A STUDY OF THE DENTO-FACIAL MANIFESTATIONS AND CEPHALOMETRIC MEASUREMENTS IN PATIENTS WITH FRAGILE X-LINKED MENTAL RETARDATION

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بسم الله الرحمن الرحيم

« اقرا باسم ربك الذى خلق. خلق الانسان من علق.
اقرا وربك الاكرم. الذى علم بالقلم. علم الانسان
ما لم يعلم »

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Tables of Contents

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List of Abbreviations

AM	Anterior mandibular height:Infradentale-Menton(Id-Me)
AS	Anterior nasal spine (ANS) to Sella Vertical (S.V.)
CA	Cranial flexure angle <NSBa
C	Case #
Cen	Centromere
CEPP	Craniofacial pattern profile
DNA	Deoxyribonucleic acid.
Fra (x)	Fragile (X)
HGL No.	Human Genetics Lab. Number
HW	Maximum head width: Eu - Eu
IQ	Intelligence quotient
KD	Kilo dalton
KV	Kilo Volt
M	mothher
MA	Milli ampere
MA	Mandibular angle: Ar-Go-Gn (Gonial angle)
ML	Mandibular Length : Gonion-Menton (Go-Me)
M.R.	Mental retardation
MP	Metacarpo-phalangeal joints
N	Number of cases
NB	Mandible to cranial base <SNB.
NP	Mandible to cranial base <SNPg
NTM	Normal transmitting males
OFC	Occipito-frontal circumference (head circumference)

List of Abbreviations (Contd)

OW	Interorbital width : Mo - Mo
P	Pedigree number
P3-007	Pedigree # 3, case # 7.
P-Value	Probability Value
PRS	Pyrimidine-rich DNA sequence
PH	Posterior Facial Height / anterior facial height : S-Go / N-Me Ratio.
PS	A. point to Sella Vertical (S.V.)
r	Correlation coefficient
S.D.	Standard deviation
SE	Standard error
SS	Supradentale (Sp) to Sella Vertical (S.V.)
TH	Total facial height : Nasion-Menton (N-Me)
TC 199	Tissue culture 199
TM	fransmitting male
UH	Upper Facial height / Lower Facial Height : N-ANS / ANS-Me Ratio.
X	mean
XB	Maxilla to cranial base <SNA
XH	Maxillary height : Supradentale-A-point (Sp-A-pt)
XLMR	X-Linked Mental Retardation
Xq	Long arm of X chromosome
XN	Maxillary Length/mandibular length : ANS-PNS/GO-Me Ratio.
ZY	Face width : ZY - ZY
#	Number

List of Tables

List of Tables (Contd)

List of Figures

List of Figures (Contd)

CHAPTER I

INTRODUCTION

Fragile X syndrome is one of the most common forms of heritable mental retardation in man. Fra (X) individuals have a fragile site on the long arm of the X chromosome at the region 2 band 7.3 (Xq 27.3) in a variable proportion of their lymphocytes (Turner and Jacobs, 1983)[1].

50% of X-linked mental retardation (XLMR) was assumed to be due to fra (X) mutation (Herbst and Miller, 1980)[2] although later on an update on X-linked mental retardation syndromes identified more X-linked conditions in which mental retardation is a major component manifestation. Nevertheless, fragile X syndrome constitutes a major health problem as it is a common condition that affects all races and most of the affected individuals, males or females, require education and support. Moreover inspite of the intensive genetic, cytogenetic and molecular investigations, there remains a lot about fragile X syndrome that is not clearly explained until now. (Ledbetter, 1991)[3].

Historical Perspective of Fra (X) Syndrome:

Lubs (1969)[4] first described a fragile site lesion on the X chromosome, or marker X, associated with a common heritable form of mental retardation in four males in a

family with X-linked mental retardation. Large families with X-linked mental retardation were well documented in human genetics at that time (Martin and Bell, 1943[5]; Renpenning et al., 1962[6]; Dunn et al., 1963[7]). Lubs observation, however, went largely unconfirmed until Grant Sutherland reported in Australia in 1977 that the fragile site on the X-chromosome and other heritable fragile sites were generally expressed in a portion of cells analyzed more frequently in tissue culture medium TC199.

In 1979, Sutherland[8a,b] produced the landmark paper in understanding and defining the heritable sites on human chromosomes and tissue culture factors that influence their expression. He showed that relative deficiency of vitamin folic acid and a DNA pyrimidine base thymidine were responsible for expression of the fra (X) using TC199. A thymidine analog 5 - bromodeoxyuridine would similarly suppress fra (X) expression and one would effectively use methotrexate (folate antagonist) to express the fragile site through folate/thymidine depletion. Glover (1981)[9] also showed that the fragile site can be elicited in medium containing normal levels of folic acid with the thymidilate synthetase antagonist 5-fluorodeoxyuridine. The percent of cells that carry the fragile site at Xq 27.3 will vary from 1% up to 50% (Turner and Jacobs, 1983)[1] although every cell contains the abnormal gene. To avoid false negative, at

least 100 lymphocyles should be analyzed for the presence of the fragile X chromosome (Glover, 1981)[9]. In heterozygous females at least 200 cells should be analyzed because an unaffected female may demonstrate a very small percentage of lymphocytes with the fragile site (Chudley et al., 1983)[10]. The presence of the Xq 27.3 fragile site should be confirmed with chromosome banding. When a frequency of less than 4% is obtained, a repeat specimen should be requested. Proper cytogenetic nomenclature used is 46, fra (X) (q27.3) Y in males and 46 X, fra (X) (q 27.3) in females. The result should include the frequency of expression and the number of cells examined (Jacky et al., 1991)[11].

