelsaar and Illus 1979b; Verma and Dosik 1979; Wachtler and Musil 1980). Short arms of acrocentrics are heterochromatic, and therefore, extensive variations are possible, usually without any detrimental effect (Soudek 1973).

The short arms of all acrocentric chromosomes are composed of three bands: p 11, p 12 and p 13 (ISCN, 1995). The p11 band contains several types of tandemly repeated DNA, including proximal satellites I, II, III, IV and distal beta-satellite (Jones et al. 1973, 1974; Gosden et al. 1975; Waye and Willard 1989; Greig and Willard 1992; Taggaro et al. 1994a, b). The p12 band contains multiple copies of ribosomal RNA genes (Evans et al. 1974a) and the p13 band includes proximal beta-satellite DNA (Greig and Willard 1992) and terminal telomeric sequences (Moyzis et al. 1988). The centromere band p10 is made of alpha-satellite tandem repeat DNA of 171- bp (Vissel and Choo 1987; Waye and Willard 1987). The beta-satellite is made up of 68-bp repeat units (Waye and Willard 1989). Satellite I is AT-rich and made up of 17- and 25-bp repeat units (Prosser et al. 1986). Satellites II and III (classical) are made up of 5-bp repeat units (Prosser et al. 1986).

The heritability of these chromosome variants has been established by documenting their transmission in simple Mendelian expectations through successive generations (Geraedts and Pearson 1974; Robinson et al. 1976; Verma and Lubs 1976b) and by observing that concordance among monozygotic twins was greater than among dizygotic twins (Van Dyke et al. 1977).

Studies on the variation in the length and the morphology of the short arm and satellite regions of acrocentric chromosomes have been reported extensively (Starkman and Shaw 1967; Battaglia et al. 1971; Lubs and Ruddle 1971; Zankl and Zang 1971; Mikelsaar et al. 1973; Rary and Borgaonkar 1973; Ferguson-Smith 1974; Bochkov et al. 1974; Cohen et al. 1975; Ghosh and Singh 1975; Ghosh et al. 1975; Hamerton et al. 1975; Nielsen and Sillesen 1975; Walzer and Gerald 1977; Funderburk et al. 1978; Kenue 1979; Buckton et al. 1980; Sofuni et al. 1980).

1. Enlargement of Short Arm Regions: Lau et al. (1979) reported the enlargement of the chromosome 14 short arm making it nearly as long as the long arm, giving the chromosome a submetacentric to metacentric appearance. In the D-group chromosomes, higher frequency of enlargement of short arm and satellite regions in chromosome 15 than in chromosomes 13 and 14 has been reported (Ferguson-Smith 1974; Nielsen et al. 1974e; Stoll et al. 1974; Tipton 1974; Sofuni et al. 1976; Tharapel and Summit 1978; Kenue 1979) and in G-group, chromosomes 21 and 22 show almost the same frequency for this character. Verma et al. (1977a) using acridine orange reverse banding (RFG) observed more large size levels in G-group chromosome short arm regions as compared to D-group chromosomes But no sex difference for the frequencies of size variation of the short arms has been observed by them.

2. Number and Size of Satellites: It has been known that the number and size of the satellites of the acrocentric chromosomes are constant from cell to cell in an individual, but vary markedly between individuals (Miller et al. 1962; Ford and Wollam 1967; Leisti 1971). In the twin study, high concordance is observed which confirms these results (Engmann 1967). In a highly inbred Amish community, Bahr and Golomb (1971) observed giant satellites in ten percent of the individuals and attributed their inheritance to a common ancestor. But Chiyo et al. (1975) and Nakagome et al. (1977) reported huge satellites in the offspring but not in either of the parents and paternity has to be established with the help of other genetic traits.

A number of cases of double satellites have been reported in the literature (Jacobs et al. 1964; Hamerton et al. 1965; Luciani 1968; Bauchinger and Schmid 1970; Lubs and Ruddle 1971; Rocchi et al. 1971; Gigliani et al. 1972; Yoder et al. 1974; Henderson and Atwood 1976; Stoll et al. 1976; Archidiacono et al. 1977; De Copoa et al. 1978; Miller et al. 1978; Martin et al. 1979; Baličeк and Žižka 1980) and the origin of the double satellites is mostly attributed to translocation of satellite

regions between two acrocentric chromosomes (Bauchinger and Schmid 1970; Rocchi et al. 1971; Gigliani et al. 1972). Ray Chaudhuri et al. (1968) reported quadripartite satellites in the acrocentric chromosomes of both D- and G- groups.

Enlarged short arm and satellite regions of acrocentic chromosomes have been reported in a number of familial cases (Ellis and Penrose 1961; Patau et al. 1961; Cooper and Hirschorn 1962; Kallen and Levan 1962; Chandra and Hungerford 1963; Dekaban et al. 1963; de la Chapelle et al. 1963a; Reitalu 1964; Summit and Patau 1964; Woly et al. 1964; Wolf et al. 1966; Luciani et al. 1968; Ray-Chaudhuri et al. 1968; Subrt et al. 1968; Sands 1969; Yunibhand 1969; Hossfeld et al. 1970; Markovic et al. 1970; Bauchinger and Schmid 1970; Bannerman et al. 1971; Rocchi et al. 1971; Vormittag et al. 1972). In a majority of the above studies it has been observed that the variant is familial and normal carriers are observed. Normal individuals carrying both maternal and paternal variants have also been reported (Wolf et al. 1966; Hirschorn and Cohen 1969). Some of these familial cases with enlarged short arm and satellite regions of acrocentric chromosomes, associated with clinical conditions such as Marfan's syndrome (Tjio et al. 1960; Kallen and Levan 1962), Down's syndrome (Dekaban et al. 1963; Subrt et al. 1968; Markovic et al. 1970), partial trisomy syndromes (Patau 1961) and other malformations (Ellis and Penrose 1961; Wolf et al. 1966; Summitt and Patau 1964) have been reported.

In general, clinically abnormal populations have shown positive as well as negative associations with enlargement of short arm regions. Various studies have reported an increase in the short arm and/or satellite regions in Down's syndrome cases (Dekaban et al. 1963; Therkelsen 1964; Edgren et al. 1966; Starkman and Shaw 1967; Subrt 1970; Hamerton 1971; Bott et al. 1975; Mikelsaar et al. 1975; Robinson and Newton 1977). In contrast to the above findings Sands (1969) and Giraud et al. (1975) have not found such an association in individuals with trisomy 21 and parents of Down's syndrome cases, respectively. The presence of prominent G-group satellite variants is associated with low birth weight and malformations (Lubs and Ruddle 1971). Higher frequencies of satellite variants have been observed in child psychiatric populations (Crandall et al. 1972; Christensen and Nielsen 1974; Say et al. 1977; Funderburk et al. 1978), adults with reproductive failures (Rosenmann et al. 1977; Tsenghi et al. 1976) and in children referred for cytogenetic examination (Krag-Oslen et al. 1980) when compared with normal population. In a study of spontaneous abortions, Holbek et al. (1974) reported statistically significant difference for the ph+ and s+ variants which are more frequent in the parents of clinically abnormal and normal abortuses. Mikelsaar et al. (1975) have also reported a high frequency of prominently fluorescent satellites of the acrocentric chromosomes in oligophrenics rather than in controls. There are other reports which show no correlation of these variants with increased risk (Nielsen et al. 1974e), developmental defects (Funderburk at al. 1978) or IQ scores (Funderburk et al. 1979).

3. Deletion in Short Arm Regions: Deletions in short arm of D- and G- group chromosomes have been reported in a large number of familial cases (Shaw 1962; Migeon 1965; Abbot 1966; Neu et al. 1966; Pfeiffer 1966; Subrt and Brychnac 1966; Ito and Makino 1966; Jagiello and Faiman 1967; Emerit et al. 1968, 1972; Mikelsaar 1969; Parker et al. 1969; Yoshida and Honda 1969; de Grouchy 1970; Juberg and Jones 1970; Kelch et al. 1971; Amarose et al. 1980). Various population survey have revealed its frequency to be very low (Lubs and Ruddle 1971; Mikelsaar et al. 1973, 1975; Rary and Borgaonkar 1973; Bochkov et al. 1974; Cohen et al. 1975; Hamerton et al. 1975; Walzer and Gerald 1977; Kenue 1979; Buckton et al. 1980).

It has been observed that the frequency of the short arm deletion of chromosomes 13 is more than that of chromosome 14 and 15 (Ferguson-Smith 1974; Nielsen et al. 1974a; Sofuni et al. 1976). The association between chronic lymphocyte leukaemia and the so called Ph^1 chromosome, a short arm G-group deletion originally postulated by Gunz et al. (1962) has not been supported by other studies (Court Borwn 1964; Gunz and Fitzernald 1964). Warren and Remoin (1970) associated Gp- with two different pathological conditions. Nielsen et al. (1974a) observed neither significant difference between institutionalised and normal population nor increases in abortion or non-disjunction in terms of short-arm deletion frequency of acrocentric chromosomes. G ph-chromosomes have also been reported in association with families of Down's syndrome children (Shaw 1962; de Grouchy 1970; Jacobs et al. 1978; Mayer et al. 1978), but no conclusive results could be gathered to establish whether G ph- chromo-

some is causal to Down's syndrome (Mayer et al. 1978). Ballantyne et al. (1977) suggested that G ph- may predispose to develop-mental anomalies and nondisjunction or both. Ballesta and Serra (1976) could not associate any anomaly with any variant in particular. It may be evaluated from the foregoing discussion that the association of pathological conditions with size and morphology of the short arm region of the acrocentric chromosomes is not direct. Further research work is needed to find more about such association.

A number of studies are available in which variations in the frequency distribution have been observed for the short arm regions of acrocentric chromosomes. The results of D- and G- group chromosomes of various populations reported in the literature are presented in Table 5 combining the frequencies for the enlargement of short arm and satellites (ph+, ps+ or pss+).

The highest frequency for the incidence of the enlargement of short arm regions (ph+, ps+ or pss+) of D- group acrocentric chromosomes has been observed among the Negro newborns (26.63 percent) as reported by Lubs and Ruddle (1971). Among the Europeans the frequency for this character has been observed from nil in Edinburgh newborns (Buckton et al. 1980) to 16.70 percent in American newborns (Lubs and Ruddle 1970b), whereas among the Jerusalem newborns (Middle East) the frequency of 3.20 percent has been observed as reported by Cohen et al. (1975). Among the Uzbeks of the Asiatic part of the USSR the frequency of 4.40 percent has been observed by Kuleshov et al. (1975). From India, high frequency for the incidence of this character has been observed which varies from 7.00 percent in Indian normal adults (Ghosh et al. 1975) to 15.50 percent Jat normal males (Kenue 1979). In the newborns of Delhi study, the incidence of the enlargement of D-group acrocentric chromosomes has been observed as 10.43 percent in males and 7.89 percent in females (Bhasin et al. 1981).

The frequency distribution for the enlargement of the short-arm region of G-group varies from 0.08 percent (Edinburgh newborns by Buckton et al. 1980) to 8.65 percent (Estonians, Mikelssar et al. 1975) among Europeans, whereas among Jerusalem newborns the incidence is 1.40 percent. Among the Negro newborns (Lubs and Ruddle 1971) the highest frequency i.e., 10.04 percent is observed as also the enlargement of the short-arm regions of D-group chromosomes. Among the Uzbeks of the USSR, the incidence is 1.20 percent. From India, in incidence for this has been observed to be highest among Jat normal males (11.50 percent). In the newborns of Delhi study, the incidence of the enlargement of the short-arm region of G-group acrocentric chromosomes is 3.04 percent in males and 2.63 percent in females, which is quite low (Bhasin et al. 1981). However, the incidence is almost similar to a few European population groups studied (German newborns studied by Zankl and Zang (1971) and Italian normal subjects reported by Battaglis et al. (1971).

Ethnic variation in the incidence of the enlargement of the short arm or satellite of acrocentric chromosomes has also been reported by several authors (Starkman and Shaw 1967; Lubs and Ruddle 1971; Muller and Klinger 1975; Funderburk et al. 1978).

The incidence of the short arm deletion of D- and G-group acrocentric chromosomes is found to be very low in various populations as listed in Table 6. Among European population groups the frequency in the short arm deletion of D-group chromosomes varies from 0.10 percent (Boston newborns by Walzer and Gerald 1977) to 0.96 percent (Estonians by Mikelsaar et al. 1975). It has been observed to be absent among the Jerusalem newborns and among the Negro population groups. Among the Asiatics the incidence for the short arm deletion of D-group chromosomes ranges from 1.25 percent in Jat normal males to 2.11 percent for Delhi newborn females. It may be observed that Asiatic population groups show a high frequency for the incidence of the short arm deletion of D- group chromosomes as compared to other population groups reported in the literature.

Among Europeans, the incidence of short arm deletion of G-group chromosomes varies from a total absence to 0.48 percent (Estonians). Jerusalem newborns from Middle East show the incidence to be 0.20 percent. Among Negro newborns deletion of the short-arm has been observed. From India, the incidence of this character has been observed as being 0.75 percent among Jat normal males, whereas in the newborns of Delhi study it is absent. It may be evaluated from the foregoing discussion that the trait in question is very rare in occurrence and a

small deviation may lead to marked fluctuations in the frequency.

German et al. (1966) suggested that small chromosomal variations in structure are transmitted in phenotypically normal individuals in the general population and constitute the chromosomal structural load: when the relatively infrequent but inevitable genetic imbalance of an embryo occurs as a consequence of such a chromosome polymorphism, it may cause embryonic maldevelopment. Similarly, increased susceptibility to nondisjunction in women carrying a G ph- chromosome has been suggested but has not been confirmed statistically (Ballantyne et al. 1977). Further Jacobs et al. (1978) suggested an association between the Gp- chromosome and families of Down's syndrome children, whereas Mayer et al. (1978) did not observe conclusive results to establish whether Gp- is causal to Down's syndrome.

Henderson et al. (1972, 1976) have shown that highly polymorphic polycistronic genes like 18S and 28S RNA are located on the short-arm regions of acrocentric chromosomes. Therefore, heteromorphisms observed in these regions may not essentially be of neutral selective value, and

Table 5: Incidence in the enlargement of the short arm and/or satellite regions (ph+ps+or pss+) of D- and G-group acrocentric chromosome in various populations

Population	*Number of individuals*	*Enlargement of shortarm or satellites (ph + and ps + or pss +)*				*Authors*
		D-Group		*G-Group*		
		No.	*Percent*	*No.*	*Percent*	
EUROPEAN						
Denmark						
Danish Newborns	5049	17	0.34	20	0.04	Friedrich and Nielsen (1973)
Danish Newborns	11148	34	0.30	47	0.42	Nielsen and Sillesen (1975)
United Kingdom						
Scots	2291	55	2.40	37	1.70	Ferguson-Smith (1974)
Edinburgh Newborns	1320	0	0.00	1	0.08	Buckton et al. (1980)
Fife Newborns	2073	3	0.11	4	0.15	Buckton et al. (1980)
West Germany						
German Newborns	280	19	6.80	8	2.90	Zankl and Zang (1971)
Italy						
Italian Normal Subjects	298	12	4.02	9	3.02	Battaglia et al. (1971)
United States of America						
American Newborns (New Haven)	2444	417	16.70	146	6.00	Lubs and Ruddle (1970)
Caucasian Newborns	3476	562	16.16	179	5.16	Lubs and Ruddle (1971)
Normal Institutionalised	4635	247	5.02	212	4.58	Rary and Borgaonkar (1973)
Boston Newborns	13751	51	0.37	51	0.37	Walzer and Gerald (1977)
Canada						
Canadian Neonates	6929	18	0.026	27	0.40	Hamerton et al. (1972)
Canadian	13939	40	0.29	78	0.56	Hamerton et al. (1975)
U.S.S.R.						
Moscow Newborns	2500	11	0.44	9	0.36	Bochkov et al. (1974)
Estonians	203	28	11.46	10	8.65	Mikelsaar et al. (1975)
MIDDLE EAST						
Israel						
Jerusalem Newborns	500	16	3.20	7	1.40	Cohen et al. (1975)
NEGRO						
Negro Newborns (U.S.A.)	807	215	26.63	81	10.04	Lubs and Ruddle (1971)
ASIATIC						
Asiatic Part of USSR						
Uzbeks	250	11	4.40	3	1.20	Kuleshov et al. (1975)
India						
Rajput Normal Males	100	9	9.00	5	5.00	Ghosh and Singh (1975)
Punjabi Normal Males	100	10	10.00	6	6.00	Ghosh and Singh (1975)
Indian Normal Adults	100	7	7.00	6	6.00	Ghosh and Singh (1975)
Jat Normal Males	400	62	15.50	46	11.50	Kenue (1979)
Delhi Male Newborns	230	24	10.43	7	3.04	Bhasin et al. (1981)
Delhi Female Newborns	190	15	7.89	5	2.63	Bhasin et al. (1981)

Table 6: Incidence of deletions in the short arm (ph-) of D-G-group acrocentric chromosomes in various populations

Population	*Number of individuals*	*Short arm deletion of acrocentric chromosomes*				*Authors*
		D-Group		*G-Group*		
		No.	*Percent*	*No.*	*Percent*	
EUROPEAN						
Denmark						
Danish Newborns	5049	2	0.04	2	0.04	Friedrich and Nielsen (1973)
Danish Newborns	11148	6	0.05	2	0.02	Nielsen and Sillesen (1975)
United Kingdom						
Scots	2486	7	0.28	1	0.04	Ferguson-Smith (1974)
Edinburgh Newborns	1320	1	0.08	0	0.00	Buckton et al. (1980)
Fife Newborns	2673	1	0.04	0	0.00	Buckton et al. (1980)
United States of America						
Causasian Newborns	3476	2	0.06	0	0.00	Lubs and Ruddle (1971)
Normal and Institutionalized Children, Maryland	4735	21	0.45	2	0.04	Rary and Borgaonkar (1973)
Boston Newborn Males	13751	13	0.10	0	0.00	Walzer and Gerald (1977)
Canada						
Canadian Neonates	6929	4	0.06	0	0.00	Hamerton et al. (1972)
Canadian (Winnipeg)	13939	9	0.06	4	0.03	Hamerton et al. (1975)
U.S.S.R.						
Moscow Newborns	2500	1	0.04	0	0.00	Bochkov et al. (1974)
Estonians	208	2	0.96	1	0.48	Mikelsaar et al. (1975)
MIDDLE EAST						
Israel						
Jerusalem Newborns	500	0	0.00	1	0.20	Cohen et al. (1975)
NEGRO						
Negro Newborns (New Haven, USA)	807	0	0.00	0	0.00	Lubs and Ruddle (1971)
ASIATIC						
India						
Jat Normal Males	400	5	1.25	3	0.75	Kenue (1979)
Delhi Male Newborns	230	3	1.30	0	0.00	Bhasin et al. (1981)
Delhi Female Newborns	190	4	2.11	0	0.00	Bhasin et al. (1981)

some of the reports suggesting positive associations with clinical anomalies could be the results of fluctuations in these regions beyond the limits of tolerance.

Schnedl et al. (1975) reported that chromosome 15 short arm regions are rich in A-T parts in comparison to other D- and G- group chromosomes and show high variability. Wachter and Musil (1980) reported in short arm of chromosome 15 up to six regions to be highly polymorphic, apparently independent of each other.

Hills et al. (1991) reported that unusual acrocentric variants may be investigated using Ag-NOR staining and *in situ* hybridization of chromosomes from the proband and the probands parents is necessary.

Reddy and Sulcova (1998) analysed three polymorphic regions in acrocentrics that have been translocated to different chromosomes. These mutations are explained with the existence of homologous sequences in the break-points. Two children show malformations, and third is sterile. In each of the cases, clinical importance is derived from the heterochromatin.

As a whole, it can be inferred that heteromorphisms of short-arm regions of D- and G-group chromosomes, persist in populations usually without any detrimental effect. Since their mode of inheritance is in simple Mendelian fashion, the frequencies of their occurrence in different population groups are preserved and vary considerably among them as population variation.

1.2.2 Heteromorphisms Shown by Paracentromeric Long Arm Regions of Chromosomes 1, 9 and 16

The secondary constrictions at sites other than the short arms of acrocentric chromosomes, namely the paracentric constrictions in the long arms of chromosomes 1, 9 and 16 show high

variation both in size and position (Ferguson-Smith et al. 1962). These heteromorphisms have been well demonstrated by C-banding (Arrighi and Hsu 1971) and other various cytochemical staining techniques (Evans et al. 1971; Bobrow et al. 1972; Gagñe and Laberge 1972; Craig-Holmes et al. 1973, 1975; Galloway and Evans 1975; Angell and Jacobs 1975; Patil and Lubs 1977b; Balíček et al. 1977; Schweizer et al. 1978; Magenis et al. 1978; Mikelsaar et al. 1978; Sigmund and Schwarz 1979; Starke et al. 2002). Paracentromeric heteromorphic regions represent constitutive heterochromatin (Brown 1966) and are composed of different classes of highly repetitive DNA. Despite uniform chromosomal locations (centromere) and staining properly (C-banding) the DNA contents in C-band regions of nonhomologues may be quite dissimilar (Jones 1973; Gosden et al. 1975).

Verma et al. (1984) demonstrated by a high resolution banding technique that the secondary constriction region (h) of human chromosomes 1, 9 and 16 is not only heterochromatic (dark staining) but euchromatic (light staining) as well, which suggests the presence of different satellite DNAs in these regions.

The great interindividual variability of centromeric heterochromatin is well known (Craig-Holmes and Shaw 1971). Different views are available to explain the length variations detected in C-band regions. Donahue et al. (1968) and Sands (1969) suggested that increase in length of paracentromeric long-arm regions is attained by the uncoiling and elongation of heterochromatic regions. On the other hand, C- and G-banding techniques indicate that elongation of the heterochromatic regions might be due to partial duplication of the heterochromatic segment itself (Holzer and Rosenkranz 1972; Lobits et al. 1972). A variety of molecular and cytogenetic evidence supports the hypothesis that heteromorphisms result from unequal double strand exchange during mitotic DNAs replication (Kurnit 1979).

Numerous studies have demonstrated that C-band heteromorphisms are stable from cell to cell and are transmitted from generation to generation in a simple Mendelian fashion (Leisti 1971; Craig-Holmes et al. 1973; Fitzgerald 1973; de la Chapelle et al. 1974; Madan and Bobrow 1974; Nielsen et al. 1974b, c, d; Craig-Holmes et al. 1975; McKenzie and Lubs 1975; Sekhon and Sly 1975; Carnevale et al. 1976; Halbrecht and Shabtai 1976; Robinson et al. 1976; Magenis et al. 1977; Phillips 1977, 1980; Baliček et al. 1978; Mayer et al. 1978; Madan and Bruinsma 1979) except in some very rare events where one gets unequal crossing over, ultimately affecting the usual transmission (Ferguson-Smith 1974). By observing absolute concordance in twin data for these heteromorphisms, Iinuma et al. (1973) and Van Dyke et al. (1977) confirmed the heritability. However, Viegas and Salzano (1978) did not observe absolute concordance in their study of monozygotic twins. Preferential segregation of C-band heteromorphisms has also been reported in some studies (Dar and Winter 1969; Palmer and Schroeder 1971; Fitzgerald 1973; Palmer et al. 1974; Carnivale et al. 1976). Reciprocal heritable alterations of 1 qh heterochromatin in fibroblast surviving mitomycin-C treatment is reported by Hoehn and Martin (1972, 1973), whereas Hoehn et al. (1977) reported somatic stability of C-band heteromorphisms.

Wegner and Pawlowitzki (1981) have used inverted, oblique illumination to study C-bands of human chromosomes 1 and 9 (Wahedi and Pawlowitzki 1987) and the advantage of Ce-bands in quantitative studies is that it is no longer necessary to rely an length measurements due to problems in these have often been pointed out (Benyush et al. 1977; Mason et al. 1978; Podugolnikova et al. 1979a, b, c).

The heteromorphisms in size and inversion of C-band have been reported among various population groups, where a wide range of variation has been observed in their frequency distribution.

Polymorphisms of C-bands are used for segregation analysis (Craig-Holmes et al. 1975), for gene mapping (Chaganti et al. 1975; Ferguson-Smith et al. 1975), for detection of inversions (Mayer et al. 1978) and dicentric translocations (Daniel 1979). Other applications are paternity testing (Müller et al. 1975) and determination of zygosity in twins (Van Dyke et al. 1977; Viégas and Salzano 1978).

1. Size Heteromorphisms: The methodical problem of size heteromorphisms is the quantification of polymorphisms. Attempts to solve the technical problems of length measurements (Benyush et al. 1977) and variable contraction of heterochromatic regions are made (Balièek et al. 1977; Schmiady and Sperling 1976).

In addition, a variety of procedures for quantification of C-band polymorphisms are described

as it is evident from the literature that various authors have utilised different scoring methods to study the heteromorphisms demonstrated by C-band constitutive heterochromatin at paracentromeric secondary constriction regions of chromosom 1, 9 and 16. Initially, Craig-Holmes et al. (1973, 1975), McKenzie and Lubs (1975) and others attempted to classify these heteromorphisms as discrete classes by the visual arbitrary scoring methods and further classified them into three size categories viz., normal (N), large (+) and small (-). Müller et al. (1975) selected 21q as the internal standard within the cell for reference, whereas Lubs et al. (1977a) and Patil and Lubs (1977b) chose the short arm of chromosome 16, which had been proved to be less variable than other chromosomal segments in the complement (Ledley et al. 1972; Lubs et al. 1975) as a standard reference within the cell and classified these into five size levels[5]. These are not discrete levels, but they represent class categorization of the continuous variations to facilitate interpretation of the distribution of different C-band sizes as described by Patil and Lubs (1977b). Balicek et al. (1977, 1978) however, recommended direct linear measurements on uniformly enlarged C-stained regions of chromosomes and have showed familial transmission to the C-band size heteromorphisms. Schmiaday and Sperling (1976) have reported allocyclic behaviour of C-band constitutive heterochromatin in man, which indicates that the linear measurement methods have yet to be verified for reliability and consistent results. With a further intracellular standard (Iq-h) different mathematical approaches were introduced to correct the variable contraction in the heterochromatic region (Balièek et al. 1977; Friedrich and Therkelsen 1982).

Different investigators have used different criteria for scoring heteromorphisms in their respective study and due to that reason it is not possible to compare these results. This makes it difficult to differentiate between the relative contributions of populational or technical factors.

The studies reported among various population groups are compiled for the size and inversion C-band heteromorphisms, and are listed in Table 7. The incidence of 1 qh+ among Europeans ranges from total absence in Caucasians of Colarado (Verma et al. 1978a) to 8.10 percent (newborns of New York; Müller et al. 1975). Among Negro population groups it varies from nil (American Blacks by Verma et al. 1981b) to 6.18 percent (Black 7 and 8 year old children by Lubs et al. 1977b). Among Indian population groups the frequencies are found to be between nil (Delhi female newborns by Bhasin et al. 1981) and 10.00 percent (Indian normal individual by Ghosh and Singh 1976).

For 1qh-, the incidence varies from nil (Estonian females by Kivi and Mikkelsar 1980) to 14.28 percent (Caucasians of Texas by Craig-Holmes 1977). Among the Negro population groups it ranges from 2.58 percent (Black 7 and 8 year old children by Lubs et al. 1977) to 10.00 percent (American Blacks by Verma et al. 1981b). Among the Asiatic groups the frequency for 1qh- varies from complete absence among female newborns of Delhi (Bhasin et al. 1981) to 24.00 percent (Orientals by Park and Antley 1974). Among male newborns of Delhi (Bhasin et al. 1981) the incidence of 1qh- is 2.50 percent which is similar to that of Edinburgh children studied by Buckton et al. (1976).

Among Europeans, the frequency of partial inversion in the C-band region of chromosome 1 ranges from total absence in many populations to 1.00 percent (Colarado Caucasians by Verma et al. 1978a). Among Negro population groups it varies from 0.03 percent (Black newborns and 7 and 8 year old children by Lubs et al. 1977b) to 17.50 percent (American Blacks by Verma et al., 1981b). Among Asiatic groups, the range of frequency varies from 0 (normal individuals of India by Ghosh and Singh 1976; Orientals by Park and Antley 1974) to 11.00 percent among male newborns of Delhi (Bhasin et al. 1981) which is a relatively high frequency. A similar frequency has been observed among Jat normal males (Kenue 1979) and Colarado Caucasians (Verma et al. 1978a).

Complete inversion of the C-band region of chromosome 1 has been observed only among Estonians of Europe and male newborns of Delhi (Bhasin et al. 1981) with the frequency range between 0.20 percent (Estonian normal adults by Tüür et al. 1974) and 3.80 percent (Estonian females by Kivi and Mikelsaar 1980). There are reports where individual familial cases of complete inversion of chromosome 1 C-band region have been cited (Nance and Engel 1967; Bhasin et al. 1973; Jacobs et al. 1974a; Lee et al. 1974; Howard-Peebles 1978)

Among Europeans, frequency of 9qh+ varies from complete absence among White newborns and Black 7 and 8 year old children (Lubs et al. 1977b), Colarado Caucasians (Verma et al. 1978a) and Estonian females (Kivi and Mikelsaar 1980) to 12.90 percent (Greek normal individuals by Metaxotou et al. 1978). Among Negro population groups it varies between nil (American Blacks by Verma et al. 1981b) and 5.15 percent (Black 7 and 8 year old children by Lubs et al. 1977b). Among Asiatic population groups the range varies from total absence among both the sexes of newborns of Delhi (Bhasin et al. 1981) to 8.30 percent among Indian normal individuals (Ghosh and Singh 1976). The frequency distribution for the incidence of 9qh- among Europeans varies from nil (White newborns and Black 7 and 8 year old children by Lubs et al. 1977 and Estonian females by Kivi and Mikelsaar 1980) to 24.40 percent among Colarado Caucasians (Verma et al. 1978a). Among Negro population groups it ranges from 1.55 percent (Black 7 and 8 year old children by Lubs et al. 1977b) to 13.75 percent. Among Asiatic population groups it varies from nil among both the sexes of the newborns of Delhi (Bhasin et al. 1981) to 9.70 percent (Jat normal males by Kenue 1979).

Among Europeans, the frequency of complete inversion in the C-band region of chromosome 9 varies from nil (Barras populations by Buckton et al. 1976; Colarado Caucasians by Verma et al. 1978a and Winnipeg newborns by Wang and Hamerton 1979) to 6.30 percent (Estonian females by Kivi and Mikelsaar 1980). For Negro population groups the range is between 0.56 percent (Black newborns and 7 and 8 year old children by Lubs et al. 1977b) to 1.30 percent (American Blacks by Verma et al. 1981b). Among the Asiatic groups, the incidence varies from 0.87 percent (Jat normal males by Kenue 1979) to 3.30 percent (Indian normal individuals by Ghosh and Singh 1976).

The incidence of 16qh+ varies from nil (Barras population by Buckton et al. 1976; adults of Texas by Craig-Holmes et al. 1973; newborns of New York by Müller et al. 1975; Colarado Caucasians by Verma et al. 1978a and Estonian females by Kivi and Mikelsaar 1980) to 6.00 percent (Indiana Caucasians by Palmer et al. 1975). Among Negro population groups the range is between 0.63 percent (American Blacks by Verma et al. 1981 b) and 2.06 percent (Black 7 and 8 year old children by Lubs et al. 1977b). Among Asiatic population groups the range varies from nil (Newborns of Delhi by Bhasin et al. 1981) to 9.00 percent (Orientals by Park and Antley 1974). The frequency for 16qh- ranges from 0.04 percent (Estonian females by Kivi and Mikelsaar 1980) to 23.60 percent (New York newborns by Müller et al. 1975). The incidence of 16qh- is relatively high among Negro population groups, varying from 19.58 percent (Black 7 and 8 year old children by Lubs et al. 1977b) to 40.00 percent (American Blacks by Verma et al. 1981b). Among Asiatic groups the range is between 1.00 percent (Delhi newborns by Bhasin et al. 1981) to 18.20 percent (Jat normal males by Kenue 1979).

Partial inversion in the C-band region of chromosome 16 has been observed only among New York newborns (1.40 percent), whereas complete inversion in C-band region of chromosome 16 has not been reported in various population studies. However, individual cases have been reported in the literature (del Solar and Uchida 1974; Fonatsch 1977). This could be because the C-band on chromosome 16 is much smaller than on chromosomes 1 or 9, and partial minor inversion may be very difficult to visualize and a transfer of C-band to the short arm from the long arm may not bring an overall change in morphology.

The frequency of partial inversion among Europeans for the C-band region of chromosome 9 ranges from nil (Estonian females by Kivi and Mikelsaar 1980) to 16.00 percent (Greek individuals by Metaxatou et al. 1978). Among Negro populations the range is from 0.25 percent (Black newborns) to 2.60 percent (American Blacks by Verma et al. 1981b). Among Asiatic populations the range is relatively high, varying from total absence (Indian normal males by Ghosh and Singh 1976) to 22.50 percent among male samples of Delhi (Bhasin et al. 1981).

Using densitometric C-band measurements, Cavalli et al. (1984) and Zanenga et al. (1984) reported smaller C-band sizes in Japanese than in Caucasians and in Blacks when compared to Caucasoid in their respective studies suggesting ethnic/racial variations of C-band size heteromorphisms in chromosomes 1, 9 and 16. Ethnic/racial variation in C-band size heteromorphisms has not been concluded yet because of varied scientific methodology used in different studies (Erdtmann 1982). Ethnic variation in chromosomal polymorphisms of 1, 9, 16 and Y has been recorded from amniotic fluid specimens also

Table 7: Precentage of C-band size and inversion heteromorphisms of chromosomes 1, 9 and 16 in various populations

S. No.	Population	No. of individuals	1q12					
			Size heteromorphism			Inversion heteromorphism		
			+	-	T	PI	CI	T
EUROPEAN								
United Kingdom								
1.	Edinburgh Newborns	467	3.00	4.10	-	1.40	0	-
2.	14 year Old Children (Edinburgh)	101	5.40	2.50	-	0.50	0	-
3.	Barra Population (Scotland)	149	3.70	1.70	-	1.70	0	-
Greece								
4.	Greek Individuals	600	-	-	-	-	-	-
France								
5.	French (Paris)							
Sweden		70++	0	13.6	-	-	-	4.3
6.	Swedesh (Lund)	78++	0	1.3	-	-	-	9.0
Italy								
7.	Italians (Tuscany)	469++	0	11.1	-	-	-	-
Central Europe								
8.	Whites	20	-	-	4.50	-	0	-
United States of America								
9.	Normal Adults (Texas)	20	2.50	10.00	-	0	0	-
10.	Causcasians (Texas)	43	-	-	-	-	-	-
11.	Caucasians (Texas)	53	-	-	-	-	-	-
12.	Caucasians (Indiana)	74	1.00	9.00	-	-	-	2.00
13.	Newborns (Colarado)	77	1.90	4.50	-	0	0	-
14.	Newborns (New York)	376	8.10	0.60	-	1.60	0	-
15.	White 7 & 8 year Old Children	95++	5.70	1.05	-	-	-	-
16.	White Newborns and 7 & 8 Year Old Children	3084	-	-	-	0.22	-	-
17.	Causcasian (Texas)	35	4.28	14.28	-	0	0	-
18.	Caucasians (Colarado)	80++	0	10.00	0	-	-	-
Canada								
19.	Winning Newborns	165	-	-	-	0.90	0	-
USSR								
20.	Estonian Normal Adults	208	0.70	-	-	0	0.20	-
21.	Estonian Females	40++	0.01	0	-	0	3.80	-
Highland Mongoloids								
22.	Kirghiz of Pamir	110++	0	5.0	-	-	-	-
23.	Kirghiz of Tien Shan	100++	0	5.5	-	-	-	-
Steppe Mongoloids								
24.	Kazakhs	50++	0	6.0	-	-	-	-
25.	Chinese (Dunghans)	115++	0	4.8	-	-	-	-
26.	Mongolians	72++	0	6.2	-	-	-	-
NEGRO								
27.	Black 7 & 8 year Old Children	97++	6.18	2.58	-	-	-	-
28.	Black Newborns and 7 & 8 Year Old Children	1780	-	-	-	0.03	-	-
29.	American Blacks	80++	0	10.00	-	17.50	0	-
ASIATIC								
30.	Orientals (Indians)	49	4.00	24.00	-	0	-7.00	
Japan								
31.	Japan Normals	29	-	-	15.50	-	-	-
32.	Japanese (Hiroshima)	993	0.40	-	-	0.30	0	-
China								
33.	Han	56	0	0	-	-	-	-
34.	Li	19	0	0	-	-	-	-
Indian								
35.	East Indians	100++	0	14.0	-	16.5	1.0	-
36.	Normal Individuals	30	10.00	1.70	-	0	0	-
37.	Jat Normal Males	400++	1.50	5.25	-	7.25	0	-
38.	Punjabis	100	7.00	1.50	-	0	-	-
39.	Rajputs	100	6.50	3.50	-	0	-	-
40.	Delhi Male Newborns	100++	1.00	2.50	-	11.00	0.50	-
41.	Delhi Female Newborns	100++	0	0	-	5.00	0	-
Central Europe								
42.	Whites	20	-	-	4.50	-	-	0

* Percent per Chromosome = Twice the Number of Subjects. ++ Level 5 for + and Level 1 for - Heteromorphisms
PI = Partial Inversion CI = Complete Inversion

Table 7: contd.....