Frequency and Prevalence in Different Populations

Mental retardation is one of the most common devastating handicaps in societies and its prevalence varied from 1/1000 in Wales to 3% in the U.S. (Symanski and Crocker, 1985)[12].

In a door to door survey on the prevalence of mental retardation in an Upper Egyptian village in Assiut governorate, it was found to be 4.4% with an excess of males relative to females 1.29 : 1 (Demerdash et al.,1985)[13]. This study was carried on 720 individuals from 337 families examined from El-Shahabia village and 604 healthy matched controls.

Another field investigation on a studied population of 3000 individuals (age 2-18 years) conducted by a door to door survey in Assiut governorate over one and a half years (1987-1988) revealed 3.9% prevalence of mental retardation (Temtamy et al., 1991 a)[14a].

Among 4400 cases referred to the clinic of Human Genetics Department, National Research Center, Cairo, Egypt, mental retardation was the diagnosis on referral in 1056 cases (24.2%) from 1979-1989 (Temtamy et al., 1991 b)[14b]. This percentage increased to 38.2% in a following study by Abd-Elsalam et al in 1992 in the same clinic in the 3-year period of (89-91). This increased percentage was attributed to the increased knowledge of and awareness of the Egyptian population to genetic diseases, to their possibly favorable prospect, management and control as well as to the growing skilled diagnostic, prenatal diagnosis techniques and genetic counselling (Abd-Elsalam et al., 1992)[15].

The Martin-Bell syndrome was named on XLMR associated with the X chromosome cyrogenetic marker (the fra X site) after the first published pedigree by Martin and Bell (1943)[5] and was reevaluated later and found to show both macroorchidism and the cytogenetic marker on the X chromosome.

Different approaches have been taken to estimate indirectly the contribution of the fra (X) syndrome to XLMR.

Some have estimated the proportion of XLMR that is due to fra (X) syndrome by screening mentally retarded populations for the fra (X) syndrome. Others have screened populations with particular characteristics such as autism, macroorchidism or a specific level of mental retardation to determine the contribution of the fra (X) syndrome to morbidity (Hagerman and Silverman, 1991)[16].

In the period from June 1987 to December 1988. Martin Bell phenotype (fragile X positive or negative was described in 10.3% in the survey done in Assiut governorate(Temtamy et al., 1991 a)[14a] and later Abd-Elsalam et al[15] in 1992 described the Martin Bell phenotype in 17% of mentally retarded cases.

Opitz and Sutherland in 1984[17] assumed fragile X syndrome to constitute 20% of all mental retardation. X-linked mental retardation amounted to 33.3% of mental retardation in males and 50% of XLMR was assigned to fra (X) mutation (Opitz,1986)[18].

Prevalence estimates of the fra X syndrome in a predominantly Caucasian population range from 0.4/1000 to 0.8/1000 in males and from 0.2/1000 to 0.6/1000 in females (Turner et al.,1986[19]; Webb et al., 1986[20]; Sutherland, 1985)[21]. These numbers are underestimated because they are

based on screening of individuals with overt MR and do not include those with borderline or nearly normal intelligence. Nevertheless these values make it clear that the fra (X) syndrome is the most common inherited cause of MR, after trisomy 21, the most common identified cause of MR.

The frequency rates of fragile (X) males were 1.9% and 0.3% fra (X) females in three populations studied by Jacobs et al.,1986[22] in Hawaii: individuals in community placement, in day - care facilities and those in special education schools.

Fragile X syndrome prevails among different ethnic groups. Jacobs et al., 1986[22] found 1.9% of fragile X syndrome in a racially mixed population of 376 Hawaiian Oriental and Filipino individuals. Table I.3 presents a list of non European groups in which fra (X) syndrome has been identified (Hagerman and Silverman, 1991)[16].

Neri et al in 1992[23] updated the classification of the XLMR syndromes at the Fifth International Workshop on the Fragile X and XLMR in Strasbourg, 1991.

They identified 77 X-linked conditions in which mental retardation was a major component. These conditions were submitted into two categories designated respectively "X-

linked mental retardation syndromes" and "Non-specific X-linked mental retardation".

XLMR has become such a complex and crowded field that it is increasingly difficult to deal with matters of nosology and definition. This was apparent at the Fifth International Workshop on the Fragile X and X-linked Mental Retardation in Strasbourg, 1991)[23].

XLMR syndromes were reported in Table I.1 after Neri et al in 1992[23] with a total number of 62, including fra X syndrome. Of these, 26 are regionally mapped into the X chromosome.

Non specific XLMR conditions were reported in Table I.2 This report confirms that the number of XLMR genes may not greatly exceed 70 as was indicated by Opitz and Sutherland in the first XLMR conference report (1984)[17]. There is a prevailing belief that splitting will occur as much as possible until regional mapping of all potential genes will justify some lumping.