S. No.	9q12						16q11						Authors
	Size heteromorphism			Inversion heteromorphism			Size heteromorphism			Inversion heteromorphism			
	+	-	T	PI	CI	T	+	-	T	PI*	CI*	T	
1.	2.20	4.80	-	3.70	0.70	-	2.10	2.20	-	0	0	-	Buckton et al. (1976)
2.	3.50	6.40	-	1.00	1.00	-	4.90	4.90	-	0	0	-	Buckton et al. (1976)
3.	3.00	3.70	-	0.30	0	-	0	3.00	-	0	0	-	Buckton et al (1976)
4.	12.90	7.90	-	16.00	2.00	-	-	-	-	-	-	-	Metaxatou et al. (1978)
5.	0	33.6	-	-	-	10.0	0	85.0	-	-	-	0	Berger et al. (1983)
6.	0	9.5	-	-	-	21.8	0	61.5	-	-	-	2.6	Berger et al. (1983)
7.	0	35.6	-	-	-	-	0	77.1	-	-	-	-	Simi and Tursi (1982)
8.	-	-	14.00	-	-	0.50	-	-	1.00	-	-	-	Kalz and Schwanitz (2004)
9.	5.00	7.50	-	-	2.50	-	0	17.50	-	0	0	-	Craig-Holmes et al. (1973)
10.	7.00	1.00	-	-	-	0	-	-	-	-	-	-	Palmer et al. (1975)
11.	-	-	-	-	-	0	-	1.00	-	0	0	-	Palmer et al. (1975)
12.	-	-	-	-	-	-	-	-	-	-	-	-	Palmer et al. (1975)
13.	7.10	4.50	-	-	-	3.90	5.20	11.70	-	0	0	-	McKenzie and Lubs (1975)
14.	8.00	0.40	-	10.70	0.60	-	0	23.60	-	1.40	-	-	Muller et al. (1975)
15.	3.60	2.63	-	-	-	-	1.05	17.36	-	-	-	-	Lubs et al. (1977b)
16.	0	0	-	0.27	0.06	-	-	-	-	0	0	-	Lubs et al. (1977b)
17.	1.00	1.00	-	-	2.85	-	2.85	12.85	-	0	0	-	Craig-Holmes (1977)
18.	0	2.44	-	11.25	0	-	0	48.10	-	0	0	-	Verma et al. (1978a)
19.	-	-	-	3.30	0	-	-	-	-	-	-	-	Wang and Hamerton (1979)
20.	-	-	-	-	-	-	-	-	-	-	-	-	Tuur et al. (1974)
21.	0	0	-	0	6.30	-	0	0.04	-	0	0	-	Kivi and Mikkelsaar (1980)
22.	0	13.2	-	-	-	-	0	84.6	-	-	-	-	Ibraimov et al. (1982b)
23.	0	7.5	-	-	-	-	0	89.5	-	-	-	-	Ibraimov et al. (1982b)
24.	0	9.0	-	-	-	-	0	90.0	-	-	-	-	Ibraimov et al. (1982b)
25.	0	8.7	-	-	-	-	0	86.9	-	-	-	-	Ibraimov et al. (1982b)
26.	0	9.0	-	-	-	-	0	88.9	-	-	-	-	Ibraimov et al. (1982b)
27	5.15	1.55	-	-	-	-	2.06	19.58	-	-	-	-	Lubs et al. (1977b)
28.	-	-	-	0.25	0.56	-	-	-	-	0	0	-	Lubs et al. (1977b)
29.	0	13.75	-	20.60	1.30	-	0.63	40.00	-	0	0	-	Verma et al. (1981)
30.	6.00	8.00	-	-	-	3.10	9.00	18.00	-	0	0	-	Park and Antley (1974)
31.	-	17.24	-	-	-	-	-	17.20	-	-	-	-	Iinuma et al. (1973)
32.	0.15	-	-	-	-	0.55	0.30	-	-	0	0	-	Sofuni et al. (1977)
33.	0	0	-	-	-	-	0	0	-	-	-	-	Li et al. (1982)
34.	0	0	-	-	-	-	0	0	-	-	-	-	Li et al. (1982)
35.	0	7.0	-	21.0	0	-	0	370	-	15	0	-	Verma et al. (1982b)
36.	8.30	6.70	-	0	3.30	-	5.00	8.30	-	0	0	-	Ghosh and Singh (1981)
37.	1.10	9.70	-	10.37	0.87	-	0.50	18.20	-	-	-	-	Kenue (1979)
38.	4.00	3.00	-	1.00	-	-	7.50	10.50	-	0	-	-	Nand et al. (1981)
39.	5.00	4.00	-	2.50	-	-	5.50	15.00	-	0	-	-	Nand et al. (1981)
40.	0	0	-	22.50	1.00	-	0	1.00	-	0	0	-	Bhasin et al. (1981)
41.	0	0	-	15.50	1.00	-	0	1.00	-	0	0	-	Bhasin et al. (1981)
42.	-	-	-	14.00	-	-	0.50	1.00	-	-	-	-	Kalz and Schwanitz (2004)

(Shapiro et al. 1984; Hsu et al. 1987; Kalz and Schwanitz 2004). Kalz and Schwanitz (2004) who observed that the frequencies of polymorphisms for amniocytes are significantly higher than for lymphocytes for 1, 9, and 16 chromosomes.

Thompson and Roberts (1987) and Pinel et al. (1988) reported four and two cases of a new variant of chromosome 16 with an additional euchromatic segment in the proximal region of the short arm, respectively. Thompson et al. (1990) reported another case of this variant (with GTG and CBG banding) in which they have carried out replication studies by RBG staining and observed additional maternal to be light staining, similar to the inactive X and late replicating chromosome regions.

1) meiotic or mitotic crossing over in those heterochromorphic regions which are composed of various classes of repetitious DNA (Ferguson-Smith 1974) and

2) a two break event leading to the insertion or an interbinary deletion (Hansman 1976). Although crossing over in these regions is very rare, the study of Page (1973) however, revealed that in male meiosis, paracentromeric heterochromatin in chromosome 9 remained extended, and some chromosome 9 bivalents had chiasmata in position, suggesting crossing over between the centromere and heterochromatic region.

Hulten (1974) reported that 2 out of 34 chromosome 9 bivalents had chiasmata in their long arm very close to the centromeres, thus supporting Page's study (Page 1973). As the inverted heterochromatic segments get larger relative to the length of the chromosome involved, the chances of one chiasmata formation increase. This could lead to the production of duplication-deficiency gametes which may or may not be genetically balanced, whereas in the case of inversion heteromorphisms involving a short segment, the chances of chiasma formation are very low, and they would generally produce genetically balanced gametes. Therefore, theoretically inversion (9) with the smaller C-band size should be more frequent than with the larger C-band size if these regions have some biological functions in the genome, the alteration of which could produce deleterious effects. As evidence, some of the reports have suggested association of inv (9) with reproductive failures, mental development and non-disjunction; but the hypothesis is yet to be proved conclusively on the basis of cause and effect. Boue et al. (1975a) and Osztovics et al. (1977) observed a high male ratio among the carriers of inv (9), and suggested that the development of the female gametes with inv (9) may be disturbed. Earlier, Moorhead (1976) reviewed the data on inversion in man, and concluded that inversion itself may not directly cause clinical anomalies and the proportion of clinically abnormal offsprings due to crossing over induced duplication deficiency is small. In most of the cases, the inversion heteromorphisms either cause little clinical harm or the undesirables are selected against at an earlier embryonic stage. Verma et al. (1978a, 1981b) however, observed interrelationship between the size of the heterochromatic region and the inversion. Most of the inversions in these studies have found to have a large C-band chromosomessize than the chromosomes without inversion. These results suggest the maintenance of these heteromorphisms in normal populations by morphological alterations occurring very rarely in C-band regions, on the one hand as reported by Craig-Holmes et al. (1975), and selective pressures operating against them on the other.

C-band size and inversion heteromorphisms have also been associated with various clinical conditions. Atkin (1977) observed that heteromorphisms for the size of C-bands of chromosome 1 are more frequent in patients with malignant diseases, than in controls. Atkin and Baker (1977a, b) and Shabtai and Halbrecht (1979) also reported partial pericentric inversions, along with size heteromorphisms, to be more common in the patient group as compared to the controls. However, Kivi and Mikelsaar (1980) found no correlation between presence of C-band heteromorphism and elevated risk to ovarian or breast carcinoma. Nielsen et al. (1974b) have not found significant differences in the prevalence of 1qh+ between normal and institutionalized individuals. The variability of centromeric heterochromatin in chromosome 1 is said to bear a relationship to foetal wastage (Kunze and Mau 1975) and recurrent abortion (Tsenghi et al. 1976; Ford 1977); but the same is not observed by Hemming and Burns (1979). Heteromorphism of 1qh+ has been associated with congenital malformations (Gardner et al. 1974; Kunze and Mau 1975; Halbrecht and Shabtai 1976) including the Chediek-Higashi syndrome (Salamance-Gomez et al. 1978), and it has been postulated by Gardner et al. (1974) that although heterochromatin itself is harmful, its potential to harm may usually be

masked by an unstimulating genome. Kim (1973) has observed three distinct types of C-bands on A-1 segregating among five offspring. Wegner and Pawlowitzki (1981) reported that Ce-band pattern adds some further but still preliminary evidence, that variation of 1qh is based on discrete blocks of heterochromatin. Ce-bands may be successfully used for segregation analysis. Possibly they might help in studies depending upon quantification of C-band polymorphisms such as paternity testing, gene mapping etc.

Heteromorphism 9 ph+ has been associated with repeated spontaneous abortions and malformed stillborn infants (Boue and Boue 1975a). Holbek et al. (1974) observed a high frequency of 9qh+ in parents of chromosomally abnormal abortions, whereas Hemming and Burns (1979) have not encountered significant difference in the 9qh+ regions between aborting and non-aborting couples. Kunze and Mau (1975) reported high frequency of 9qh+ heteromorphism in patients with multiple congenital malformations. Nielsen and Sillesen (1975) observed 9 qh+ heteromorphism in 8.00 percent of the members of children with *de novo* major chromosomal aberrations; where as the incidence of 9 qh+ was 0.04 percent among newborns. Lubs et al. (1977b) observed a steady drop in intelligence quotient score as the amount of 9qh material increased in Negro children. Soudek and Sroka (1979) observed a higher incidence of 9qh+ in the mentally retarded as compared to normal controls. Contrary to this, Madan and Bobrow (1974) did not observe any adverse effect of 9qh+ in their study. Ford and Lester (1978) suggested that 9qh and inv (9) play significant roles in non-disjunction. Shabtai and Halbrecht (1979) observed significantly increased incidence of 9qh and inv (9) in patients with malignant and premalignant diseases. Inversion 9 heteromorphisms have been shown to be significantly more frequent in mentally retarded children than in newborns (Lubs and Lubs 1972). Inversion has been associated with reproduction failures (Boue et al. 1975; Tsvetkova and Yankova 1979; Tsvetkova 1980; Tibiletti et al. 1981). Osztovics et al. (1977) also reported a higher incidence of inv (9) in subjects with reproductive failures in comparison with the malformed subjects or parents of subjects with chromosomal anomalies. However, Lubs (1977) did not find any significant foetal loss in families with inv (9). Tharapel and Summitt (1978) reported a high frequency of inv (9) in unclassifiable mentally retarted patients as compared to normal controls. In none of these conditions, however, could the role C-band variants be proved unequivocally (Erdtmann 1982)

16qh+ heteromorphisms have been frequently associated with congenital heart disorders (Makino 1963; Sasaki et al. 1963; German et al.1966; Kelly and Almy 1971). Nielsen et al. (1974c) have not observed any association of 16qh+ with developmental or reproductive effects. Frequency of 16qh+ is found to be almost equal in institutionalized and normal individuals. Soudek and Sroka (1979) noticed high frequency of 16qh+ in the mentally retarded when compared to the controlled group.

Say et al. (1977), using C-banding technique, reported a high prevalence of qh+ heteromorphisms in psychiatric patients. Kucerova and Palivkova (1977) studied the following four groups:

(1) persons with abnormal karyotype and abnormal phenotype,

(2) persons with only abnormal phenotype,

(3) healthy nearest relatives of persons with abnormal phenotype and karyotype and

(4) normal healthy persons with normal phenotype and karyotype, without congenital malformation in family history.

They did not, however, observe significant difference between these groups for qh heteromorphisms. Similarly, Wang and Hamerton (1979) studied C-band polymorphisms of chromosomes 1, 9 and 16, in

(1) newborns

(2) Down's syndrome patients

(3) patients with acquired mental retardation

(4) idiopathic patients and

(5) idiopathic with multiple congenital malformations.

The C-band size of chromosomes 1, 9 and 16 showed a similar normal distribution in all five groups, and no significant sex difference in the data from any of the five groups is noticed. A significantly higher frequency of C-bands, some of which are located on the short arm of chromosome 9, is observed in the groups of patients with Down's syndrome and with idiopathic mental retardation. Any relationship could not be established between qh+ heteromorphisms and chromosomal anomalies or reproductive failures (Osztovic et al. 1977; Hemming and Burns 1979;

Brown et al. 1980; Blumberg et al. 1982; Maes et al. 1983; Rodriguez-Gómez et al. 1987). These results are inconsistent (Tho et al. 1982; Verma et al. 1983b) mainly due to the lack of objective C-band evaluation and well paired controls (Erdtmann 1982).

Some reduction of C-segment lengths and their variability on chromosomes 1, 9, 16 and Y is exhibited by children who had some disturbances at early stages of morphogenesis (Podugolinikova and Blumina 1983). From data, they suggested that this may be due to certain activity of the heterochromatic regions during embryo development.

Centromeric instability of chromosomes 1, 9, and 16 has been described in eight patients with variable immunodeficiency (Hulten 1978; Tiepolo et al. 1979; Carpenter et al. 1988; Marsachio et al. 1988; Turleau et al. 1988). Although the pathogenetic relationships of these cytogenetic abnormalities with the clinical symptoms are not clear, it has nevertheless been proposed that they are a hallmark of this syndrome. Based on the clinical, immunological and cytogenetic data from the literature, Haas (1990) presented a model suggesting that the cytogenetic changes are not causatively involved in the immunodeficiency syndrome, but result from specific virus infections occurring as a consequence of the immunodeficiency in genetically predisposed individuals.

Precise knowledge of the role of constitutive heterochromatin in the developmental or reproductive cycle of an individual is yet to be acquired. No heteromorphism has exclusively been attributed to one or a group of clinical anomalies. Lubs (1977) postulated that future researches may reveal subclasses of these heteromorphisms and that one or a group of these subclasses may be associated with clinical abnormality.

It can be concluded that the variations in the incidence of C-band heteromorphisms are mainly due to population difference. At times, they may be associated with some clinical conditions because they may carry some structural load; otherwise populations bearing these heteromorphisms are apparently normal.

1.2.3 Variation in the Length of Y Chromosome

Extreme variation in the long arm of Y chromosome was first suggested at the London Conference (1963) after Patau's (1960) reported observation of such variability. Even before the advent of banding techniques, the length of human Y chromosome has been known to vary from man to man and in different population groups (Cohen et al. 1966). This variability is evident in the heterochromatic regions, specifically in the distal two-third of the long arm of Y chromosome (Bobrow et al. 1971; Borgaonkar and Hollander 1971; Laberge and Gagne 1971; Lewin and Conen 1971; Robinson and Buckton 1971; Schnedl 1971b; Wahlström 1971; Knuutila and Gripenberg 1972; Müller et al. 1972; Nielsen and Friedrich 1972; Tishler et al. 1972; Soudek et al. 1973; Jalal et al. 1974; Geraedts et al. 1975; Brogger and Urdal 1978; Mckay et al. 1978), simultaneously it has been suggested that genetically active material is located in the non-banded segment, and it is considered to be invariable in size (Babrow et al. 1971; Laberge and Gagne 1971; Knuutila and Gripenerg 1972). However, some authors have reported modest variation (Schnedl 1971b; Soudek et al. 1973; Verma et al. 1978b; Kenue 1979).

Variation in the length of Y chromosome is being postulated to be owing to the difference in coiling of the chromatin (Wenström and de la Chapelle 1963; Court Brown 1967), whereas other studies suggested that it is due to duplication and deletion in the large heterochromatic segment of the Y chromosome (Sperling and Lackmann 1971; Wahlström 1971; Knuutila and Gripenberg 1972; Tishler et al. 1972; Drets and Seuanez 1974; Jalal 1974; Verma et al. 1978b). Skawiñski and Parcheta (1984) observed that changes in the DNA content and length of Y chromosome are correlated both with the length of heterochromatin as well as length of euchromatin.

1. Distribution of Y/F Index: The results using the Y chromosome length relative to the larger chromosome may not give reliable results since it was reported that the process of the chromatids at a given stage of the metaphase could stain the larger chromosomes more intensely than the smaller ones (Sasaki 1961; Fitzgerald 1965; Brogger et al. 1977). Cohen et al. (1966) examined different methods and suggested that the most reliable method[6] is to compare the length of the Y chromosome with the average length of the F group chromosomes, which has been reported to be a less variable group in comparison with other groups (Ledley et al. 1972; Lubs et al. 1975).

The mean values of Y/F ratio, standard deviation coefficient of variation and variance are presented in Table 8. Among Europeans, the mean Y/F distribution varies from 0.8400 (Danish newborns by Nielsen and Friedrich (1972) and Danish normal males by Nielsen and Nordland, (1975) to 1.0220 (Caucasians by Verma et al. 1978b), whereas among Negroes the value is 0.9223. Among Asiatic population groups, the range of mean Y/F varies from 0.6215 (Jats by Yadav et al. 1996) to 1.0200 (Japanese by Kadotani et al. 1971). Among Australian aborigines its value is 0.8843; Cohen et al. (1966) reported that the mean length of Y chromosome in Japanese males is significantly greater than that in American Negroes, Jews of Eastern Europe, Non-Jews of Anglo-Saxon origin and Asiatic Indians. Similarly, Angell (1973) noted that the mean length of the Y chromosome in the Australian aborigines is significantly shorter than in White Australians.

Table 8: The value of mean Y/F, their standard deviation, coefficient of variation and variance in various population groups

Population	*No. of males studied*	*Mean Y/F*	*Standard deviation*	*Coefficient of variation*	*Variance*	*Authors*
EUROPEAN						
Sweden						
Swedish Normal Males	49	0.8800	0.0700	7.950	0.004900	Akesson and Wahlstrom (1977)
Denmark						
Danish Newborns	140	0.8400	0.0700	8.300	0.004900	Nielsen and Friedrich (1972)
Danish Normal Males	508	0.8800	0.0676	7.680	0.004570	Zeuthen and Nielsen (1973a)
Danish Normal Males	48	0.8400	0.0700	8.330	0.004900	Nielsen and Nordland (1975)
United Kingdom						
Non-Jews	20	0.8621	0.0887	10.300	0.007868	Cohen et al. (1966)
Germany						
Germans	40	0.9856	0.0828	8.400	0.006848	Schnedl (1971b)
France						
French Normal Males	50	0.9210	0.0840	9.120	0.007056	Benezech et al. (1976)
Eastern European Jews	20	0.9416	0.0998	10.600	0.009960	Chen et al. (1966)
United States of America						
Caucasian Normal Males	60	1.0220	0.0900	8.810	0.008100	Verma et al. (1978b)
Canada						
Canadian Normal Males	38	0.9700	0.0625	6.400	0.003906	Soudek and Laraya (1974)
Royal Military College Cadets	100	0.9455	0.0901	9.533	0.008125	Soudek and Sroka (1979)
Australia						
White Australians	15	0.9833	0.0562	5.713	0.03156	Angell (1973)
NEGRO						
Blacks (U.S.A.)	60	1.09	0.1000			Verma et al. (1982a)
Negroes (U.S.A.)	20	0.9223	0.0868	9.400	0.007531	Cohen et al. (1966)
ASIATIC						
Japan						
Japanese	11	0.8730	0.0510	5.800	0.002601	Makino and Takagi (1965)
Japanese	20	1.0019	0.1527	15.200	0.023317	Cohen et al. (1966)
Japanese	51	1.0200	0.0860	8.400	0.007396	Kadotani et al. (1971)
India						
Indians	20	0.8842	0.1081	12.200	0.011606	Cohen et al. (1966)
Punjabis	100	0.7971	0.1025	12.900	0.010506	Ghosh and Singh (1975)
Rajputs	100	0.9019	0.1429	15.800	0.020420	Ghosh and Singh (1975)
Jat Normal Males	400	0.8807	0.1567	17.790	0.024554	Kenue (1979)
Delhi Newborns	170	0.8056	0.0897	11.132	0.008042	Bhasin et al. (1981)
Jat	20	0.6215	0.1620	20.000	0.026300	Yadav et al. (1996)
Ahir	20	0.6710	0.1669	14.800	0.027890	Yadav et al. (1996)
Saini	20	0.7080	0.1793	15.300	0.032230	Yadav et al. (1996)
Kamboj	20	0.6370	0.1976	13.000	0.039170	Yadav et al. (1996)
Ror	20	0.6495	0.1846	12.400	0.034250	Yadav et al. (1996)
ABORIGINALS						
East Indians (U.S.A.)	70	1.20	0.1000			Verma et al. (1983a)
Australian Abroriginals	14	0.8843	0.0811	9.174	0.006582	Angell (1973)

Ethnic differences are also observed between Rajputs and Punjabis - two endogamous groups of north India (Ghosh and Singh 1975). Müller and Walter (1996) applying computer supported analysis system reported that the indices of the Y chromosome, like the Y/F-Index, are not suitable for population genetic studies, because standard deviations of most of these investigations are too large to distinguish different populations. And, the range of most Y/F indices, therefore is not spread wide enough to make statements concerning the relationship of different populations. They concluded that it seems much more informative to study Y-specific DNA-polymorphisms, like Restriction Fragment Length Polymorphisms (RELPs) or Variable Number of Tandem Repeats (VNTR's).

2. Incidence of Long and Short Y Chromosome: Incidences of the long and short Y chromosome in various populations are listed in Table 9. The frequency of long Y chromosome among Europeans ranges from 0.14 percent in Edinburgh newborns (Buckton et al. 1980) to 40.00 percent in Australian Whites (Angell 1973).

Among Jerusalem newborns the frequency is found to be 5.76 percent. Among Negroes it is 14.83 percent. Among Asiatic groups the incidence varies from 0.85 percent (Uzbecks of the Asiatic part of USSR by Kuleshov et al. 1975) to 12.12 percent (Ainus population by Komatsu and Hirai 1975).

As is evident from Table 9 the short Y chromosome has not been recorded in some populations. Among Europeans, the range of short Y chromosome varies from 0.11 percent (Military Cadets of Canada by Soudek and Sroka 1979) to 7.00 percent (Estonians by Mikelsaar et al. 1975). Lubs and Patil (1975) suggested that there exists a north/south gradient in the length of the Y chromosome in Europeans; men of Mediterranean origin have a longer Y chromosome. Among Jerusalem newborns from the Middle East (0.4 percent) and the Negro population (0.48 percent) the incidence is almost similar. Among Asiatic population groups, the incidence of short Y chromosome ranges from 0.75 percent (Jat normal males by Kenue 1979) to 6.06 percent (Ainus population by Komatsu and Hirai 1975).

The incidence of pericentric Y [inv (Y)] in various populations (males only) is 5 in 10634 (0.5) among Whites (Cohen et al. 1966; Lubs and Ruddle 1971; Patel et al. 1977; Verma et al. 1983a; Cavalli et al. 1984; Shapiro et al. 1984; Bernstein et al. 1986) 14 in 28280 (0.49) in Whites (ethnic groups are not specified; but presumed to be Caucasoids from the area of survey) (Jacobs et al. 1964, 1971, 1974; McIlree et al. 1966; Sergovich et al. 1969; Gerald and Walzer 1970; Friedrich and Nielsen 1973; Laurent et al. 1973; Zeuthen and Nielsen 1973b; Bochkov et al. 1974; Hamerton et al. 1975; Nielsen and Rasmussen 1974; Lin et al. 1976; Price et al. 1976; Funderburk et al. 1978; Podugolinkova and Blumina 1983), 3 in 1343 (2.2) in Hispanics (Shapiro et al. 1984); 1 in 4543 (0.22) in Blacks (Cohen et al. 1966; Lubs and Ruddle 1971; Hara et al. 1976; Patel et al. 1977; Verma et al. 1983a; Sharpiro et al. 1984; Bernstein et al. 1986); 9 in 231 (39) in East Indians (Cohen et al. 1966; Verma et al. 1982c, 1983a; Bernstein et al. 1986), 3 in 244 (12.3) in Asians [(Ethnic origins of "Asians" not specified apart from one Phillipino with an inv (Y)] (Sharpiro et al. 1984); 0 in 47 (0) among Japanese (Cohen et al. 1966; Cavalli et al. 1984); 0 in 258 (0) in Coloured (Bernstein et al. 1986) and 0 in 15 (0) in others (Patil et al. 1977a, b). The pericentric Y is more common in East Indians, Asians and Hispanics (Shapiro et al. 1984 recorded polymorphism from amniotic fluid).

The biological significance of variation in the length of the Y chromosome is not clear (Verma and Dosik 1979b). They observed group differences might indeed represent true chromosomal heteromorphisms in the population not known (Monsolve et al. 1980).

Verma and Pandey (1987) reported the distribution of length of Y chromosome to examine whether the variation was due to f and/or nf segment(s) as reported earlier that there is increasing evidence that the nf segment is also responsible for the length variation (Schnedl 1971b; Soudek et al. 1973; Verma et al. 1978b, 1982 a, b, 1983 a, b) and they concluded that nf segments contributed to the non-random distribution of the total length of Y Chromosome and in future studies it might be interesting to correlate the chemical findings with variable nf segments also because at least two genes have been localized in this segment which may play an important role in the development of tooth size (gene TS) and spermatogenesis factor 3 (SP3) (McKusick 1984).

Beltron et al. (1979) reported that the Y chromosome from cord blood appears more condensed than from venous blood and the consequences are not removed by the use of the Y/F index.

Table 9: Incidence of the long and short Y chromosome in various normal populations

Population	*No. of males studied*	*Long Y chromosome+*		*Short Y chromosome+*		*Authors*
		No.	*Percent*	*No.*	*Percent*	
EUROPEANS						
Finland						
Finnish Males	30	4++	13.40	-	-	Unnerus et al. (1967)
Spanish Males	43	8	18.60+	-	-	de la Torre and Gimenez-Martin (1970)
Sweden						
Swedish Males	74	7	9.40++	-	-	Lins and Sundequist (1971)
Denmark						
Danish Newborns	140	2	1.40	2	1.40	Nielsen and Friedrich (1972)
Danish Newborns	2615	27	1.03	15	0.57	Friedrich and Nielsen (1973)
Danish Normal Males	508	25	4.92	-	-	Zeuthen and Nielsen (1973a)
Danish Normal Individuals	48	1	2.08	-	-	Nielsen and Nordland (1975)
Danish Newborns	5761	58	1.01	18	0.39	Nielsen and Sillesen (1975)
United Kingdom						
Scots	207	3	1.50	-	-	Court-Brown (1967)
Edinburgh Newborns	694	1	0.14	-	-	Buckton et al. (1980)
Fife Newborns	1379	11	0.80	-	-	Buckton et al. (1980)
Germany						
German Newborns	147	3	2.10	-	-	Zankl and Zang (1971)
Poland						
Polish Students	71	2	2.90	-	-	Huebner (1971a)
Italy						
Italians		187	12	6.41	-	2.14 Battaglia et al. (1971)
United States of America						
Jews	20	3	15.0	-	-	Cohen et al. (1966)
Non-Jewish Whites	20	1	5.00	-	-	Cohen et al. (1966)
American Newborns (New Haven)	2768	155	5.60	-	-	Lubs and Ruddle (1970)
Caucasian Newborns	1741	259	14.87	7	0.40	Lubs and Ruddle (1971)
Maryland Boys	4635	187	4.04	33	0.71	Rary and Boragaonkar (1973)
Boston Newborns	13751	240	1.74	52	3.78	Walzer and Gerald (1977)
Caucasian	60	11	18.3	0	0.00	Verma et al. (1978b)
Canada						
Canadian Neonates	3478	32	0.92	7	0.20	Hamerton et al. (1972)
Canadian (Ontario)	66	6	9.10	-	-	Soudek et al. (1973)
Canadian Newborns	7176	67	0.93	8	0.11	Hamerton et al. (1975)
Royal Military College Cadets (Kingston)	100	28	28.00	-	-	Soudek and Sroka (1979)
USSR						
Moscow Newborns	13.03	9	0.69	2	0.15	Bochkov et al. (1974)
Estonians	100	4	4.00	7	7.00	Mikelsaar et al. (1975)
Australia						
White Australians	15	6	40.00	-	-	Angell (1973)
MIDDLE EAST						
Israel						
Jerusalem Newborns	259	15	5.76	1	0.40	Cohen et al. (1975)
NEGRO						
Blacks (U.S.A.)	20	2	10.0			Cohen et al. (1966)
Negro Newborns (U.S.A.)	411	61	14.83	2	0.48	Lubs and Ruddle (1971)
Blacks (U.S.A.)	60	24	40.00	0	0.00	Verma et al. (1982a)
Asiatic Part of USSR						
Normal Uzbeks	117	1	0.85	2	1.70	Kuleshov et al. (1975)
Turkmen	45	-	-	5	11.11	Ibraimov (1983)
Dunghans (Chinese)	52	9	17.31	1	1.82	Ibraimov (1983)
Kingwir	126	19	15.08	10	7.93	Ibraimov (1983)
Chukchi	55	1	3.64	3	5.45	Ibraimov (1983)

Table 9: contd.....

Population	*No. of males studied*	*Long Y chromosome+*		*Short Y chromosome+*		*Authors*
		No.	*Percent*	*No.*	*Percent*	
Khakase	49	1	2.04	8	16.33	Ibraimov (1983)
Karak	40	1	2.50	9	22.50	Ibraimov (1983)
Russian	106	3	2.83	8	7.55	Ibraimov (1983)
Japan						
Japanese Normal Fertile Males	51	1	1.96	-	-	Kadotani et al. (1971)
Ainus Population	33	4	12.12	2	6.06	Komatsu and Hirai (1975)
Japanese (U.S.A.)	20		45.00	-	-	Cohen et al. (1966)
Japanese (U.S.A.)	20		25.00	-	-	Park (1976)
Korea						
Koreans (U.S.A.)	61		26.20	-	-	Park (1976)
China						
Chinese (U.S.A.)	28		28.6	-	-	Park (1976)
India						
East Indians	70	58	83.85	0	0.00	Verma et al. (1983a)
Rajput Normal Adults	100	5	5.00	-	-	Ghosh and Singh (1975)
Punjabi Normal Adults	100	3	3.00	-	-	Ghosh and Singh (1975)
Indian Normal Males	63	3	4.80	-	-	Ghosh and Singh (1975)
Jat Normal Males	400	15	3.75	3	0.75	Kenue (1979)
Delhi Newborns	170	5	2.95	10	5.88	Bhasin et al. (1981)
Asiatic Indians	20		10.00			
ABORIGINAL						
Australia						
Australian Aboriginals	14	-	-	-	-	Angell (1973)

+ Long Y (Y/F > 1.00) and short Y (Y/F < 0.70)
++ Results converted from Y/E ratio used by authors (cited from Soudek et al. 1973)
Results converted from Y/2 ratio used by authors (cited from Soudek et al. 1973).

Earlier, it has been reported that the Y chromosome is genetically the least active (Stern et al. 1964; Cohen et al. 1966; Court Brown 1967). Later the gene loci on the short arm of chromosome is localized for body growth (Bühler et al. 1972; German et al. 1973), spermatogenesis (Chandley and Edmand 1971) and the development and maturation of testis (Siebers et al. 1973; Bühler et al. 1974). The proximal euchromatic segment of the long arm has been attributed to gene loci for body growth (Jacobs and Ross 1966), differentiation of testis (Ferguson-Smith et al. 1969; Siebers et al. 1973), spermatogenesis (Tiepolo and Zuffardi 1976), male determining factors (Krympotic et al. 1972) and H-Y antigen (Wachtel et al. 1975; for review see Müller 1996).

Even though the heterochromatic distal two third of the Y chromosome has been considered as genetically inert by many authors, some abnormal conditions have been associated with Y chromosome heteromorphisms. Nielsen (1968) noted a relationship between the long Y and symptoms of character disorder, alcohol use or criminality. Nordland (1969) and Kahn et al. (1969) also observed a high incidence of long Y chromosomes in individuals with behavioural problems when compared to normal controls. It has been reported that men with extremely long Y chromosome showed similar clinical appearance as men with double chromosomes (EI-Alfi 1970; Harvey et al. 1970). Hubner (1971a) suggested that the long Y may be associated with non specific malformations. However, Hubner (1971b) reported that the long Y chromosome occurs more frequently in a criminal group than in control individuals. Nielsen and Friedrich (1972) noted significant differences in the mean chromosome length between criminal males and randomly selected newborn boys. Christensen and Nielsen (1974) observed a higher incidence of long Y in prisoners than in control group. Similarly Soudek and Laraya (1974) reported increased incidence of long Y in children with mental disorders when compared to controls. Nielsen and Nordland (1975) found a correlation between length of Y and the level of activity in boys. Mikelsaar et al. (1975) observed that the incidence of unusually long Y chromosome is higher in children with

mental disorders in comparison with normal children. A higher incidence of long Y chromosome is reported in criminal populations in comparison with normal controls (Martin-Lucas and Abrisqueta 1976; Tajmirova and Ondrejack 1976). In contrast to these reports, Benezech et al. (1973) have not observed any increase in the Y chromosome size in mentally-ill prisoner group, and also reported that the differences between two normal French populations was greater than the difference between criminals and controls.

Some of the other population reports also have not shown elevated frequency of long Y in criminals (Schwinger and Wild 1974; Urdal and Brogger 1974). Baégaard and Nielsen (1975) did not observe any correlation with extroversion, however, association between long Y and high neuroticism score was observed. Benezech et al. (1976) have not encountered any difference in the distribution of Y/F index between criminal and controls. Likewise, Genest and Dumas (1976) have not found increased criminality in families with long Y chromosome. Brogger et al. (1977) also observed no evidence for a correlation between the size of the Y chromosome and behaviour. Akesson and Wahlström (1977) reported non-significant difference in the Y/F distribution between forensic psychiatric patients and normal controls. Keeping all these contradictory reports in mind, Soudek (1977) further confirmed his previous results (Soudek and Laraya 1974) by comparing data of criminals with a larger control sample, and remarked that differences between the two population groups could not be attributed to ethnic variations. Moreover, Dorus (1978) emphasized that stature and behaviour are determined by a range of interacting genetic and environmental factors and, therefore, the contribution of the Y chromosome alone to stature and behaviour may be small. Funderburk et al. (1978) reported an increased frequency of Yq+ in severely retarded males as compared to all other psychiatric patients, whereas Soudek and Sroka (1979) observed identical distribution of Y/F index both in patients with idiopathic mental retardation and the Royal Military College Cadets of Kingston (Canada).

Kadotani et al. (1971) have found no difference in the mean length of the Y chromosome between fertile and infertile series. Kjessler (1972) reported a higher incidence of the short Y chromosome in infertile male patients, whereas Chandley et al. (1975) have not observed higher incidence of short Y in infertiles. Koulischer (1976) has not observed higher incidence of short Y in infertiles. Koulischer (1976) suggested that a large Y is not likely to impair fertility, but a short Y could be directly related to severe oligospermia or azoospermia. Žižka (1972) and Giraud et al. (1975) and Verma et al. (1982c) have found a higher incidence of Yq- in fathers of Down's syndrome children. Some reports have indicated an increase in the frequency of long Y chromosome in habitual abortions (Kadotani et al. 1969; Kulazenko et al. 1972; Kaösaar and Milelsaar 1973; Papp et al. 1974; Robertson et al. 1981; Westlake et al. 1983). Supporting them it has been reported that there is an increased risk of spontaneous abortions when the male partner has a larger Y chromosome (Patil and Lubs 1977a; Nielsen 1978; Genest 1979). However Blumberg et al. (1981) and Verma et al. (1983b) found no relationship between Y chromosome length and foetal loss. Furthermore, Verma et al. (1983b) suggested that the definition of large Y be revised, as majority of normal males have a Y/F index of more than 1.0, so a Y/F ratio of greater than 1.0 should not be considered a long Y chromosome. Rodriguez-Gómez et al. (1987) suggested that Y chromosome length variability is a normal polymorphism in human males, unassociated with reproductive problems.

From this text it can be concluded that the Y chromosome shows a wide range of variation not only between individuals but also within and between different population groups. The clinical concomitants of a long Y chromosome are still not certain.

1.2.4 Heteromorphism Shown by Other Chromosomes

Familial aberrant chromosome 17ps have been found in phenotypic normal persons and do not participate in association of acrocentric chromosome (Summit and Atnip 1966; Schmid and Bauchinger 1969; Berg et al. 1969; Priest et al. 1970; Zankl and Zang 1974; Ferguson-Smith 1974; Nielsen and Sillesen 1975; Hamerton et al. 1975). Satellited X-chromosome has been reported in one family by Lubs (1969) where some carriers were normal and some mentally defective.

Some rare polymorphisms do occur like increased paracentric region of chromosomes 2 (Lubs and Ruddle 1970a; Zankl and Zang 1971; Ferguson-Smith 1974) and inv (2) (Ferguson-

Smith, 1974; Cohen et al. 1975). 2qh+ variants have been reported to be 0.2 percent in a New Haven population (Lubs and Ruddle 1970a), 0.4 percent in the Germans (Zankl and Zang 1971) and 0.04 percent in the Scots (Ferguson-Smith 1974).

Similarly inv (2) were reported in the Scots to be 0.04 percent (Ferguson-Smith 1974) as compared to 0.6 percent in the Jerusalem newborns (Cohen et al. 1975).

Variant 17 p+ ranges between 0.4 percent in German newborns (Zankl and Zang 1971) to 2.83 percent in Estonian population (Mikelsaar et al. 1975). Another variant shown by the chromosome is possessing of satellites. Its incidence is 0.75 percent in the Scots (Ferguson-Smith 1974) and is in very low frequency of 0.02 percent in the Danes newborns (Nielsen and Sillesen 1975) and 0.04 percent in Canadian newborns (Hamerton et al. 1975).

1.2.5 Heteromorphism Shown by Q-banding Techniques

Q-banding adds more polymorphic sites to the list of human chromosomal polymorphism with the bright fluorescence in the region of the long arm adjacent to the centromere of chromosome 3 (Caspersson et al. 1970; Schnedl 1971a). This feature can be found either in the homozygous state or the heterozygous state. In chromosome 4 also a similar spot is found in the centromeric region of either the long arm or the short arm and is smaller and less intensely fluorescent than the fluorescent spot of chromosome 3 (Schnedl 1973).

D and G group chromosomes show enhanced fluorescence in their centromeric regions and satellites (Caspersson et al. 1970) and as has been dealt with in conventional polymorphism, these could further be more accurately identified as those chromosomes having a variant (Tables 10, 11). The heterochromatic distal end of the Y chromosome could be further studied with the help of fluorescence. Secondary constriction regions which are Q-band negative areas have also been studied by comparing the two homologues for negative areas[7].

Chromosome 3: Schnedl (1971a) in a sample of fifty individuals reported 34.0 percent homozygous for fluorescent spot at chromosome 3. Fifty percent are heterozygous for fluorescent spot and 16 percent lacking the spot in either of the homologue. Wahlström (1971) in a sample of 46 individuals reported 13 percent individuals with a fluorescent spot in the homozygous state, 30.4 percent were heterozygous for this trait and 56.4 percent lacked it totally. Iinuma et al. (1973) reported five out of twenty six individuals to be homozygous for this trait whereas sixteen are heterozygous and five lacked it totally. The gene frequency calculated for this trait with the help of the Hardy-Weinberg law is 0.50. Pearson et al. (1973) reported in samples of 170 from Oxford and 60 from Leiden (Netherlands) that the frequency of chromosomes with a fluorescent spot is 0.42 percent and 0.56 percent, respectively. Schnedl (1974) reported 26 individuals homozygous, 48 heterozygous and 26 lacking any fluorescent band out of 100 individuals studied. Geraedts and Pearson (1974) in 221 individuals of a Dutch population studied, found 48 subjects homozygous for a fluorescent segment of chromosome whereas 118 are heterozygous and 55 lacked the spot. The gene frequency has been calculated to be 0.484. Mikelsaar et al. (1975) in 207 Estonian individuals reported 87 individuals (42.0 percent) homozygous for the fluorescent spot, 95 heterozygous (45.9 percent) and 25 (12.1 percent) lacking any fluorescent spot in both the homologues. The gene frequency for a homologue with a brilliant band is calculated to be 0.650. McKenzie and Lubs (1975) reported in 77 individuals, 63 regions out of 154 chromosomes to be intensely fluorescent (40.5 percent)

Müller et al. (1975) reported the percentage of chromosome 3 with a brilliant spot in 357 neonates to be 55.0 percent, whereas Hauge et al. (1975) in a study of 50 Danes and 40 Icelanders subjects have found the frequency of chromosome 3 with a brilliant band to be 0.87 and 0.86, respectively. Lin et al. (1976) in a Canadian newborn sample of 930 neonates, have found 55.48 percent with brilliant bands whereas Sofuni at al. (1976) found 38 such persons out of 350 Japanese studied.

Thus from the above reports it may be observed that there is a high frequency of chromosome 3 with a brilliant spot in various populations so far studied, except a Japanese population studied by Sofuni et al. (1976). For this type of variant, its origin and precise knowledge of its selective advantage is still unknown.

Chromosome 4: Similarly in chromosome 4, the studies have indicated a fluorescent spot in

the centromeric position of the chromosome, but it is not as brilliant as in the case of chromosome 3. Iinuma et al. (1973) reported only 14 out of 26 individuals to be heterozygous for this trait and the gene frequency has been reported to be 0.27. Pearson et al. (1973) reported the frequency of the brilliant spot in chromosome 4 to be 0.15 and 0.11 in a study of 170 Oxford subjects and 60 Leiden (The Netherlands) subjects, respectively. Geraedts and Pearson (1974) in 221 Dutch individuals reported 12 heterozygotes for this trait and the gene frequency was calculated to be 0.027. Mikelsaar et al. (1975) reported 8 (7.8 percent) homozygous, 41 (39.8 percent) heterozygous for this spot while 54 (52.4 percent) lacked it totally in a sample of 103 Estonian population and calculated the gene frequency for the homologues with a brilliant band to be 0.278. McKenzie and Lubs (1975) in a sample of 77 individuals, thus studying 154 chromosomes found 63 with intense variants (40.91 percent).