TABLE I.1 X-Linked Mental Retardation Syndromes: Update 1992

Mim No. (Ref.)*	Syndrome Name	Locus	Description
*305400 and (20)	Aarskog	Xp11-q12	Hypertelorism, downslanting eyes, anteverted nostrils, shawl scrotum, joint hyperlaxity
304050	Aicardi		Agenesis of corpus callosum, chorioretinopathy, microphthalmia seizures, lethal in males.
309600	Allan-Herndon Dudley	Xq21	Severe hypotonia, joint contractures, muscular atrophy
(1)	Arena	Xq22-q25	Spastic paraplegia, ataxia, iron deposits in basal ganglia
(3)	Atkin-Flaitz		Macrocephaly, "coarse face" short stature, macroorchidism
312890	Baar-Gabriel		Spastic athetotic paraplegia
*301900	Borjeson-Forssman-Lehman	Xq26-q27	Obesity, hypogonadism, round face, narrow palpebral fissures, epilepsy
301950	Branchial arch		Short stature, downslanting eyes, lowset ears, highly arched palate, webbed neck
308830	Cantu		Macrocephaly, dwarfism, keratosis follicularis
(4)	Carpenter		Peculiar face, brachydactyly, short stature
*309620	Christian	Xq27-q28	Skeletal dysplasia, sixth nerve palsy
309490	Chudley-Lowry		Short stature, obesity, small genitalia
*303600	Coffin-Lowry	Xp22.1-p22.2	"Coarse face", drumstick phalanges skeletal anomalies
310490	Cowchock-Fishbeck	Xq13-q21	Motor-sensory neuropathy,deafness
309640	Davis		Spastic quadriparesis
310640	Duchenne Muscular Dystrophy	Xp21.2	Pseudihypertrophic muscular dystrophy

TABLE I.1 (Contd)

*305000	Dyskeratosis congenita	Xq28	Skin Pigmentation, nail dystrophy leukoplakia of oral mucosa
*305450	FG		Macrocephaly, agenesis of corpus callosum, gastrointestinal anomalies, deafness
309560	Fitzsimmons		Diplegia, pes cavus, palmoplantar hyperkeratosis
*309550	Fra(X)	Xq27.3	Macrocephaly, long face, long ears, macroorchidism.
(8)	Golabi-Ito-Hall		Triangular face, epicanthic folds, microcephaly, brittle hair
*312920	Goldblatt	Xq13-q21.1	Spastic paraplegia, nystagmus, optic atrophy
*305600	Goltz		Focal dermal hypoplasia, short/missing digits, polysyndactyly, microphthalmia lethal in males
(9)	Holmes-Gang		"Coarse face", epicanthic folds, flat nasal bridge, dental anom.
*208300	Incontinentia pigmenti(I.P.) sporadic	Xp11	Incontinentia pigmenti, incomplete dentition, retinal abnormalities, lethal in males
*308310	I.P., familial	Xq28	As above
*309590	Juberg-Marsidi		Growth retardation, small genitalia, deafness
*309800	Lenz		Microphthalmia, thumb and skeletal anomalies, urogenital and cardiovascular malform.
*309000	Lowe	Xq25	Hydrophthalmia, cataract, vitamin D-resistant rickets
*309520	Lujan-Fryns		Marfanoid habitus, triangular face, narrow palate, hypernasal voice
*303350	MASA	Xq28	Macrocephaly, aphasia, shuffling gait, adducted thumbs, growth retardation
*304100	Menkes-Kaplan		Partial agenesis of corpus callosum, seizures
(15)	Miles (MRX54)	Xq13-q22	Microcephaly, asymmetric face, hypogonadism, joint laxity

TABLE I.1 (Contd)

(29)	Mohr-Tranebjaerg		Hearing loss, visual impairment ataxia, spastic paraplegia
*310600	Morris	Xp11.3	Blindness, hearing loss
*311200	OFD-I		Midline clefting of face,tongue nodules, syndactyly, lethal in males
(18)	Otto-proud	Xp11.3-p21.3	Microcephaly, agenesis of corpus callosum, arthrogryposis renal dysplasia hypospadias
311400	Paine-Seemanova		Spastic diplegia, myoclonic seizures, cerebellar hypoplasia
309510	Partington (MRXS1)	Xp21-pter	Dysarthria, dystonic movements of hands, ataxia, seizures
(10,19)	Pettigrew (MRXS5)	Xq25-q27	Long and coarse face, hydrocephalus, hypotonia, spasticity, ataxia,seizures
308850	Plott		Laryngeal abductor paralysis
309610 and(32)	Prieto (MRXS2)	Xp11-q21	Peculiar face, dental anomalies sacral dimple, joint dysplasia, epilepsy
*309500	Renpenning		Microcephaly, short stature
312750	Rett		Ataxia, autism, dementia, lethal in males
312840	Schimke		Choroathetosis, spasticity, ophthalmoplegia, deafness
301790	Schmidley		Hypotonia, ataxia, sensorineural deafness, optic atrophy
(24)	Stocco dos Santos		Short stature, hip luxation, precocius puberty
*312870 and (11)	Simpson-Golabi-Behmel	Xq13.1-q22.3	Macrosomia, coarse face, polydactyly, extra nipples, heart defect
309580	Smith-Fineman Myers		Peculiar face, microcephaly, short stature, seizures
(25)	Stoll		Short stature, prominent forehead, hypertelorism, broad nasal tip, anteverted nares
309470	Sutherland (MRXS3)	Xp11-q21.3	Microcephaly, short stature, small testes, spastic diplegia

TABLE I.1 (Contd)

(27)	Tariverdian		Acromegaly, CNS anom., macroorch.
309480	Tranbjaerg I		Epilepsy, psoriasis
(30)	Tranebjaerg II		Dyspraxia, ataxia, seizures, pes equino-varus, macroorchidism
(31)	Vasquez		Hypogonadism, gynecomastia, short stature, obesity
*314500	van den Bosch		Choroideremia, acrokeratosis verruciformis, anhydrosis, skeletal deformities
311510	Waisman-Laxova	Xq27-qter	Parkinsonism, seizures, basal ganglia degeneration
311050	Went		Optic atrophy, dysarthria, tremor, dysdiadochokinesis
*314580	Wieacker-Wolff	Xq11-q22	Contractures, distal muscular atrophy, dyspraxia of ocular and facial muscles
(34)	Wilson (MRXS6)	Xp11.3-q21	Obesity, gynecomastia, tapering fingers emotional lability
(36)	Young-Hughes		Short stature, obesity, hypogonadism
(37)	Zollino		Peculiar face, dysgenesis of corpus callosum, failure to thrive, hypotonia, seizures

* Numbers in parentheses correspond to reference numbers.

(23)

TABLE I.2 Non-specific X-Linked Mental Retardation: Update 1992

REFERENCE*	SYNDROME NAME	LOCUS	DESCRIPTION
Suthers et al., 1988 and (13)	MRX1	Xp11.4-q21.31	Mental retardation only
Arveiler et al., 1988	MRX2	Xp22.2-p22.3	Macrocephaly, square face macroorchidism, short stature
Gedeon et al., 1991	MRX3	Xq28	Mental retardation only
Arveiler et al., 1988	MRX4	Xq13	Speech delay, learning disability
Samanns et al., 1991	MRX5	Xp21-q21.3	Hyperactive behavior, speech delay
Kondo et al., 1991	MRX6	Xq27	Short stature, "coarse face" short broad hands
Jedele et al., 1990	MRX7	Xq21.31	Mental retardation only
Schwartz et al., 1992	MRX8	Xq21	Mental retardation only
Villems et al., 1991	MRX9	Xq12	Mental retardation only
Kerr et al., 1992	MRX10	Xp21.3-p11.4	Hypotelorism, large ears
Kerr et al., 1992	MRX11	Xp21.3-p11.22	Hypotelorism, large ears
Kerr et al., 1992	MRX12	Xp21.3-q21.1	Hypotelorism, large ears
Kerr et al., 1992	MRX13	Xp22.3-q21.22	Large ears
(7) Glass		Xq26-27.2	Mental retardation only
(35) Tarbrough-Howard-Peebles			Hyperactivity, speech delay

* Numbers in parentheses correspond to reference numbers

TABLE I.3 First Reports of Fragile X Families.

NATIONALITY OR ETHNIC GROUP	REFERENCE
American Black	Howard-Peebles and Stoddard (1980)
North African	Mattei et al., (1981) (25)
South African	
Zulu	Venter et al. (1981) (26)
Indian	Venter et al. (1981) (26)
Cape Colored	Venter et al. (1981) (26)
White	Venter et al. (1981) (26)
Mexican	Riveria et al. (1981) (27)
Brazilian	Vianna-Morgante et al. (1982) (28)
Chilean	Lacassie et al. (1983) (29)
Sri Lankan	Soysa et al. (1982) (30)
Pakistani	Bundley et al. (1985) (31)
Indian	Ahuja et al. (1990) (32)
Japanese	Rhoads (1984) (33)
Filipino	Rhoads (1984) (33)
Hawaiian/part-Hawaiian	Rhoads (1984) (33)
Dutch Indonesian	Rhoads (1984) (33)

CLINICAL MANIFESTATIONS OF FRAGILE X SYNDROME

Physical and Facial Features in Fragile X Males

The three classic clinical features associated with fragile X are macro orchidism, large or prominent ears, and a long narrow face. Approximately 80% of adult fragile X males have one or more of these features (Hagerman et al., 1983)[34].

Macroorchidism was the first physical feature associated with X-linked mental retardation and was seen in 70% to 90% of adult males with fragile X (Partington, 1984)[35]. The measurement of macroorchidism is dependent on normative data from large population studies compiled by Prader (1966)[36] and Zachmann et al (1974)[37]. They found a mean adult volume of 18 ml and an upper limit of normal at 25 ml. The testicular volume can be measured with an orchidometer Macroorchidism has been found by Sutherland and Hecht (1985)[38] in 87% of post-pubertal males but in only 21% of prepubertal males.

The second most prominent physical feature associated with fragile (X) syndrome is the presence of large or prominent ears. Approximately 50% of the fragile X males will demonstrate an ear length measured from the top to the

bottom of the pinnae which is 2SD or greater than the mean of the population (Hagerman et al., 1983)[34]. An additional 30% will have normal sized but prominent ears. The ears are only occasionally low set.

In prepubertal patients, the large or prominent ears may be the only physical feature of the classic triad.

The third feature is a long and narrow face which is commonly seen in postpubertal males. Meryash et al in 1984[39] performed detailed anthropometric studies on 18 fragile X males and found that the mean value of the face length was more than 2 SD above the mean. The authors postulated that perhaps the ears are more likely to appear prominent when protruding from a narrow face.