Müller et al. (1975) reported 14.0 percent of the 714 chromosomes of 357 neonates possessing the brilliant band in chromosome 4. Hauge et al. (1975) in a study of 50 Danes and 40 Icelander individuals reported a very high frequency in both the populations (0.71 in Danes and 0.70 in Icelanders). Lin et al. (1976) reported on 930 Canadian neonates the frequency of the chromosome 4 with the brilliant band to be 14.14 percent. Sofuni et al. (1976) found a very low percentage of chromosom 4 with a brilliant spot (one person out of 350 Japanese individuals studied).

Chromosome 13: The short arms or satellites or both of the acrocentric chromosomes can stain brilliantly or normally with a fluorescent stain. Intensely fluorescent short arms are more common on chromosome 13 than on any other acrocentric. Size variations are also found for both the short arm and satellite regions.

Iinuma et al. (1973) observed five homozygous and 14 heterozygous individuals, for the brilliant band at the short arm and the satellite regions of 26 individuals while seven lacked intense fluorescence at these regions totally. The frequency has been calculated to be 0.46 for this trait. Pearson et al. (1973) reported the frequency to be 0.26 in 170 individuals from Oxford and 0.36 in 60 individuals from Leiden (The Netherlands). Schnedl (1974) reported in fifty normal cases a frequency of 14 percent of satellites and 54 percent of the centromeric region. Geraedts and Pearson (1974) in a sample of 221 individuals of a Dutch population reported 39 homozygous and 143 heterozygous individuals for the short arm and satellite regions of chromosome 13, whereas 39 lacked it totally. The gene frequency for this is calculated to be 0.500. Mikelsaar et al. (1975) found 148 (72.2 percent) homozygous and 50 (24.4 percent) heterozygous for fluorescent 13p region, while 7 (3.4 percent) lacked fluorescence at this region. The frequency of the homologue with an intense band was 0.844. McKenzie and Lubs (1975) reported 68 intensity variants out of 154 chromosome regions of 77 individuals studied (44.16 percent).

Müller et al. (1975) reported 7.0 percent of the chromosomes with intense satellites in 357 neonates, whereas 74.0 percent chromosomes have an intense short arm region. Hauge et al. (1975) reported the frequency to be 0.99 in 50 Dane subjects and 40 Icelanders. Lin et al. (1976) in 930 newborns reported the frequency of the brilliant short arm regions to be 31.35 percent, whereas the satellite region (intensely fluorescent) is found in 1.88 percent of chromosome 13. Sofuni et al. (1976) reported intense satellites on chromosome 13 in two persons out of 350 Japanese students, whereas the short arm region showed intense fluorescent band in 58 persons out of the 350 studied.

Chromosome 14: Iinuma et al. (1973) reported 6 heterozygous individuals for bright fluorescence out of 26 individuals examined while 20 lacked intense fluorescence at this region. The frequency of a homologue with the brilliant band is calculated to be 0.12. Pearson et al. (1973) reported a frequency of 0.04 in 60 Leiden subjects while 170 Oxford subjects showed the frequency 0.09. Schnedl (1974) in 50 normal individuals reported a frequency of 22 percent for satellites and 1 percent for the short arms. Geraedts and Pearson (1974) reported one homozygous for this trait and 61 heterozygous individuals while 159 lacked intense fluorescence. The gene frequency is calculated to be 0.143. Mikelsaar et al. (1975) found in 203 individuals, 7 homozygous, 27 heterozygous and 169 lacking the intense brilliance of fluorescent region with the frequency of homologues with the brilliant band to be 0.099. McKenzie and Lubs (1975) reported 7 variants of 14s from 154 chromosome regions of 77 individuals (4.55 percent). Müller et al. (1975) in a study of 357 newborns found 12 percent of the chromosome 14 possessing intensely stained

Table 10: Incidence of Q-band variants in various population groups

S. No.	Population	No. of individuals	Chromosome 3	4	13			14		
			3c (q11.2)	4c (q11.2)	13s (p13)	13p (p11.2)	13c	14s (p13)	14p (p11.2)	14c
EUROPEANS										
United Kingdom										
1.	Edinburgh Newborns	482	64.9	48.3	8.8	38.0		10.3	-	
2.	14 Year Old Children (Edinburgh)	109	68.4	33.5	7.8	29.8		13.3	-	
3.	Barra Population (Scotland)	149	58.3	18.1	11.2	21.2		6.0	-	
4.	English (Oxford Population)	170								
5.	Barra (Age 65 and Over Scotland)	210	62.7	20.5	10.4	19.3		5.8	-	
The Netherlands										
6.	Dutch (Leiden)	60								
7.	Dutch	221	48.4	2.7		50.0			14.3	
8.	Danes	50	87.0	71.0	75.0	99.0		68.0	95.0	
9.	Icelanders	40	86.0	70.0	69.0	99.0		64.0	98.0	
10.	Austrians	100								
Central Europe										
11.	Whites	100	39.5	6.5	11.5	63.5		21.0	1.0	
United States of America										
12.	American Newborns	77	40.9	40.9	2.6	44.2		4.6	0.0	
13.	American Newborns	357								
14.	Newborns White	222	55.4	12.8	9.8	73.8		9.3	3.2	
15.	Newborns (7-8 Years)	205	50.3	10.6	2.0	29.5		5.7	0	
16.	White	100	-	-		56.5		10.0		
Canada										
17.	Canadian Newborns	930	55.5	14.1	1.9	31.4		0.2	0.8	
USSR										
18.	Estonian	208	65.0	27.8	4.1		84.4	10.0		
19.	Russians (Kinglizia)	200	42.0	2.5	3.3	45.0		5.3	7.0	
Highland (Mongoloids)										
20.	Kirghiz of Pamir	112	30.4	5.4	5.4	32.1		8.5	4.5	
21.	Krghiz of Pamir	94	30.9	5.3	3.2	29.8		3.7	1.1	
22.	Kirghiz of Tien-Shan	113	34.1	6.6	3.1	35.0		4.9	2.2	
Steppe Mongoloids										
23.	Kazakhs (Steppe)	101	41.6	8.9	4.5	46.5		9.4	4.9	
24.	Chinese (Dunghans)	124	32.7	9.7	10.5	46.4		7.3	8.1	
25.	Mongolian (Steppe)	72	40.3	4.9	2.8	42.4		8.3	6.2	
Northern Mongoloids										
26.	Chukchi (Chukotsk)	132	36.7	1.9	0	35.2		3.0	4.5	
27.	Khakass (South East Siberia)	120	33.7	5.8	2.9	42.9		4.6	2.5	
28.	Turkmen (Kara-Kum Desert)	116	36.6	6.5	3.9	33.2		8.6	10.3	
Eastern Siberia										
29.	Yakut	157	24.5	5.4	2.9	15.6		2.9	1.6	
High Altitude-Kirghiza										
30.	Kyzyl-Dzhar	198	36.4	7.3	3.0	26.0		1.8	1.5	
31.	Mountaineers	37	28.4	1.3	2.7	25.7		2.7	2.7	
32.	Volunteer Subjects	34	26.5	0.0	2.9	8.8		5.9	2.9	
NEGRO										
33.	Newborns (7-8 Years) U.S.A.	210	58.2	4.6	5.1	50.3		6.7	-	
34.	Newborns Black (USA)	39	67.5	17.6	10.8	79.7		13.5	0.0	
35.	Black (U.S.A.)	100	-	-	3.0	48.0		13.5	1.0	
Lowland Negroids										
36.	Mozambique Natives	55	59.1	2.7	4.6	72.0		11.8	10.0	
37.	Angola Natives	41	64.6	1.2	6.1	65.9		7.3	17.3	
38.	Highland Negroids	34	41.2	4.4	4.4	52.9		4.4	23.5	
ARAB										
Kuwait										
39.	Ajman	40	80.7	48.9	18.2		61.4	5.7	0.0	
40.	Suluba	44	83.7	33.7	7.5		66.2	8.7	2.5	
41.	General	62	79.0	41.1	11.3		71.0	10.5	2.4	
ASIA										
Japan										
42.	Japanese	26								

Table 10: contd.....

S. No.	Chromosome									Authors
	15			21			22			
	15s (p13)	15p (p11.2)	15c	21s (p13)	21p (p11.2)	21c	22s (p13)	22p (p11.2)	22c	
1.	12.5	-		9.6	0.7		15.0	3.0		Buckton et al. (1976)
2.	10.5	-		16.0	0.5		13.3	1.8		Buckton et al. (1976)
3.	10.5	-		4.9	0.3		11.6	1.0		Buckton et al. (1976)
4.										Pearson et al. (1973)
5.	10.1	-		6.3	0.2		11.1	1.4		Buckton et al. (1976)
6.										Pearson et al. (1973)
7.		21.5			24.4			21.9		Geraedts and Pearson (1974)
8.	72.0	91.0		78.0	95.0		89.0	100.0		Hauge et al. (1975)
9.	64.0	94.0		70.0	91.0		71.0	100.0		Hauge et al. (1975)
10.										Schnedl (1974)
11.	23.5	0.5		20.5	0.5		23.5	9.0		Kalz and Schwanitz (2004)
12.	1.3	0.0		2.6	0.0		2.0	7.1		McKenzie and Lubs (1975)
13.										Müeller et al. (1975)
14.	7.4	3.2		16.2	3.5		23.9	19.2		Müeller and Klinger (1975)
15.	5.1	0.5		4.1	0.3		3.0	1.0		Lubs et al. (1977)
16.	10.0			15.5			10.0			Verma et al. (1977a)
17.	0.9	0.2		1.1	0.1		0.3	0.5		Lin et al. (1976)
18.	6.4	-		8.0	-		8.0	35.9		Mikelsaar et al. (1975)
19.	2.8	12.8		9.5	4.3		3.3	5.5		Ibraimov and Mirrakhimov (1982b)
20.	3.1	12.1		4.9	13.8		3.6	14.7		Ibraimov et al. 1982a)
21.	4.3	6.4		1.6	5.3		4.3	9.0		Ibraimov et al. (1982a)
22.	4.0	15.0		3.1	8.8		3.5	8.0		Ibraimov et al. (1982a)
23.	1.5	14.8		13.4	9.4		9.9	13.4		Ibraimov et al. (1982a)
24.	5.2	20.6		10.1	9.7		7.3	7.3		Ibraimov et al. (1982a)
25.	6.2	18.1		13.2	10.4		7.6	8.3		Ibraimov et al. (1982a)
26.	1.5	10.6		9.5	0.4		4.9	1.5		Ibraimov and Mirrakhimov (1982a)
27.	2.9	14.2		10.8	0		2.5	3.7		Ibraimov and Mirrakhimov (1982a)
28.	4.3	15.1		6.0	13.4		3.0	10.3		Ibraimov and Mirrakhimov (1983)
29.	1.9	5.7		7.3	7.6		2.5	3.8		Ibraimov et al. (1986a)
30.	4.0	5.3		3.5	6.3		2.8	4.3		Ibraimov et al. (1986b)
31.	2.3	4.1		5.4	4.1		1.3	4.1		Ibraimov et al. (1986b)
32.	0.0	4.4		0.0	2.9		4.4	2.9		Ibraimov et al. (1986b)
33.	5.1	1.5		6.7	1.0		7.3	2.0		Lubs et al. (1977)
34.	8.1	1.4		17.6	5.4		37.8	27.0		Müeller and Klinger (1975)
35.	19.0	0.0		12.5	0		15.5	0		Verma and Dosik (1981b)
36.	1.8	26.4		10.0	14.6		10.9	15.5		Ibraimov and Mirrakhimov (1982c)
37.	3.7	26.8		8.5	13.4		2.4	25.6		Ibraimov and Mirrakhimov (1982c)
38.	2.9	10.3		1.5	11.8		0	16.2		Ibramiv and Mirrakhimov (1982c)
39.	6.8	5.7		11.4	1.1	0.0	57	1.1		Al-Nassar et al. (1981)
40.	11.2	2.5		13.8	1.2	1.2	16.2	1.2		Al-Nassar et al. (1981)
41.	8.1	1.6		9.7	1.6	1.6	8.9	4.8		Al-Nassar et al. (1981)
42.										Iinuma et al. (1973)

Table 11: Incidence of Q-band variants in various normal populations

Chromosome	Chromosome region	Bands classified	Dutch (Leiden, The Netherlands) Pearson et al. (1973)		English (Oxford Poulation) Pearson et al. (1973)		Japanese Iinuma et al. (1973)		Austrians Schnedl (1974)		Dutch Population Geraedts & Pearson (1974)	
			No.	%	No.	%	No.	%	No.	%	No.	%
1	1qh+		60	1.00							213	1.8
	1qh-		60									
			60	56.0	170	42.0	26	50.0	100	50.0	213	48.4
3	3c											
	3p											
			60	11.0	170	15.0	26	27.0			213	2.7
4	4c											
	4p											
			60	28.0							213	13.8
9	9qh+											
	9qh-											
									100	14.0		
13	13s											
	13p	13pIIqII	60	36.0	170	26.0	26	46.0	100	54.0	213	50.0
		13p13										
							26	12.0	100	22.0		
14	14s											
	14p	14p13	60	4.0	170	9.0			100	1.0	213	14.3
							26	2.0	100	12.0		
15	15s											
	15p	15p13	60	24.0	170	17.0					213	21.5
			60	13.0							213	0.7
16	16qh+											
	16qh-		60	6.0	170	5.0	26	13.0	100	28.0		
21	21s											
	21p	21p13							100	1.0	213	24.4
		22p13	60	24.0	170	13.0	26	9.0	100	21.0	213	21.9
22	22s											
	22p	22pII	60									

Table 11: contd. ....

Chromosome	*Chromosome region*	*Bands classified*	*Estonian (U.S.S.R) Mikelsaar et al. (1975)*		*American newborns McKenzie & Lubs (1975)*		*American newbowrs Mueller et al. (1975)*		*Danes Hauge et al. (1975)*		*Icelanders Hauge et al. (1975)*		*Canadian newborns Lin et al. (1976)*	
			No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
1	1qh+								50	8.0	40	6.0		
	1qh-								50	2.0	40	1.0		
			207	65.0	77	40.91	357	55.0	50	87.0	40	86.0	930	55.48
3	3c													
	3p													
			103	27.8	77	40.91	357	14.0	50	71.0	40	70.0	930	14.14
4	4c													
	4p								50	19.0	40	16.0		
9	9qh+													
	9qh-								50	2.0	40	5.0		
					77	2.60	357	7.0	50	75.0	40	69.0	930	1.88
13	13s													
	13p	13p11q11	205	84.4	77	44.16	357	74.0	50	99.0	40	99.0	930	31.35
		13p13	203	4.1										
					77	4.55	357	12.2	50	68.0	40	64.0	930	0.16
14	14s													
	14p	14p13	203	9.9			357	2.0	50	95.0	40	98.0	930	0.81
					77	1.30	357	10.0	50	72.0	40	64.0	930	0.86
15	15s													
	15p	15p13	203	6.4			357	3.0	50	91.0	40	94.0	930	0.16
									50	6.0	40	1.0		
16	16qh+								50	3.0	40	2.0		
	16qh-													
21	21s				77	2.60	357	16.0	50	78.0	40	70.0	930	1.08
	21p	21p13												
		22p13	203	8.0			357	2.0	50	95.0	40	91.0	930	0.11
22	22s		203	8.0	77	1.95	357	27.0	50	89.0	40	71.0	930	0.32
	22p	22pII	82	35.9	77	1.14	357	34.0	50	100.0	40	100.0	930	0.54

satellites, whereas the short arm of only 2 percent of the chromosome 14 was intensely stained. Hauge et al. (1975) reported a very high frequency in 50 Danes and 40 Icelanders studied. The frequency of chromosome 14 with satellites was 0.68 in Danes and 0.64 in Icelander population whereas the short arm intense fluorescence was 0.95 in Danes and 0.98 in Icelanders.

Lin et al. (1976) reported from a sample of 930 Canadian neonates the frequency of chromosome 14 with satellite to be 0.16 percent while the short arm is intensely fluorescent in 0.81 percent of the total chromosome 19.

Chromosome 15: Iinuma et al. (1973) reported only heterozygous out of 26 individuals studied and the frequency of homologue with brilliant band is calculated to be 0.02. Pearson et al. (1973) reported in an Oxford population of 170 subjects the frequency 0.17 whereas in the Leiden sample of 60 subjects it is 0.17. Schnedl (1974) reported frequency of 15s variant to be 12 percent and 15p variant to be 1 percent out of 50 individuals studied. Geraedts and Pearson (1974) reported one homozygous, 93 heterozygous and 127 lacking a variant out of 221 individuals studied. The frequency of homologue with brilliant band has been calculated to be 0.215. McKenzie and Lubs (1975) reported 2 variants (15s) out of the 154 regions studied among 77 individuals (1.30 percent). Müller et al. (1975) found 10 percent of 15s and 3 percent of 15p with intense fluorescence in a sample of 357 individuals. Hauge et al. (1975) reported the frequency of 15s to be 0.72 and 0.64 in Danes and Icelander sample, respectively, whereas the 15p fluorescence frequency is found to be 0.91 in Danes and 0.94 in Icelanders. Lin et al. (1976) reported in 930 neonates the frequency of chromosome 15 with intense satellites to be 0.86 percent and for the short arm intense fluorescent it was 0.11 percent. Sofuni et al. (1976) reported one subject with satellites out of 350 individuals studied and 3 subjects with a bright short arm of chromosome 15.

Chromosome 21: Iinuma et al. (1973) reported seven heterozygous out of 20 individuals studied. The frequency of a homologue with the brilliant band is calculated to be 0.13. Pearson et al. (1973) reported the frequency of intensely fluorescent satellites and short arms of chromosome 21 to be 0.06 in a Leiden population of 60 individuals and 0.05 in 170 Oxford subjects studied. Schnedl (1974) in 50 normal individuals studied reported 28 percent with satellites and 1 percent with short arm with bright fluorescence. Geraedts and Pearson (1974) reported 10 individuals homozygous, 88 heterozygous for this variant and 123 individuals did not have any variant on this chromosome. The frequency of a homologue with the brilliant band is calculated to be 0.244. Mikelsaar et al. (1975) reported out of 203 individuals, 3 homozygous and 27 heterozygous individuals for 21p 13 intense brilliant fluore-scence. The frequency of a homologue with the brilliant band is 0.08. McKenzie and Lubs (1975) reported 4 out of 154 regions of 77 individuals (2.60 percent) to be intensely brilliant. Müller et al. (1975) reported the percentage of 21s with intense fluorescence to be 16.0 percent whereas the short arm of only 2 percent is intensely fluorescence in a sample of 357 neonates. Hauge et al. (1975) found the frequency of 21s with intense fluorescence to be 0.78 in Danes and 0.70 in the Icelanders studied whereas the 21p intense fluorescence showed a frequency of 0.95 in the Danes and 0.91 in the Icelanders. Lin et al. (1976) reported a very low frequency of these variants in the 930 consecutive newborns - 1.08 percent with intense fluorescence in 21s and only 0.11 percent chromosome 21 had intense fluorescence in short arm region. Sofuni et al. (1976) reported only two persons with intense satellites out of 350 Japanese studied.

Chromosome 22: Iinuma et al. (1973) reported five heterozygous individuals out of 26 studied. The frequency of homologue with the brilliant band is calculated to be 0.09. Pearson et al. (1973) reported the frequency of intensely stained chromosome 22 to be 0.24 in Leiden (The Netherlands) subjects and 0.13 in an Oxford population. Schnedl (1974) found the brilliant satellite frequency to be 21 percent and of short arm 11 percent in 50 normal individuals. Geraedts and Pearson (1974) in 221 individuals reported 6 homozygous, 85 heterozygous individuals for intense fluorescence of the short arm and satellite regions whereas 130 lacked fluorescence in both the homologues. The frequency of the homologue with a brilliant band is calculated to be 0.219. Mikelsaar et al. (1975) reported 4 homozygous, 25 heterozygous out of 203 individuals studied and the frequency of a homologue with the brilliant band to be 0.080 of 22p 13 whereas 22p 11 showed 16 homozygous and 27 heterozygous individuals for the brilliant band out of

203 individuals studied with the frequency for the homologue with a brilliant band to be 0.359. McKenzie and Lubs (1975) reported 3 variants of 22s and 11 variants of 22p in each of the 154 regions examined in 77 individuals.

Lubs et al. (1977a) examined QFQ intensity heteromorphisms in 415 children (205 White and 210 Black) with IQs of above and below 85. Racial differences are noted in satellited regions (band p13) of chromosomes 13 and 22, while no racial difference is found for other acrocentric chromosomes (Lubs et al. 1977b).

Ibraimov and Mirrakhimov (1982) observed that inversion of the Q heteromorphism band in chromosome 3 may prove to be a valuable taxonomic feature in ethnic anthropology as a distinctive "Europoid cytogenetic marker" provided that this receives due attention in further population cytogenetic studies. The frequency of this inversion is high in the Russians (6 percent).

Among eight Asian Mongoloid populations, Ibraimov et al. (1982) observed inversion in four, with a frequency of 0.3 to 3 percent and they explained this by the presence in their gene stock of European admixture. Further no case of the inversion has been observed in the Japanese (Yamada and Hasegawa 1978). The frequency of this inversion reached 11 percent in the Europoid population (Soudek and Sroka 1978; Al-Nassar et al. 1981; Herva 1981). They further stated that no inversion is observed among Mozambique and Angola natives whereas among Ethiopians it is 2.9 percent which is due to European admixture (Ibraimov and Mirrakhimov 1982c).

Ibraimov (1983) observed that sex differences in the frequency of Q bands in all 12 polymorphic loci of seven autosomes have been observed to be non significant. He further added that they also found no statistically significant differences between the sexes in homo (+/+ and –/–) and heteromorphic (+/–) frequencies and in the frequency of inverted chromosome 3. However the comparisons of the mean number of Q bands show increased mean number of Q bands per individual in females. For this they advanced the explanation that there seems to be some mechanism that can compensate for the dosage difference in chromosomal Q heterochromatin material in females due to the absence of a chromosome in their genome, capable of "compensating" for the large Q band of the chromosome Y which is only present in the genome of males. In support of this hypothesis, they have reported the frequency of large Y chromosome in their series and observed that the greater the difference (percent) between the sexes in the mean number of Q bands per individual, the greater the number of large chromosome Y in males. But they added that the final answer to this question will only be obtained after the development of accurate methods for determining the amount of Q-heterochromatin bands in the genome of each individual and in the population as a whole.

Ibraimov et al. (1982 a, b, 1986 a, b), Ibraimov (1983), Ibraimov and Mirrakhimov (1982 a,b,c; 1983) reported the selective value of chromosomal heterochromatin material, of polymorphic Q variants, in the adaptation of human populations to certain extreme environmental factors, particular to cold and hypoxia whereas for the C-heterochromatin material, Ibraimov et al. (1982b) observed that this has no selective value in the process of human adaptation to extreme environmental factors. They have stated that there are decreased mean number of Q bands per individual in aboriginal populations living under certain extreme environmental conditions of Eurasia and further added that somewhat different picture is obtained when Q-band frequencies are expressed as percentages of the total number of Q bands rather than as percentages of the number of analyzed chromosomes. They have ascertained that heterogeneity of human populations in the absolute number of Q bands is not due to the different degrees of polymorphism in any chromosomal area having Q hands but to uniform increases or decreases in the absolute number of Q bands in all the 12 polymorphic loci of seven autosomes. Therefore, they believe that any significant change in the mean number of Q bands per individual in a population deserves special attention, since it is the only parameter that can reflect an actual increase or decrease in the number of Q bands in the gene stock of any population.

They have also pointed out that the existence of certain difference between the sexes in the mean number of Q bands per individual in a population is also in favour of a possible selective value of chromosomal Q-heterochromatin material. They further added that thus, if their hypothesis of dosage compensation of chromo-

somal Q-heterochromatin material in females is confirmed in future, it may be indirect evidence for a selective value of chromosomal Q-heterochromatin material in the adaptation of human populations to certain extreme environmental factors. Indeed, there seems to exist some rigorous equilibrium in the total amount of Q-heterochromatin material between the sexes at the population level.

These studies provide base line data for normal population and can be used for comparison with abnormal populations since it has been suggested that certain hetero-morphisms have clinical significance (Gardner et al. 1974; Boue et al. 1975b; Kunze and Mau 1975; Harbrecht and Shabtai 1976; Khan et al. 1978). Fluorescence polymorphisms have been recorded for 3, 4 and acrocentric chromosomes also from amniotic fluid specimens (Kalz and Schwanitz 2004). They observed significant differences between frequencies of polymorphism between amniocyte and lymphocyte specimens.

Cytogenetic technology has proved useful in excluding wrongfully alleged men in paternity disputes (de la Chapelle et al. 1967; Olson et al. 1983, 1984; Nora et al. 1985). Olson et al. (1986) reported that although chromosome heteromorphism analysis has not yet been accepted as a routine test in paternity disputes, it is being used in a limited number of cases in which neither HLA nor blood group testing has led to exclusion (Olson et al. 1984). They have used this in disputed paternity cases and suggested that due to the quite high cost, chromosome heteromorphism analysis may be done only after no exclusions are found with red cell antigens and enzymes, serum proteins and HLA.

1.2.6 Heteromorphisms by Other Techniques:

1. RFA (R-Bands by Fluorescence using Acridine Orange) Technique: Heteromorphisms of human genome have been demonstrated by several techniques (Verma and Lubs 1975a, b, 1976a, b; Jacobs 1977; Verma et al. 1977a, b; Verma and Dosik 1979a, b). Verma et al. (1977a b) have extensively demonstrated colour heteromorphim by RFA technique (Verma and Lubs 1975a, b, 1976; Verma et al. 1977a). They have suggested that RFA colour heteromorphisms can be classified into six colours; red, red-orange, orange-yellow, pale yellow, bright yellow and pale green[8]. These colours are inherited as a Mendelian trait. Verma and Dosik (1981a) observed that the RFA technique is more useful than the QFQ (Q bands by fluorescence with quinacrine) for characterizing heteromorphisms of chromosomes 14, 15, 21 and 22.

The RFA heteromorphisms in the Caucasians and the American Blacks show that the most frequent colour of D-group chromosomes is orange-yellow (level 3) while for the G-group chromosomes it is pale-yellow (level 4). The frequencies of colour heteromorphisms are higher among American Blacks for chromosomes 13, 14, 15, 21 and 22, these are 49.5, 50.5, 49.0, 61.5, and 42.0 percent, respectively as compared to heteromorphism with the Caucasians for chromosomes 13, 14, 15 21 and 22, heteromorphisms are 33.0, 38.0, 28.0, 50.0 and 24.5 percent, respectively.

Baliček et al. (1982) investigated the extent of Reverse Banding by Heat Denaturation (RHG)-band variations of short arms of human acrocentric chromosomes in 100 subjects by visually comparing variants with size of reference R-band positive (1. very small = absent 2. small = <7p22; 3. Average e"7p22, <21q22; 4. Large = e"21q22, <11q13 and 5. very large e" 11q 13) and observed marked differences among the chromosomes in the distribution of variants; the largest mean size of RHG-band was associated with chromosome 21, whereas variants of chromosome 22 had the smallest band size.

2. DA/DAPI (Distamyein A/4'-6- diamidino-2-phenylindole) Staining Technique: Tofanelli et al. (1993) reported that with the distamycin A/4'-6-diamidino-2-phenylindole (DA/DAPI) staining technique (Schweizer et al., 1978) the large C-band regions of chromosomes 1, 9, 16 and Y and the short arm of chromosome 15 also stained positively. Bühler and Malik (1988) and Verma et al. (1991) have reported DA/DAPI intensity variants for the short arm of acrocentric chromosomes other than chromosome 15 and the centromeric region of chromosome 10. Tofanelli et al. (1993) reported parallel analysis of DA/DAPI and C heteromorphic sites from Lucca (Tuscany, Italy) and observed that DA/DAPI heterochromatin differed significantly from C heterochromatin, showing a lower average amount and a higher variability at each site and concluded that this suggests a differential staining of DNA of the two banding systems.

1.2.7 Heteromorphism of Ag-stained Nucleolar Organizer Regions (NORs)

The NOR is that region of a chromosome which contains the main r-RNA genes (18S and 28S r-DNA). The nucleolus is the structure visible in interphase which comes into existence by the action of the genes present in the NOR. Thus the NOR is by definition part of a chromosome and the nucleolus is a structure containing this chromosomal part and in addition the material which accumulate around the NOR, most notably the rRNAs and their precursors as well as specific ribosomal proteins (for review see Schwarzacher and Wachtler 1983). Verma and Lubs (1975b) described the scoring criteria for nucleolar organizer regions[9].

Ag-staining can be used to measure nucleolar organizer activity. The quantity of deposited silver is directly associated with the NOR activity, and apparent heritable trait as demonstrated by twins and family studies (Mikelsaar et al. 1977b; Markovic et al. 1978; Weltens et al. 1985). Only the NORs active during the interphase preceding the metaphase studied are sensitive to staining (Miller et al. 1976). The number of Ag-stained acrocentric chromosomes varies from one individual to other (Howell et al. 1975; Bloom and Goodpasture 1976; Goodpasture et al. 1976; Mikelsaar et al. 1977a) and subject to slight geographic variations (Mikelsaar et al. 1977a, 1979). By the amount of the silver precipitate, the Ag-NOR can be identified as more or less active (Miller et al. 1977). Observation relying on metaphases stained first with quinacrine mustard, then with silver nitrate, suggest that the silver reaction of a given NOR is generally constant from one cell to another (Mikelsaar et al. 1977b). However the results of the study of a centric fusion (13:13) by Zankl et al. (1979) and two 14p+ (Miller et al. 1978; Lau et al. 1979) suggest that the activity of the NORs shows intercellular variations and that this may even be a compensatory phenomenon. NOR activity is a fixed characteristic of a chromosome and constitutes a hereditary property whose mode of transmission could be of the Mendelian type (Mikelsaar et al. 1977b; Markovic et al. 1978; Dev et al. 1979).

The modal number of Ag-positive NORs per individual varies from 7.8 among an Estonian population (Mikelsaar et al. 1977a) to 8.7 in the Vienna-Ulm (Mikelsaar and Ilus 1979). Among the East Indians (Verma et al. 1981a) it is observed as 8.05 and in a population from Moscow, the value is 8.4 (Zakharo et al. 1982). The East Indians show only 55.7 percent 8 to 10 modal number Ag-positive NORs as compared to others where about 90 percent of the individuals had a model number of 8-10 Ag-positive NORs, which indicates that the distribution of Ag-positive NORs is variable from population to population.

Verma et al. (1981) observed a higher incidence of the presence of NORs by the NSG technique in comparison to the RFA technique, which may be due to a small or very small NORs not being detected by RFA at the microscopic level.

Sozansky et al. (1984) reported a new modification of the Ag I technique which involves ultra-violet irradiation of chromosome preparations during incubation in $AgNO_3$. With the refined Ag-staining procedure, acrocentric marker chromosomes are studied which show one or two satellite stalks within the same individual.

Due to the impregnation, the NSG technique may have preferential staining properties. These findings indicate that for population heteromorphisms of NORs the NSG technique is more useful than RFA.

Jackson-Cook et al. (1985) reported that silver-staining variants of the nucleolar organizing region (NOR) are more frequent among parents of children with trisomy 21, whereas Spinner et al. (1989) do not find a demonstrable risk of nondisjunction of chromosome 21 in individuals with silver-staining variants.

1.2.8 Structural Variation and Lateral Asymmetry

Based on staining properties heterochromatin is different from euchromatin. Constitutive heterochromatin is composed of highly repetitive DNA located in specific sites on the chromosomes and it is associated with visible chromosome heteromorphisms. It is well documented that every human chromosome contains one or more regions of constitutive heterochromatin which is associated with the centromere or the short arm (usually acrocentric chromosomes). The heterochromatin is variable in size, position and colour depending upon the staining technique used.

Lin and Alfi (1976, 1978) reported lateral asymmetry in the secondary constriction regions of chromosome 1 using the BrdU-DAP I technique. They observed a high frequency of

asymmetry of heterochromatin in the population.

Angell and Jacobs (1975) reported lateral asymmetry in C-band heterochromatin regions of chromosomes 1, 15, 16 and the Y.

It has been estimated that approximately 400 copies of the rRNA genes are distributed among the human acrocentric chromosomes (Bross and Krone 1972; Bross et al. 1973; Schmid et al. 1974; Dittes et al. 1975).

1.2.9 Sister Chromatid Exchange

Among newborns, Hatcher and Hook (1981a) studied chromosome damage related to environmental factors in infants of different birth weights and evaluated chromosome aberrations, specifically chromosome breaks and rearrangements (CBR), in neonatal (cord) blood and postnatal blood from infants of low birth weight (LBW) and high birth weight (HBW) and from matched control infants of normal birth weight (NBW) by analysing the possible correlations between CBR frequency and abnormal birth weight. They observed no such associations for cord blood. For postnatal blood, a significant increase was found only in one group of LBW infants with intrauterine growth retardation compared with matched controls.

Hatcher and Hook (1981b) also assessed structural chromosome aberrations and sister chromatid exchanges (SCE) both in the same blood sample of infants of different birth weights. They observed no correlation between neonatal or postnatal SCE frequency and birth-weight, nor is there evidence of association of chromosome aberration rates with SCE frequency. In all groups of infants, however mean postnatal SCE frequencies are significantly lower than mean neonatal SCE frequencies.

From chorionic villus cells, Shulman et al. (1991) analysed for sister chromatid exchange (SCE) and observed that chorionic villus cells may become useful in measuring the response of foetal tissues to clastogens or mutagens or for prenatal diagnosis of chromosome breakage syndromes. They observed differences between cytotrophoblastic cells and mesenchymal core cells in directly prepared and cultured cells and concluded that SCE analyses involving chorionic villi must take into account cell type.

1.2.10 Size Variation in Kinetochores

Aneuploidy, the addition or deletion of whole or partial chromosomes from cells is one of the cytological landmarks and possible causal agent of cancer (Evans 1985). In addition aneuploidy is a major factor in clinical abnormalities of the newborn. The mechanism involved in generating chromosomally imbalanced cells are not clear, but are likely in many cases to involve the kinetochore, the site of attachment of spindle microtubules, a vital component in the meiotic apparatus that ensures correct division of chromosomes in eukaryote cells. Cherry and Johnston (1987) analyzed human fibroblast cells with antikinetochore-antibody indirect immunofluorescence and noted an apparent heterogeneity in the sizes of kinetochores among different chromosomes. The Y chromosome, in particular, always shows minute kinetochores, an observation which they quantified and substantiated using computer-assisted image analysis.

Human chromosomal heteromorphisms are inherited in a Mendelian fashion, are stable and have a low mutation rate. The heteromorphisms are used: to study the origin of the extra chromosome, for example in Down's syndrome; to study the mechanism producing triploidy in human abortuses; to study the origin of additional chromosome; to detect the maternal cell contamination of amniotic fluid culture; to establish paternity; to elucidate the chromosomal mechanisms involved in the production of mosaics; in studying chimeras; to apply in zygosity testing in twins and other multiple births; to study the gene mapping in somatic cell hybridization.

1.2.11 Heteromorphism Analysed by Bivariate Flow Karyotyping

Chromosome heteromorphisms can also be studied using flow cytometry (Green et al. 1984; Harris et al. 1985, 1986, 1987; Trask et al. 1989a, b). Flow cytometry can be used to identify mitotic chromosomes and to quantify DNA content differences among them. The heteromorphic regions coincide with the sites of long arrays of repeated sequences. Many thousand copies of satellite sequences map to centromeres and heterochromatic regions. Repeated copies of rDNA genes form large arrays on the short arms of acrocentric chromosomes. The visible variation in the size of these regions reflects differences in the number of repeats in these arrays (Trask et al. 1989a; Mahtani and Willard 1990; Haaf and Willard 1992). These significant

differences in chromosomal size can be quantified by flow cytometry and this technique is called flow karyotyping. Flow karyotypes of normal individuals reveal marked variation in the DNA content of many chromosomes, including 1, 9, 13, 14, 15, 16, 21, 22 and Y (Harris et al. 1986; Trask et al. 1989a). Family studies showed that these size variants are inherited in a Mendelian fashion (Trask et al. 1989b). Variation in chromosomal DNA content can be ascribed largely to variation in the size of long arrays of repeated sequences (Trask et al. 1989a). Given the variation that has been observed, the number of repeats in these arrays would not appear to be tightly constrained by selection pressure. The spectrum of variants and their frequency might therefore vary among geographically separated human populations as a consequence of genetic drift (Maynard Smith 1989). On the other hand population differences might be minimized if the size of arrays changes frequently by unequal crossing over or sister chromatid exchange (Strachan and Read 1996). Mefford et al. (1997) studied seven population groups (two African pygmy groups, two American tribes, Druze, Khmer Cambodians and Mexanesians) and they observed large degree of variation in chromosome size among these individuals.

1.2.12. Molecular-Cytogenetic Analysis of Constitutive Heterochromatin

The constitutive heterochromatin of chromosomes 1, 9, 16, and Y represents most prominent part of human chromosomes as demonstrated by C-banding. However most human chromosomes have relatively small regions of heterochromatin and the possibility of polymorphic variations in these regions remain therefore uninvestigated. Advances in molecular analysis of repeated DNA sequences of the human genome have enabled one to identify number of satellite DNA sequences specific to particular chromosomes.

The sequences of satellite DNA hybridized *in situ* exclusively to constitutive heterochromatin on chromosomes 1, Y, and 9 are detected (Gosden et al. 1981a; Lau et al. 1984; Yurov et al. 1986a). The sequences of alpha-satellite DNA with specific localization in centromeric heterochromatin of chromosomes X and Y have been determined (Yang et al. 1982; Erickson et al. 1984). A number of alphoid DNA sequences specific to centromeric hetero-chromatin of chromosomes 1, 3, 4, 10, 11, 17, 18 and X have been cloned and described (Yakovlev 1983; Yurov 1984; Zaitzen 1984; Alexandrov et al. 1986a). Such satellite DNA sequences may be used as probes for detection and evaluation of polymorphic variants of all human chromosomes (Yurov et al. 1987). Yurov et al. (1987) reported that it may be possible that the application of these probes may open new ways for understanding the genetic significance of heterochromatin and the discovery of new types of heredity pathology, connected with effect of heterochromatin.

Since chromosomal variation have important role in genomic evolution (Bernardi 1995) by employing FISH using satellite DNA probes, Samonte et al. (1996) have revealed four unique types of inversions involving 9qh region.

1.3 Fragile Sites

Chromosomal fragile sites (FS) are by definition specific points on chromosomes that exhibit "fragility" under appropriate conditions of induction. Cytologically, this fragility is almost always seen as a non-staining chromosome or chromatid gap[10], less frequently as a break, and only rarely as a deletion occurring at the same location in the metaphase of an individual or a group of individuals. Their expression may be spontaneous in suitable culture media or induced by the addition of particular chemicals. Seven groups falling in two major classes (rare and common FS) have been identified according to the mode of induction and occurrence in the population (Sunderland and Richards 1999) [11]. According to induction criterion there are several groups based on culture conditions in which they are expressed. Hence CFS can be divided into aphidicolin inducible, 5-azacitidine inducible and BrdU inducible; RFS can be classified as folate sensitive, distamicine A inducible, and BrdU inducible (Sutherland and Hecht 1985; Sutherland 1991). According to criterion of occurrence in the population, they are classified as common fragile sites (CFS) when they can be observed in virtually every individual and as rare fragile sites (RFS) when they are observed in a relatively small percentage of the population (Hecht et al. 1990). There are 114 different FS according to Human Gene Mapping Project (McAlpine et al. 1990).