Fragile X males were reported to have planovalgus deformity of the feet (Hagerman et al., 1983)[34] Davids et al (1990)[40] found 50% of fra (X) patients at their institutions with flat feet and 57% had excessive laxity of joints and ten had scoliosis. Orthopedic problems reviewed by Davids et al., 1990[40] were treated with a foot orthosis or with orthopedic shoes and this improved the gait pattern due to pes planus. Turner et al., 1980[41] reported soft velvety skin with cutis hyperelastica especially on the hands, and joint laxity with hyperextensible finger joints (Hagerman et al., 1984)[42] and scoliosis. Davids et al., (1990)[40] reported

that joint laxity is found more in children than in adults suggesting that ligaments tighten with age.

A defect in connective tissue has not been proven but studies by Waldstein et al. (1986)[43] demonstrated abnormal elastin fibres in the skin, aorta and cardiac valves by light microsopy in fra X males. Opitz et al., in 1984[44] based on the finding of flat feet, pectus excavatum (in 43% of cases in Denver) and high palate suggested the existence of a connective tissue dysplasia with fragile X syndrome.

Loehr et al., 1986[45] evaluated 40 fra (X) patients, including 6 females and found mitral valve prolapse (MVP) in 55% diagnosed by echocardiographic findings together with the clinical findings of a click or systolic murmur. Sreeram and his colleagues in 1989[45] examined twenty three fra (X) patients for cardiovascular assessment. Echocardiography showed dilation of the aortic root in 12/23 (52%)and mitral valve prolapse in 5/23(22%), four of whom had an apical midsystolic click on auscultation. These cardiac defects are similar to those seen in other disorder defects of connective tissue such as Marfan's syndrome and Ehler-Danlos syndrome which suggests an underlying connective tissue dysplasia in fra (X) syndrome.[47] Hagerman (1987) reported a child with Pierre Robin syndrome associated with fra (X) and Lachiewicz et al (1989)[48] reported four additional similar cases. This frequency of association was

not coincidental and suggested that the connective tissue abnormalities place these patients at a higher risk for Pierre Robin sequence.

Unusual growth patterns were also reported by several authors in fra (X) syndrome including increased birth weight, macrocephaly, increased or decreased height and an acromegalic appearance in many adults (Borghgraef et al., 1990 [49]; Sutherland and Hecht, 1985 [38]; Meryash et al., 1984 [39]; Fryns, 1984 [50]; Turner et al., 1980 [41]).

A characteristic pattern of dermatogliphic findings has been described including increased frequency of radial loops, whorls and arches on the fingertips, a lower total ridge count, abnormal palmar creases and a helical crease in the sole (Hagerman et al., 1983 [34]).

Facial features in fra X syndrome,while not diagnostic, may be a valuable adjunct in clinical evaluation (Jennings et al., 1980 [51]; Meryash et al., 1984 [39]).

Partington in 1984 [35] examined 61 fragile X males and found a small increase in mean occipito - frontal circumference (OFC) and earlength 60% of affected males have a characteristic physical appearance, recognizable in childhood with an elongated face, long narrow chin and prominent jaw. The ears are (large, ill-shaped and sticking

out. Schwartz et al., 1988 [52], found that the craniofacial traits of fra (X), namely long face, midface hypoplasia, large jaw and simple pinnae, were far less frequent in black fra (X) positive males and in prepubertal boys of both races. The nose was described as large and bulbous, the nose breadth slightly increased, the average ear height was unchanged and the average ear breadth was decreased. Storm et al., 1987 [53] reported that strabismus (lazy-eye) was the most prevalent opthalmologic abnormality and was observed in six out of fifteen (40%) with fragile (X) syndrome.

The distinctive facial appearance of fragile X males was summarized by Turner and Jacobs in 1983 [1] as: a large forehead with supraorbital fullness, a long nose, prominent chin, and large ears. Many others have confirmed this appearance. It has been described as midfacial hypoplasia with prominent ears and prognathism by Jennings et al in 1980 [51]. While this appearance may be typical of many fragile X males, it is certainly not universal, and the facial appearance can be unremarkable (Kaiser-McCaw et al., 1980) [54].

Young children with fragile X tend to look normal. The characteristic facial appearance is believed to emerge at about age 8-12 years, just prior to or at puberty (Nielsen 1983) [55].

Physical features in fragile-X males from the Children's Hospital in Denver were summarized in table I.4 (Hagerman and Silverman, 1991)[18].

Oral findings in fragile X individuals compared to those of normal age-matched patients showed low caries rate, minimal intra oral hard or soft tissue disease, cross-bite and open bite. Severe occlusal wear was found more in the fra (X) teeth than the teeth of the matched sample (Shellhart et al., 1986)[56].

Malpositioned teeth and high arched and/or narrow palate were described by Loesch and Hay in 1988[57]. Palatal dimensions of fra (X) did not differ significantly from those of the matched sample. Cleft palate was found in five of sixty-one (8%) cases by Partington in 1984[35]. A high arched palate has been reported by several authors (Partington, 1984[35]; Sutherland and Hecht, 1985[38]; Hagerman et al., 1983[34]) and found in 48% of fra (X) males followed in Denver (Table I.1). This was associated with dental crowding or malocclusion. Tooth crown - size as asymmetry was significantly increased in fra (X) males compared to normal control individuals (Peretz et al., 1988)[58].

Table 1.4: Physical features of Fragile X males Summarized from Hagerman and Silverman 1991,[16] from the Children's Hospital in Denver

Feature	Percentage of Patients with feature
Long face	74
Macroorchidism	74
Long ears	66
Flat feet	65
Hyperextensible metacarpophalangeal joints	64
Prominent ears	63
High arched palate	48
Hand Calluses	45
Pectus excavatum	43
Double jointed thumbs	41
Single palmar crease	35
Strabismus	33
Prominent Jaw	28
Scoliosis	20

Hagerman R.J. and Silverman A.C. (1991): Epidemiology in fragile X syndrome: Diagnosis, treatment and Research. The John Hopkins University Press, p. 71

Behavioral Features in Fragile X Males:

The social behavior of fragile-X males is highly variable. Most of fragile-X males appear friendly and cooperative with a level of social maturity similar to or better than their intellectual functioning (Turner and Jacobs, 1983)[1]. However there are many others who are hyperactive and difficult to manage (Turner et al., 1980,[41] Mattei et al., 1981;[25] and Brown et al., 1987)[59].

Infantile autism is a severe personality disorder manifested in early childhood by abnormal development of language and relations with autistic-like features such as poor eye contact, hand flapping and hand biting are often seen by four or five years of age (Hagerman and Silverman, 1991)[16].

Many scientific papers, have appeared in the "Third Fragile X Workshop", in 1988, reporting a high and strong association between autism and the fragile X syndrome especially in childhood. However, a "strong" association has not been a universal finding : Brown et al., 1986[60], cited three studies which did not find any fragile-X individuals in surveys of autistic males.

Stewart L. Einfeld,et al.,1989.[61] summarized the association between fra X syndrome and autism and suggested that we should be cautious before counselling parents of fra-x children that autism is likely to be a prominent handicap.

The young fra (X) males who do not usually demonstrate the physical phenotype of fra (X) may represent a rather consistent behavioral phenotype to fragile (X). Tantrums, hyperactivity, hypotonia, irritability and preseveration in speech and behavior are usually complicating features.

The spectrum of cognitive involvment is broad and ranges from normal IQ and learning disabilities to profound mental retardation. Non-penetrant or transmitting males have been identified beginning with the Martin and Bell pedigree (1943)[5] and subsequently documented by many others (Dunn et al., 1963[7] , Fryns, 1984[50] ; Sherman et al., 1985)[62] They are typically fragile (X) negative and physically and cognitively unaffected.

Physical and Facial Features in Heterozygous Females

There are two main groups of heterozygotes:the affected heterozygotes and the unaffected heterozygotes with variable degrees of involvement (Sutherland and Hecht, 1985)[38].

Escalante (1971)[63] was the first to report mental retardation in females in association with the marker X chromosome. His clinical description included a high palate, genu valgum and flat feet.

Years later, Sherman et al. (1985)[62] reported a penetrance of approximately 35% for mental impairment (IQ less than 85) in females who carry the fra (X) gene.

Loesch and Hay (1988)[57] studied 90 adult and 20 prepubertal heterozygotes and found hypermobility of finger joints in 40% of adults and 52% of girls. Flat feet were seen in 19% of both groups. All of the features were more prevalent in mentally impaired heterozygotes compared to normal IQ heterozygotes.

Borghgraef et al (1990)[49] reported macrocephaly as a significant finding in 7 prepubertal fra (X)-positive girls. However Hagerman et al. (1991)[64] compared 32 fra (X) positive prepubertal girls to 18 fra (X) negative sisters and found no significant differences in height, weight, and head circumference. Significant differences were seen in ear

prominence, face length, and the presence of shyness, poor eye contact, hand flapping, and hand biting. Voluntary thumb dislocation and hyperextensible MP joints were more frequent in normal IQ heterozygotes compared with normal controls. The fra (X) positive girls had more physical and behavioral features typical of the syndrome than their fra (X) negative sisters.

Cronister et al. (1991)[65] showed a significant correlation between the number of typical physical features transformed into physical index score and the percentage of fragility in heterozygotes.

Fryns (1986)[66] analyzed the physical features in 135 female heterozygotes and found facial features similar to those in males, including a long face, a prominent forehead, and mandibular prognathism in 28%. These findings were present in 14% of subjects with normal intelligence and in 55% of those with mental retardation. Loesch and Hay (1988)[57] described typical facial features in 37% of adults and 14% of girls and occasionally more significant malformations, such as cleft palate have also been reported. Hagerman et al. (1991)[64] found significant differences in ear prominence and face length between 32 fra (X)-positive prepubertal girls and 18 fra (X) negative sisters.

Behavioral Features in Heterozygous Females:

The degree of involvement in regard to cognitive abilities differ according to the percentage of fragility found in heterozygous females (Chudley et al., 1983)[10].

Cognitive functioning in fra (X) females ranges from normal to severely retarded (Hagerman and Smith, 1983[67] and Webb et al., 1982)[68]. Importantly, one third to one half of fra (X) females exhibit mild to moderate mental retardation. Their behavioral problems are similar to fra (X) males but usually less severe. Poor eye contact, hand flapping, hand biting, impulsivity, and attending problems as well as shyness, anxiety, and depression may be present (Hagerman and Sobesky, 1989)[69].

Three quarters of fra (X) positive females showed some degree of mental impariment ranging from learning disabilities to mental retardation.

Shyness was reported to be a more frequent finding in impaired heterozygotes compared with impaired controls (Cronister et al., 1991)[65].

Association of Fragile X with Other Syndromes

The fragile (X) syndrome was found to be expressed in a XXX woman, who was mentally and physically normal, and in her son who was mentally retarded and showed behavioral and physical features characteristic of the fragile X syndrome (Fuster et al., 1988)[70].