FS have received considerable attention in medical literature because of their potential

clinical implications and, in particular, because of their association with *de-novo* chromosome breaks occurring in tumor cells and in subjects with birth defects. The possibility that certain FS predispose to chromosome breakage has been investigated by studies in which distribution of break point (bp) in constitutional chromosomal rearrangements has been compared with location of FS. Despite circumstantial evidence pointing to an intriguing correlation between FS and breakpoints of structural chromosome rearrangements, most authors have cautioned against misusing available data in genetic counselling or offering prenatal diagnosis to carriers of rare FS (Sutherland and Hecht 1985).

Porfirio et al. (1987) analysed the distribution of 6391 break points (bp) found in constitutional rearrangements collected from the literature to understand the relationship between fragile site bands and chromosome abnormalities. They concluded that the relationship between FS and meiotic chromosome abnormalities need to be re-evaluated by prospective studies on homogeneous and properly characterized material. Available data simply point to a significant clustering of constitutional chromosome breakage at or in the neighbourhood of FS bands. This does not prove that FS predispose to chromosome rearrangements at meiosis.

The genetic or molecular basis for chromosome fragility at these sites is not known, nor are the biological consequences of fragile site expression fully understood. Tommerup (1986) and Glover and Stein (1987) have shown that fragile sites predispose to intrachromosomal recombination as measured by sister chromatid exchanges. This finding suggested that fragile sites often, if not always, result in DNA strand breakage at some point during expression. Glover and Stein (1988) reported that fragile sites can also predispose to deletions and interchromosomal recombination (translocations) following induction in a somatic cell hybrid system. They added that these findings demonstrate that a fragile site expression is a consequence of, or can result from DNA strand breakage. Furthermore the resulting translocation chromosomes with one breakpoint at a fragile site in a human chromosome and the other in a rodent chromosome provide useful tools for gene mapping around fragile sites and for cloning fragile sites by isolation translocation breakpoints containing heterologous human rodent DNA junctions.

1.3.1 Types of Fragile Sites

Fragile sites can be classified on the basis of two characteristics; frequency and mode of induction, which are the only practical criteria available for use in classifying the fragile sites (Sutherland and Hecht 1985):

(1) *Frequency:* Fragile sites show a great range of frequencies from very rare to very common and

(2) *Mode of Induction:* Fragile sites in many cases differ from one another in their mode of induction.

Fragile sites show a very broad range of frequencies from very rare to very common. The *rare fragile sites* might be illustrated by that of 6p23, 17p12 (less than 1 percent). The extremely *common fragile sites* can, of course be illustrated by that at 3p14, 1q42, 9p21 (more than 50 percent). Certain fragile sites defy being classified as rare or common, like 10q25 which has been observed to be present in about 1 in 40 persons in the Australian Caucasian population (Sutherland 1982b). It is classified as polymorphic variant (Sutherland and Hecht 1985). The division between rare and common fragile sites is therefore not very distinct. The division is merely a convenience for classification (Hecht 1986). Sutherland and Mattei (1987) proposed that the two terms be retained i.e. common (C) and rare (R).

Smeets et al. (1986) took note of the fact that "Two main classes of FS (fragile sites) can be recognized in man:

1. The rare or heritable fragile sites and
2. The common or constitutional fragile sites which are also referred as "hot points" and autosomal "lesions".

1.3.2 Nomenclature

The system of nomenclature for the gene symbol will be modified by the use of an allele notation because it does not indicate the chromosome band involved. The letter R for rare or C for common will be followed by the present location e.g. FRA 16B* RQ 221 describes the rare distamycin A fragile site at band q22.1. The common fragile site at this point is FRA 16C* CQ 211. A more extensive nomenclature is given in ISGN (International System for Human Gene Nomenclature 1988) (Sutherland and Mattei 1987).

Hecht (1986) reported that the division between "heritable" and "constitutional" fragile sites is nonsensical and misleading. All fragile sites are by definition heritable, since every fragile site studied in regard to the transmission pattern has been shown to be heritable as a codominant trait. Thus the term "heritable" applies to all fragile sites and it cannot be used to distinguish between fragile sites at this time for no fragile site has yet been demonstrated as heritable. Berger et al. (1985) suggested that common fragile sites have to be ubiquitous and to have expression frequencies dependent on environmental factors (Kao-Shan et al. 1987; Smeets et al. 1989; Sugio and Kuroki 1989) and may represent loci predisposed to evolutionary change (Miro et al. 1987; Smeets and van de Klundert 1990).

Identical consideration applies to the term 'constitutional' used to denote the very common fragile sites. The term 'constitutional' fragile site fails to distinguish between fragile sites, since all fragile sites are constitutional in the sense that they are, by definition, elements of chromosomes. No fragile site has been shown not to be constitutional. This quality of constitution ability holds for every fragile site and hardly requires mention. The term 'Hot-point' which has been used to refer to the common fragile site, also seem inappropriate (Hecht 1986).

1.3.3 Differences Between the Types of Fragile Sites

Rao et al. (1988) pointed that the differences between rare or heritable fragile sites (h-fra) and common or constitutive fragile sites (c-fra) are many. The h-fra is rare and segregates in simple Mendelian fashion, whereas c-fra is frequent and may be induced by several environmental factors. The h-fra is present in one homologue and is commonly seen as chromosome or chromatid breaks, deletions and triradials. On the other hand C-fra is sometimes present on both homologues and is usually seen as chromatid lesions.

1.3.4 Mode of Induction and Frequency of Fragile Sites

Rao et al. (1988) studied the frequency, distribution and analysed the fragile sites induced by fluorodeoxyuridine (FUdR), caffeine and aphidicolin and observed that some sites are susceptible to different methods of induction; some appear unique to a specific agent. Agents that induce fragile sites also induce a high number of apparently random breaks. Therefore in order to establish the presence of fragile sites in an individual, the total number of breaks in the cells observed is important. The use of 4 percent of total breaks as a means of delineating fragile sites from random breakage is suggested by them. The classification of fragile site should be based on their frequency in a population.

1.3.5 Fragile X (FRAXA) Syndrome [MIM 30095500]

Despite the studies that have taken place, only one rare fragile site at Xq27.3 is known to be associated with a clinical entity, the fragile X syndrome (Hagermann 1992; Fisch 1993; Tarleton and Saul 1993). It is most common cause of familial mental retardation, with an incidence of ~1/1,500 in males and 1/2500 in females (Sherman 1991).

Currently available procedures for the diagnostic evaluation of the FRAXA syndrome include cytogenetic, Southern-blot, Polymerase Chain Reaction (PCR), Reverse Transcription PCR (RT-PCR) and immunohistochemical analysis (Rousseau et al. 1991a; Brown et al. 1993; Cao et al. 1994; Pai et al. 1994; El-Aeem et al. 1995; Wang et al. 1995; Carrel and Williard 1996; Haddad et al. 1996; Holden et al. 1996; Spence et al. 1996; Willemsen and Oostra 2000; Weinhäusel and Haas 2001).

The fragile X (FRAXA) syndrome [MIM 30095500] is the most prevalent cause of inherited mental retardation in males (Turner et al. 1996). It has perplexing molecular genetic pathomechanism and its unusual pattern of inheritance pose an extraordinary challenge for its diagnostic evaluation in the laboratory and for genetic counseling of affected families (de Vries et al. 1998; Bardoni et al. 2000; Jin and Warren 2000; Kooy et al. 2000). The clinical phenotype of the FRAXA syndrome consists of moderate reverse intellectual impairment, macroorchidism, large ears, a prominent jaw and high-pitched jocular speech (de Vries et al. 1998; Bardoni et al. 2000). It results from the functional abolishment or, less often, deprived expression of the FMR I gene, which is located in the telomeric region of the long arm of the X chromosome, X (q27) (de Vries

et al. 1998; Bardoni et al. 2000; Jin and Warren 2000; Kooy et al. 2000). In the vast majority of cases, gene transcription is impaired by an unphysiological expansion of polymorphic CGG-triplet repeat within the untranslated exon of the FMR I gene (de Vries et al. 1998; Bardoni et al. 2000; Jin and Warren 2000; Kooy et al. 2000).

Worldwide cytogenetic surveys of the fragile X syndrome have found the disease among ethnic groups representing Caucasians, Amerindians, Africans, Asians (Rhoads 1984; Venter et al. 1984; Bundey et al. 1985; Arinami et al. 1986; Jacobs et al. 1986; Li et al. 1988; Aoi et al. 1989) diverse. These data have led the conclusion that there is no ethnic predilection to the development of the disease (Richards et al. 1994).

In a few studies that have been published on its frequency in unselected populations the prevalence rates vary from about 0.3/1000 to 1.0/1000. Blomquist et al. (1983) estimated the prevalence of fragile X-syndrome to 0.3/1000 newborn children in northern Sweden; Webb et al. (1986 a, b) and Turner et al. (1986) have studied its prevalence among educationally subnormal children. In England, Webb et al. (1986 b) calculated overall prevalence to be 1.0/1000 and based on the frequencies of fragile X among boys and girls in the study of Turner et al. (1986) in Australia a prevalence of about 0.3/1000 is calculated. The only study on unselected newborns (Sutherland and Hecht 1985) has not shown any fragile X positive cases among 3458 children studied. Kähkönen et al. (1987) reported 0.8/1000 in boys and 0.4/1000 among the girls from Finland. The frequency of the syndrome is about 1 in 4000 males for White (Turner et al. 1996) and American Blacks (Schwartz et al. 1988; Crawford et al. 1999).

Strong evidence has been produced that indicates parental origin of the premutation and occurrence of the premature ovarian failure (POF) in female carriers in families with fragile X, ascertained through mentally retarded patients (Cronister et al. 1991; Schwartz et al. 1994; Vianna-Morgante et al. 1996, 1999, 2000; Murray et al. 1998; Uzielli et al. 1999).

There have been two reports that the association of Klinefelter's syndrome and the fragile (X) syndrome is greater than can be expected by chance (Filippi et al. 1988; Fryns and van der Berghe 1988). In addition to the reported association between constitutional sex chromosome abnormalities and the fra (X) syndrome, suggesting an effect of the fra (X) mutation of chromosome segregation at meiosis, there have been two reports of an excess of X aneuploid cells in blood cultures of individuals carrying the fra (X) mutation, implying an effect of the fragile (X) gene on the segregation of the X chromosome at mitosis (Kähkönen 1983; Bröndum and Nielsen 1986). Jacobs et al. (1986) reported from their observations on 41 patients with Klinefelter's syndrome and their parents that none of the patients or parents is found to carry the fra (X) and the proportion of aneuploid cells in the parents is not correlated with their status with respect to meiotic non-disjunction. However, they observed a significant correlation between the proportion of aneuploid cells and the age of the patient at the time the sample is drawn.

1.3.6 Common Fragile Sites and Cancer

The common fragile sites have been suggested to be associated with the origin of chromosomal rearrangements in cancer (Yunis 1983, 1984; Hecht and Glover 1984; Hecht and Sutherland 1984; LeBeau and Rowley 1984; Yunis and Soreng 1984; Berger et al. 1985; De Braekeleer et al. 1985; LeBeau 1986; De Braekeleer 1987; Kao-Shan et al. 1987; Miro et al. 1987; Vernole et al. 1988; Furuya et al. 1989; Smeets et al. 1989; Sugio and Kuroki 1989; Watanable et al. 1990).

1.3.7 Other Disorders and Fragile Sites

Association of expression of chromosomal fragile sites with human psychiatric disorders has been reported in the literature. The finding of fragile sites on chromosomes 2, 3, 9, 10, 17, 18 and 19 in schizophrenic patients is described (for review see Basset 1992; Garofals et al. 1992, 1993; Turecki et al. 1995; Fananas et al. 1997; Smith et al. 1997; Chen et al. 1998).

Common fragile sites can be induced in a high percentage of the cells by a variety of chemicals and are classified into group according to the induction-aphidicolin (APD)-inducible (BrdU)-inducible and adenvirus 12 inducible fragile sites.

It has been suggested that CFS are present in all individuals and might be ubiquitous in nature (Berger et al. 1985). The frequency distributions of common fragile sites have been

reported in general population (Craig-Holmes et al. 1987; Hecht 1988; Tedeschi et al. 1992). The reported studies have demonstrated that chromosomal breakage is nonrandom and occurs at CFS, reflecting the presence and locations of hereditary fragile sites. The CFS have been shown to recombinational hot spots where both intrachromosomal (Glover and Stein 1987a) and interchromosomal (Glover and Stein 1987b) exchanges occur.

It has been observed from the above studies that increase in mean frequency of CFS is found in adults, and age and sex influence the expression of some of the commonest fragile sites. Therefore, the influence of these factors should be considered in view of the possible use of CFS expression as a tool for studying cancer proneness and/or mutagenicity risk.

The biological and medical meaning of the remainder of FS is unclear and controversial (Sutherland et al. 1985; Le Bau 1986; Laird et al. 1987; Kähkönen et al. 1989; Chudley et al. 1990; Jordan et al. 1990; Rassool et al. 1992).

1.3.8 Population Cytogenetics of Fragile Sites

Population cytogenetics of autosomal rare fragile sites in several different European groups (Sutherland 1982 a,b, 1985; Snhfilippo et al. 1983; Kähkönen et al. 1986, 1989; Petit et al. 1986; Schmid et al. 1986; Fryns and Petit 1986; Chudley et al. 1990) and Mongolian groups (Takahashi et al. 1985 a,b, 1988) has been reported for normal and patients. It has been observed that the incidences of a given fragile site seemed to be less between normal subjects (about 1 in 200) as compared to mentally retarded (about 1 in 50) and also among different ethnic groups (Table 12). Although biological significance of these polymorphisms remains unknown it would be interesting to know if the frequency of FS differs between populations. The relationship between racial distribution and fragile X site has been analysed (Sutherland and Hecht 1985).

1. Folate-sensitive Fragile Sites: Sutherland (1982a, 1985) has reported the incidence of autosomal sites in normal neonates, institutionalized mentally retarded patients and patients referred for chromosome studies as 0.14 percent, 0.95 percent and 0.38 percent, respectively. 11q13 (FRA11A) fragile site is found in both Japanese and Australian normal subjects. 10q23 (FRA10A) fragile site which is commonly found in Australian normal subjects and patients, has not been detected in the Japanese. The only autosomal rare fragile site found is at 2q11 (FRA2A).

2. Distamycin A-inducible Fragile Sites: In Japan, fragile sites 16q22 (FRA16A) (1.42 percent) and 17p 12 (FRA 17A) (3.08 percent) are found more commonly than the other two groups. Two reports have been published on a population survey of 16q 22 (FRA16A) fragile site. Sutherland (1985) evaluated the incidence as 1.63 percent in Australian patients. Schmid et al. (1986) reported that its incidence, when induced by berenil was 5.10 percent in a normal German population. The incidence among Japanese (1.42 percent) is much lower than that of the German population but similar to that of the Australian patients. For 17p12 (FRA 17A) fragile site the incidence (3.08 percent) in Japan was much higher than that in Australian normal neonates (0.27 percent) (Sutherland 1985).

3. BrdU-requiring Fragile Sites: According to Sutherland (1982b) the incidence in Australia of 10q25 (FRA10A) fragile site is 2.34 percent, 2.44 percent and 3.45 percent in normal neonates, patients and mentally retarded individuals, respectively. On the other hand, Sanfilippo et al. (1983) have found 8 carriers (0.55 percent) in 1444 patients in Italy. The 10q25 (FRA10A) fragile site in Japan (0.29 percent) appears to be as frequent as in Italy, but much less frequent than in Australia.

4. Spontaneous Expression and Genetic Heterogeneity: Sanfilippo et al. (1983) reported 16q22 (FRA 10A) fragile site in 4/155 (2.58 per cent) mentally retarded individuals and in 14/1, 444 (0.97 percent) patients by addition of BrdU, but not by distamycin A treatment from Italy (Table 12). Enhanced expression by BrdU has also been reported in other carriers (Sutherland et al. 1984).

Izakovic (1984) observed that 17p12 (FRA17A) which was detected to media (standard EPL and low folate M-199) without distamycin A, was frequently reported in a normal Czechoslovakian population in 8/798 (1 percent) (Table 12).

To understand the behaviours of fragile sites and their genetic heterogeneity, Takashashi et al. (1988) suggested that combined assay systems be used for the detection of folate-sensitive, distamycin A-inducible and BrdU-requiring sites.

Table 12: Frequencies of the autosomal rare fragile sites (AFRs) among different population groups

Category	*Population/Country*	*Subject*	*Site*	*Incidence (Perent)*	*Authors*
Folate-sensitive	Australian	Neonate	a	5/3,458 (0.14)	Sutherland (1982a, 1985)
	Australian	Patient	b	16/4.173 (0.38)	Sutherland (1982a, 1985)
	Australian	Retarded	c	5/524 (0.95)	Sutherland (1982a, 1985)
	Japanese	Normal	d	5/1,022 (0.49)	Takahashi et al. (1988)
	Finland	Children Patient	e	2/180 (1.11)	Kähköhen et al. (1989)
	Finland	Retarded	f	14/1265 (1.11)	Kähköhen et al. (1989)
	Belgium	Retarded	g	13/405 (3.20)	Patit et al. (1986);
		Retarded	h	24/400 (6.00)	Fryns and Petit (1986)
		Normal	h	13/200 (6.50)	Fryns and Petit (1986)
	Canadian	Normal	i	3/790 (0.38)	Chudley et al. (1990)
	Basque	Normal	j	4/50 (8.00)	Arriela et al. (1996)
		Normal	k	16/10,000 (0.16)	Quack et al. (1978)
		Normal	l	17/7786 (0.22)	Guichaoua et al. (1982)
Distamycin-A-inducible	Australian	Patient	16p22	8/491 (1.63)	Sutherland (1985)
	German	Normal	16q22	18/350 (5.10)[e]	Schmid et al. (1986)
	Japanese	Normal	16q22	12/845 (1.42)	Takahashi et al. (1988)
	Australian	Neonate	17p12	1/368 (0.27)	Sutherland (1985)
	Japanese	Normal	17p12	26/845 (3.08)	Takahashi et al. (1988)
	Czechoslovakian	Normal	17p12	8/798 (1.00)[f]	Izakovic (1984)
BrdU-inducible	Australian	Neonate	10q25	24/1026 (2.34)	Sutherland (1982b)
	Australian	Patient	10q25	22/901 (2.44)	Sutherland (1982b)
	Australian	Retarded	10q25	3/87 (3.45)	Sutherland (1982b)
	Italian	Patient	10q25	8/1,444 (0.55)	Sanfilippo et al. (1983)
	Japanese	Normal	10q25	3/1,022 (0.29)	Takahashi et al. (1988)
	Italian	Retarded	16q22	4/155 (2.58)	Sanfilippo et al. (1983)
	Italian	Patient	16q22	14/1,444 (0.97)	Sanfilippo et al. (1983)

a 8q22, 10q23, 11q13, 12q13
b 2q11, 2q13, 6q23, 9q21, 9q32, 10q23, 11q13, 12q13, 16q12
c 2q11, 10q23, 11q13, 20q11
d 2q11, 11q13, 11q23, 17, 12
e induced by berenil
f Detected without distamycin A
e,f : 2q11, 9p21, 10q23, 12q13, 16p12, 22q13.
g : 2q11, 10q23
h : 2q11, 8q22, 10q23
i : 2q11, 9p13
j : 2q22, 10q24, 10q23, 12q24
k: 2q11, 10q23, 11q13, 12q13
l : 2q11, 10q23, 11q13, 12q13

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NOTES

1. Constitutive Heterochromatin: It forms very polymorphic regions of human chromosomes. The regions of constitutive heterochromatin contain a particular type of tandemly repeated DNA sequences - satellite DNAs. Molecular analysis of the human genome

has revealed two types of DNA sequences characteristic of heterochromatin- "classical" satellite I, II, III, IV DNAs and alpha-satellite (alphoid) DNA (for a review see Singer 1982). In the last few years the satellite DNA sequences specific to individual human chromosomes were determined. For example classical satellite III DNA contains special sequences of DNA specific to variable heterochromatin regions of chromosomes Y and 1 (Bostock et al. 1978; Cooke and Hindly 1979; Gosden et al. 1981b); alpha satellite DNA contains sequences specific to centromeric heterochromatin X (Yang et al. 1982; Willard 1985; Alexander et al. 1986a); chromosome Y (Erickson et al. 1984) and to many other chromosomes. Chromosome-specific variants of satellite DNA sequences may be very useful as probes for investigation of the molecular nature of heterochromatin on many human chromosomes for correlation of cytological variants of chromosomes variable (C-and Q-bands) with special types of DNA sequences and for the detection of new polymorphic variants of human chromosomes. Using molecular cytogenetic techniques a number of cloned satellite DNA sequences with specific localization in heterochromatic regions of individual human chromosomes for example, chromosomes 1,3,4,9,11,17,18, X and some others have been discovered (Yurov 1984; Alexandrov et al. 1986a,b; Yurov et al. 1986a, b).