Another case reported by Arinami et al in 1987[71] of a fragile X female with Down syndrome had most of the facial features observed in trisomy 21 together with some features related to the fra (X) syndrome such as long face with prominent forehead and lower jaw together with large ears.

It has been reported that female carriers of fra (X) chromosome may be predisposed to meiotic nondisjunctional events. Recently the first case of a 46 XY/47XYY mosaic male with fra (X) expression in both cell lines was reported by Milunsky et al.,1993[72].

Genetic Aspects of Fragile X Syndrome

A. Inheritance of Fragile X Syndrome

The fragile X syndrome was considered an X -linked recessive disorder (Mckusick,1986)[73]. However,several aspects not characteristic of classical X-linked inheritance have

been observed in families with fra-X syndrome. These include:-

A- The presence of the so-called intellectually normal transmitting males, i.e. transmission of fra-X syndrome through unaffected hemizygous "Carrier" males who inherit the fra-X mutation (Nielsen et al., 1981)[55] Howard Peebles and Friedman, 1985)[74].

B- The number of mentally retarded males in families segregating fra X syndrome is about (20%) less than expected (Sherman et al.,1984[75] and 1985)[62], this is probably due to the occurrence of carrier males.

C- Variable penetrance and expressivity of IQ in both sexes with fra-X syndrome:

- Daughters and mothers of intellectually normal transmitting males have very low penetrance, i.e. are rarely, if ever mentally impaired (Sherman et al., 1985)[62].
- Sons of mentally impaired transmitting females have very high penetrance may be even (100%), while sons of mentally normal transmitting females have about (76%) penetrance (Sherman et al., 1985)[62].
- Daughters of mentally impaired transmitting females have distinctly higher penetrance than those of intellectually normal transmitting females (Sherman et al., 1985)[62].

- Most difficult of all to be explained by X-linked inheritance or any other conventional genetic mechanism is the observation that carrier mothers of unaffected transmitting males are much less likely to have mentally retarded offspring than the unaffected carrier daughters of the same carrier transmitting males, this phenomenon is called Sherman paradox (Sherman et al., 1985)[62].

D- Mental retardation occurs in about 35% of females who are carriers of fra-X syndrome (Sherman et al..1984)[75] This frequency of serious clinical abnormalities among female carriers is much greater than that seen in typical X-linked recessive conditions such as hemophilia A.

E- Segregation analysis of "110" pedigrees by Sherman et al., (1984)[75] suggested that, new mutations for the "gene" of this syndrome are entirely confined to sperm and the mutation rate in sperm is estimated to be $7.2X10^{-4}$, a rate which is at least 10 times greater than that estimated for other X-linked genes in human.

F- Fra-X syndrome differs from all other monogenic diseases in that the abnormal phenotype is associated with the presence of an inducible cytogenetic marker (Xq 27.3).

These unusual genetic characteristics in the Fra-X syndrome suggest that this condition is not a standard X-linked recessive trait.

A number of hypotheses have been proposed to account for the peculiar genetic behavior of the fragile X syndrome and these involve:

1) Autosomal modifier loci

2) Maternal effect on the genetically susceptible embryos (Van Dyke and Weiss, 1986)[76]. This is based on the observation reported by Sherman et al., 1985[62].

They reported that in fra X syndrome, if the mother is the gene carrier, her daughters (and sons) with the fra X mutation are at a high risk of mental retardation. But if the father is the fra (X) mutation carrier "TM", his daughters have no risk of mental retardation.

There are two main types of maternal effects:-

a. Maternal contribution to the egg cytoplasm.

b. Effects of the intrauterine environment (uterus, placenta and factors in the maternal blood).

3) Transposable genetic element hypothesis:-

Friedman and Howard-Peebles, 1986[74] hypothesise that Martin Bell syndrome is a manifestation of a

transposable genetic element with both chromosomal and extrachromosomal activity.

They postulated that, this transposable element can exist in three different chromosomal states or "genotypes" and affect two different extrachromosomal environments or cytotypes. They call the genotypes "0", "1" and "2", and the cytotypes "+" and "-".

The proposed transposable genetic element exhibits the following characteristics.

* Genotype "0" is the common wild type state in which the element is stably integrated in the genome.
* Genotypes "1" and "2" are relatively uncommon alternative integration states on the "X" chromosome, probably in the region of the Xq27 fragile site.
* The "+" cytotype usually develops during oogenesis if the individual genotype is "2". Maintenance of the "+" cytotype in an individual requires the continuing presence of genotype "2". Neither genotypes "0" nor genotype "1" can support a "+" cytotype, so individuals with these genotypes "0" or "1" always exhibit a "-" cytotype and they would be clinically unaffected.
* The genotype is inherited as an X-linked trait.

* The "+" cytotype once established exhibits maternal transmission.

The mutation for the fragile X syndrome may result from the insertion of transposable elements (TE's). Loss of genetic function could result from either the insertion of TE's within or adjacent to a normal chromosomal gene, or from the loss of genes distal to the site of TE insertion following the subsequent TE excision without ligation of the resulting discontinuity.

The "normal transmitting male" are interpreted not as "non penetrant" transmitters of a fully formed fragile-X but rather as transmitter of some or all of the factors necessary for TE insertion at Xq27.

This transposition into the X-chromosome depends on the state of cytoplasm whether it is restrictive or permisssive, and the competence of the normal X chromosomes as not all X-chromosomes are equally competent for TE insertion at Xq 27.