2. Heterochromatin: It is formed by tandemly organized highly repeated sequences (satellite DNA) that do not encode proteins. Large amounts of heterochromatin are usually associated with the pericentromeric regions of chromosomes. The functions of satellite sequences and heterochromatin in general are not known but a number of hypotheses have been proposed. Doolittle (1982) states that satellite DNAs have no cell function at all and represent "selfish DNA". However Yunis and Yasmineh (1971) and Bostock (1985) have proposed a range of important functions, connected with the stabilization of chromosome structure and the three dimensional organization of the nucleus for satellite DNA. It has also been proposed that satellite DNA plays an important role in the recognization of homologous chromosomes. Defects in this function may have an important role in evolution leading to reproductive isolation. Alexandrov et al. (1988) state that the most important conclusion to be derived from the recent studies of satellite DNAs is that these sequences constitute a very unstable part of the genome. Satellite sequences are also unstable within one species. The commonly observed consequence of this instability is inter-individual variability of the sizes of heterochromatic block of certain chromosomes. It has been shown that this phenomenon reflects the variations in copy number of chromosome-specific satellite DNA in individual chromosomes (Bostock 1985; Yurov et al. 1986a, b). Detailed studies of the structure and evolution of satellite DNAs will possibly reveal whether some parameters of these sequences are affected by selective pressure and thus provide an approach to an understanding of their function and possible consequences of their genetic instability.

3. Hook et al. (1984) denote the ratio of trisomy cases to all fetuses (or livebirths) observed as proportion of those affected. This value is usually (but erroneously referred to as a "rate". Technically, however the term "rate" denotes measure of change of one variable with another (Cornfield 1976).

4. Scoring Criteria: Variation in length of hetrochromatic segments (h), satellite stalks (stk) or satellites (s) should be distinguished from increases or decreases in arm length as a result of other structural alternations by placing a plus (+) or minus (-) sign after symbol h, stk or s following the appropriate chromosome and arm designation (ISCE 1995).

For homeomorphisms of short arm region of D- and G-Group acrocentric chromosomes measurements are carried out with the help of a Vernier caliper to an accuracy of 1/20th of a millimeter. The following scoring criteria are employed to examine the types and frequencies of heteromorphisms (Lubs and Ruddle 1971).

(1) Elongation of the short arm (ph+) of D- and G-group chromosomes is recorded when it is equivalent to or greater than the short arm of chromosome 18.

(2) Increased length of the satellite region (ps+, pss+) of the acrocentric chromosomes is scored when these regions are greater in size than the short arm of the same chromosome.

(3) Deletion (ph-) of the short arm region of D- and G- group acrocentrics is recorded when the short arm is completely absent.

5. Scoring Criteria: Size and inversion heteromorphisms of paracentromeric long arm regions of chromosomes 1, 9 and 16:

(1) Size heteromorphisms are recorded as described by Lubs et al. (1977a) and Patil and Lubs (1977b) employing the size of the short arm of the chromosome 16 from the same cell as standard. The 9h/16p lengths on chromosomes 1, 9 and 16 are classified into the following five size levels:

Level 1:	< 0.5 x16 p	Very Small
Level 2:	0.5-1.0 x 16 p	Small
Level 3:	1.0-1.5 x 16 p	Intermediate
Level 4:	1.5-2.0 x 16 p	Large
Level 5:	> 2.0 x 16 p	Very Large

(2) Inversion heteromorphisms are scored according to the method of Verma et al. (1978a), dividing them into 5 classes as following:

Level 1: No Inversion (NI): h region is confined to the long arm.
Level 2: Partial Inversion Minor (MIN): less than half of h region present on the short arm.
Level 3: Half Inversion (HI): half of h region present on the short arm and the other half on the long arm.
Level 4: Partial Inversion Major (MAJ): more than half of the h region present on the short arm.
Level 5: Complete Inversion (CI): complete shift of h region from the long arm to the short arm.

6. Scoring Criteria: The chromosome measurements for length variation in Y chromosome are taken by a Vernier caliper. To study the length variations of the Y chromosomes five "Y indices are calculated using five different sets of chromosomes as "Standard chromo-

somes" namely A2, D, E, F, and G. These proportional indices are calculated to enable the comparison of different cells from different individuals. Y/F index is calculated as follows:
Y/F= Total length of the Y chromosome/Average total length of F group chromosomes

The F group chromosomes are measured diagonally from one end of the chromatid to the other end of the chromatid, and the Y chromosome from the end of the short arm to the end of the long arm. Long Y chromosome is recorded if Y/F index is more than 1.0, and short Y is recorded if this index is less than 0.70 (Nielsen and Fridrich 1972). The average Y/F index value obtained from 5 cells is taken as an individual's value for further analysis.

By quantitative evaluation, Borovik et al. (1977) and Beltron et al. (1979) observed significant heterogeneity between individuals in the length of the Y chromosome. From family studies it was reported that the Y chromosome is inherited at a constant length by the son from the father (Bishop et al. 1962; Unnerus et al. 1967; Borgaonkar et al. 1969; McKenzie et al. 1972; Baliček et al. 1978; Beltron et al. 1979).

Variation in the length of the Y chromosome has been reported in clinically normal as well as in abnormal persons (Bender and Gooch 1961; Cone et al. 1961; Muldal and Ockey 1961; Vaharh et al. 1961; Bishop et al. 1962; Kallen and Levan 1962; Van Wijck et al. 1962; Dekaban et al. 1963; de la Chapelle 1963b; Gropp et al. 1963; Makino et al. 1963; Tonomura and Ono 1963; Makino and Muramoto 1964; Nakagome et al. 1965; Nuzzo et al. 1967; Sugahara and Sakurai 1967; Nielsen 1969; Jeske and Hubner 1970; Retief and Van Niekerk 1971; Kjessler 1972; Meisner and Inhorn 1972; Chandley et al. 1975; Koulischer 1976).

Slight differences in the frequency of the chromosome length between different populations have been attributed to the scoring criteria since different authors have used different chromosomes as a standard measure within the cell so as to correct the mitotic contraction differences of the Y chromosome in different studies, while studying the Y chromosome length variation, such as.

Y/A2 (Cohen et al. 1966; de la Torre and Giemenez-Marting 1970; Ghosh and Singh 1975; Nasjleti et al. 1979),

Y/A3 (Tisler et al. 1972; Brogger et al. 1977),

Y/D (Makino and Takagi 1965; Sugahara and Sakurai 1967; Kadotani et al. 1971; Ghosh and Singh 1975),

Y/E (Sugahara and Sakurai 1967; Unnerus et al. 1967; Battaglia et al. 1971; Lins and Sundequist 1971; Ghosh and Singh 1975)

Y/F (Makino and Takagi 1965; Chen et al. 1966; Court Brown 1967; Sugahara and Sakurai 1967; Kadotani et al. 1971; Nielsen and Friedrich 1972; Angell 1973; Zeuthen and Nielsen 1973a; Christensen and Nielsen 1974; Schwinger and Wild 1974; Soudek and Laraya 1974; Ghosh and Singh 1975; Nielsen and Nordland 1975; Benezech et al. 1976; Akesson and Wahlström 1977; Patil and Lubs 1977b; Nielsen 1978; Genest 1979; Kenue 1979; Nasjleti et al. 1979; Soudek and Sroka 1979 and others).

Y/G (Tonomura and Ono 1963; Makino and Takagi 1965; Sugahara and Sakurai 1967; Kadotani et al. 1971; Ghosh and Singh 1975; Yamada and Hasegawa 1978).

7. Scoring Criteria: The Q-band by fluorescence using quinacrine (QFQ) technique identifies heteromorphic bands which can be classified according to their fluorescent intensity. Different intensities are classified into five levels established at the Paris Conference (1971) with the brightest level being assigned a code of 5 and the least fluorescent a code of 1.

Table 1: Criteria for classification of Q-band by Fluorescence using Quinacrine (QFQ). Intensity level (Paris Conference, 1971)

Code	*Description*	*Comparison*
1	Negative	No fluorescence
2	Pale	As in distal 1 p
3	Medium	As in major bands 9q
4	Intense	As in major distal 13q bands
5	Brilliant	As in distal Y

The bands in the centromeric regions (q 11) of chromosomes 3 and 4, the short arm (bands p11 and p13) of the acrocentric chromosomes (13, 14, 15, 21 and 22) and the long arm of Y are found heteromorphic by QFQ technique. Using the intensity of the centromeric region of chromosome 3, it has become possible to identify inversions of the pericentromeric heterochromatin. Pericentric inversion in chromosome 3 inv (3) (p15q12) has been observed.

8. Scoring Criteria: For heteromorphisms by RFA (R-Bands by fluorescence using Acridine Orange) Technique. The colour and size of the short arm of human acrocentric chromosomes by acridine orange reverse banding (RFA) is defined subjectively. Colour variations are classified into six different colours: red, red-orange, orange-yellow, pale yellow, bright yellow and pale green. Size heteromorphisms are classified into five sizes: very small, small, average, large and very large (after Verma and Lubs 1975b).

Photograph RFA cells on Kodachrome 64 colour film. Determine the pale green colour from RFA metaphases directly by projecting colour slides using a point light source enlarger or by projecting the mounted transparency slides from a 35 mm projector on to an opaque rear projection screen.

9. Scoring Criteria: For heteromorphisms of Ag-stained Nucleolar Organizer Regions (NORs) criteria used to classify the size of NORs are defined subjectively. 18p is used as a reference point to have internal cell standards to determine the different sizes of NORs. Five sizes of NORs namely: very large, large, medium, small and very small are suggested and pictorial examples.

The NOR technique revealed darkly segments (N-

Table 2: Criteria for classification of Nucleolar Organizer Regions (NORs) size after Verma and Lubs (1975)

Code	*Size*	*13-15*	*21-22*
1	Very small	Virtually absent	Virtually absent
2	Small	< 0.5 x 18 p	< 0.25 x 18 p
3	Average	> 0.5 to 1.5 x 18 p	0.25 x 18 p
4	Large	> 1.5 to 2.0 x 18 p	= 18 p
5	Very large	> 2.0 to 18 p	> 18 p

bands) at the regions corresponding to the satellite stalks. No colour variation has been noted in these regions (Verma and Lubs 1975b) nevertheless size variation has been noted even using acridine orange reverse banding (RFA) technique.

Photograph NSG (N-bands by silver staining using Giemsa) cells on high contrast copy film. Prepare partial karyotypes of NSG banded chromosome.

Table 3: Criteria for classification of Nucleolar Organizer Regions (NORs); colour after Verma and Lubs (1975)

Code	*Colour*	*Like*
1	Red	3c
2	Red-Orange	Mid 2q (q21-q24)
3	Orange-Yellow	18p
4	Pale Yellow	Distal 1q (q32 and 42) (also 20p)
5	Bright Yellow	Distal 1p (p3) (also 22q and 19)
6	Pale Green	Present only in secondary constriction regions of acrocentric chromosomes

10. Viral modification Sites: These on chromosomes are non-staining gaps (which can resemble fragile sites) which are caused by the virus or viral products (Sutherland and Mattei 1987)

11. A. Rare Fragile Sites: Group I (Folate sensitive); Group 2 (Distamycin A inducible); Group 3 (BrdU inducible);

11.B. The Common Fragile Sites: Group 4 (Aphidicolin; inducible); Group 5 (5-Azacytidine inducible); Group 6 (BrdU inducible) and Group 7 (Adenovirus 12 inducible) (after Sutherland and Richards 1999).

APPENDIX

2. VARIABLE CHROMOSOME FEATURES

2.1 Variation of Secondary Constrictions or Satellites in Non-Banded Chromosomes

Increases or decreases in the length of secondary constrictions, in that of negatively staining regions, or in the size of satellites should be distinguished from increases or decreases in arm length owing to other structural alterations by placing the symbol h or s between the symbol for the arm and the + or - sign. e.g.:

46, XY, 16qh+ Male karyotype with 46 chromosomes, showing an increase in length of the secondary constriction on the long arm of chromosome 16

46, XY, 21S + Male Karyotype with 46 Chromosomes showing an increase in the size of the satellite on Chromosome 21

Duplicated Chromosome Structures are indicated by repeating the appropriately, designation. Thus, 46, XY, 21 pss would describe the karyotype of a female in which one chromosome 21 has double satellites on the short arm. White 46, XX, 18ps indicates a chromosome 18 with satellites on the short arm, 46, XX, 21 psqs designates a chromosome 21 with satellites on the long and short arms. While 46, XX, 18ps indicates a chromosome 18 with satellites on the short arms, 46, 21psqs designates a chromosome 21 with satellites on the long and short arms.

2.2 Variation in Heteromorphic Regions in Banded Chromosomes

2.2.1 Short Terminology

The short form, such as 1qh+ and 13s+, may still be used, but appropriate, a description of the technique used should be included, e.g., 1qh+ (CBG), 21s (QFQ) (Table 1). Any code should be defined in the text of the publication in which it is first used. Examples of the use of code are given (2.2.2).

Table 1: Examples of code to describe banding techniques. In the one-, two- or three-letter code, the first letter denotes the type of banding, the second letter the general technique, and the third letter the stain. Some examples are given below.

Q.	Q-bands
QF	Q-bands by fluorescence
QFQ	Q-bands by fluorescence using quinacrine
QFH	Q-bands by fluorescence using Hoechst 33258
G	G-bands
GT	G-bands by trypsin
GTG	G-bands by trypsin using Giemsa
GAG	G-bands by acetic saline using Giemsa
C	C-bands
CB	C-bands by barium hydroxide
CBG	C-bands by barium hydroxide using Giemsa
R	R-bands
RF	R-bands by fluorescence
RFA	R-bands by fluorescence using acridine orange
RH	R-bands by heating
RHG	R-bands by heating using Giemsa
RB	R-bands by BrdU
RBG	R-bands by BrdU using Giemsa
RBA	R-bands by BrdU using acridine orange

2.2.2 Complete Description

Heteromorphic chromosome can be described if the term variable, abbreviated to var, is used before the chromosome number, e.g. var (13). Additional information regarding the variable region can then be conveyed by means of symbols set within brackets in the following order:

(1) The location of the variable structure on the chromosome by either band numbers or code letters, such as cen, h, s, etc. This is followed by a comma.

(2) The banding techniques used (see examples in Table 1)

(3) A numerical designation for the size and staining intensity of all variable regions, with higher numbers indicating greater size or staining intensity. Such numerical designations must be clearly defined (examples are given in Table 2). A zero indicates that the size of intensity was not quantitated. The number of digits used to describe size must equal the number of digits used to describe intensity.

When several techniques are used, each description should be separated by a comma. Their order is arbitrary.

Table 2: Example of how size and intensity descriptions can be expressed numerically

Size[1]	*Intensity (Paris Conference, 1971)*
Q-banding	
1 Very small	1 Negative (no or almost no fluorescence)
2 Small	2 Pale (as on distal 1p)
3 Intermediate	3 Medium (as the two broad bands on 9q)
4 Large	4 intense (as the distal half of 13q)
5 Very large	5 Brilliant (as on distal Yq)
C-banding	
1 Very small	0 No quantitation intensity[2]
2 Small	
3 Intermediate	
4 Large	
5 Very large	

1. The definition of "small", "large", etc., should be clearly presented in specific publications where the terminology is employed. A zero (0) may be used in any instance where quantitation is not used.
2. If quantitation of intensity of C-bands becomes possible, then an analogous series of definitions will be necessary

If more than one variable structure is present on the same way, with parentheses, rather than a comma, used to separate the descriptions.

If the same variant appears on more than one homolog, an equal sign (=) followed by a number, e.g., var (13=2), can be used to designate the number of chromosomes that can confirm to the initial *var* description. The parental origin of a chromosome can be identified by inserting *pat* or *mat* after the last parenthesis.

When more than one variable chromosomes of a complement are described , the chromosomes in question are listed in descending order of chromosome size, the terms relating to each chromosome being separated by a comma. Bands on a given chromosome should be listed sequentially from the centromere outward with those bands in the short arm listed first and those in the long arm last e.g.: 46, XY, var (3) (cen, Q 35).

Chromosome 3 with a centromeric region that, when Q-banded, is of intermediate size and fluoresces brilliantly 46, var (13=2) (p13, Q 35).

Two chromosomes 13 with satellites (p13) that, when Q-banded, are of intermediate size and fluoresces brilliantly.

46,XY, var (13) (p13, QFQ 545, CBG 545) (q11,QFQ35,CBG30)

One chromosome 13 with very large satellites (p13) seen for both Q- and C-bandings. These are brilliant after Q-banding, but C-banding intensity was not determined. In addition, band q11, when Q-banded, is of intermediate size and fluoresces brilliantly, and when C-banded, it is likewise intermediate in size. C-banding intensity was not determined.

46,XY,var (13) (p13, QFQ45, CBG40) (q11,QFQ35, CBG30) one chromosome 13 with large satellites (p13) seen after both Q-banding by quinacrine fluorescence and C-banding by barium hydroxide pretreatment followed by Giemsa staining. These are brilliant after Q-banding, but C-banding intensity was not determined. In addition, band q11, when Q-banded, is of intermediate size and fluoresces brilliantly, and when C-banded, it is likewise intermediate in size. C-banding intensity was not determined.

46,XY,var (13) (q11, QFQ 55), var (21) (p13, QFQ44), var (22) (p13, QFQ35). Three variant chromosomes seen after Q-banding by quinacrine fluorescence

47,XY,+21,var (21), (p13, Q12), var (21=2) (p13,Q54)mat

Male with 47 chromosomes and trisomy 21. One chromosome 21 has very small satellites of pale intensity after Q-banding; the two remaining chromosomes 21 are identical, with very large and intensely fluorescent satellites, and both are of maternal origin.

2.3 Fragile Sites

Specific chromosome loci where constitution of chromosome and/or chromatid gaps and/or breaks occurs regularly are called *fragile sites,* abbreviated *fra.* These fragile sites are inherited in a co-dominant Mendelian fashion and may result in chromosome abnormalities such as deletions, multiradial figures, and acentric fragments. While there may be several different types of fragile sites inducible by culturing cells in media containing different may occur as normal variants or be associated with specific diseases and/or phenotype abnormalities components (ISCN 1995) may occur as normal variants or be associated with specific diseases and/or phenotypic abnormalities all these will be covered by a single nomenclature.

Thus:

fra (10) (q25.2): A fragile site on chromosome 10 in subband 10q25.2

fra (10) (q22.1q25.2): Two fragile sites on the same chromosome

fra(10) (q22.1) fra (10)(q25.2): Two fragile sites on different homologous chromosomes

fra(10) (q23.2) fra (16)(q22.1): Two fragile sites on different chromosomes

46, X, fra (x) (q27.3): A fragile site in subband xq 27.3 on one X chromosome in a female

46, Y, fra (X) (q27.3): A fragile site in subband Xq 27.3 on the X chromosome in a male

45, fra (X) (q27.3): A fragile site in subband Xq 27.3 on the X chromosome in a Turner syndrome patient

47, XY fra (X) (q27.3): A fragile site in subband Xq 27.3 on one X chromosome in a Klinefelter syndrome patient.

It has been agreed that for the purpose of gene mapping a modified version may be used using capital letters and omitting punctuation, e.g., FRAXQ27. Note, however, that only two digits are available for band designation so that, for instance, fra (10) (q25.2) would become FRA10Q25.

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