This thinking has been further articulated by the following:

4) Premutation hypothesis (Pembrey et al., 1985).[77]

5) Recombination and amplification of pyrimidine rich sequences (PRS) (Nussbaum et al., 1986)[78].

Nussbaum et al., 1986[78], postulated that, a pyrimidine-rich DNA sequence (PRS) is present in many, if not all individuals in the population in the Xq27 region. Such a simple PRS in human DNA may be an incipient constitutive folate sensitive fragile site.

When a "simple" PRS is present on both homologous X chromosomes during oogenesis, there is a small but definite probability that an unequal crossing over will occur, producing one X chromosome with up to twice the usual amount of PRS. This partial amplification of a simple PRS is the initial lesion of the fragile X(premutation). Carriers of such initial lesion will be unaffected transmitting females or males, since this initial lesion is generally still below the threshold of cytogenetic detection and phenotypic expression.

When such X-chromosome bearing the initial lesion is paired with a homologous X carrying a simple pyrimidine rich sequence during oogenesis, a much higher rate of further amplification may occur resulting in progression to an even longer stretch of pyrimidine rich DNA in this region

This increased length of the pyrimidine rich segment makes the region too long to be repaired, Furthermore, this

amplified lesion may interfere with expression of a gene or set of genes in this region and produce the phenotype of Martin Bell syndrome.

The "PRS" model explains many of the puzzling features of fragile X syndrome. The apparent high mutation rate can be explained as the product of the probability of a woman being homozygous for a common PRS DNA and the probability of an unequal crossing over producing the initial lesion of the fra X which may be much more common events than the base-change mutations responsible for many human genetic defects.

The "Sherman paradox" states that mothers of transmitting males have 9% risk of having affected sons whereas the daughters of transmitting males have 37% risk.

This could be explained on the PRS model as daughters of the transmitting male would be only carriers for such as initial lesion present on their X chromosome derived from their transmitting father. Accordingly, these carrier daughters are rarely affected since this initial lesion is beyond clinical expression. Progression of this lesion may occur during oogenesis of these daughters putting them at risk of producing affected sons. If they are just a homozygote for a simple PRS DNA, in which case, an initial lesion may

only originate during their oogenesis and be passed on to their offspring producing normal carrier transmitting sons.

B. Cytogenetics of the Fragile (X) Syndrome

During the last twenty years, the potential for diagnosis and treatment of genetic disorders has rapidly expanded. Patients with multisystem abnormalities that include retarded physical growth and delayed development such as fragile X syndrome are candidates for chromosome analysis unlike most other chromosomal abnormalities, the fragile site lesion is present in only a portion of dividing cells examined from an affected individual. This is probably due to the fact that expression of the fra (X) lesion is a function of the tissue culture conditions that are imposed on cells during chromosome preparation in the laboratory.

A fragile site is defined as a localised region of a particular chromosome showing an interrupted continuity in one or both of its chromatids at metaphase (Sutherland, 1979)[8a]. This interruption may occur as a gap or a break with or without dislocation of the distal end.

When the correct cellular metabolic requirement for fragile X expression is achieved, the fragile X lesion on the chromosome is evident and when they are not, it is absent.

A medium deficient in folic acid is essential for expression of fragile X site (Sutherland, 1979)[8] and this can be obtained by one of the following methods.

a. Lymphocytes cultured in medium TC 199, which is deficient in folic acid (Sutherland, 1977)[80].

b. Addition of methotrexate which is a folic acid inhibitor, 24 hours before harvesting (Sutherland, 1977)[80].

c. Addition of fluorodeoxyuridine (FUdR) 24 hours before harvesting inhibits thymidilate synthetase, causing deficiency of thymidine monophosphate which is essential for normal DNA synthesis (Sutherland, 1979)[8a].

d. Exposure of cultures to be a combination of FUdR and aphidocolin, demonstrated both common and rare fragile sites at bands Xq27.2 and Xq27.3 respectively confirming Sutherland and Baker's original observation(1990)[79].

Although the fra (X) site seems to be quite a reliable cytogenetic marker for the diagnosis of the syndrome in individuals the relationship is not clear between the expression of the chromosomal lesion and the underlying mutation responsible for the manifestations of the mental retardation syndrome (Hagerman and Silverman, 1991)[16].

The behavior of the fra (X) can also be different in affected and unaffected individuals. It is relatively easy to elicit fra (X) site in mentally retarded males and females but difficult to elicit in unaffected female or male carriers. This may be explained by the random X chromosome inactivation mechanisms that are normally produced in all females to suppress genetically one of the X chromosomes (Lyon hypothesis).

Cytogenetic diagnosis of the fragile X has been faced with many difficulties:

a- Many carrier females do not express the fragile site or do so only at low levels.

b- Normal transmitting males show no cytogenetic expression (Ledbetter et al.,1986[81]; Young et al., 1986[82] and Howard Peebles and Friedman, 1985[74]).

c- Prenatal diagnosis by amniocentesis or chorionic villus sampling is technically difficult and has led to false positive and false negative predictions.

The frequency of fra X expression does not correlate with the degree of phenotypic expression in fra X patients or with the degree of mental impairment (Turner et al.,1980[41] and Turner and Jacobs, 1983[1]).

C. *Molecular Studies on Fragile X Syndrome*

The fragile X syndrome has been one of the most important, yet most frustrating genetic disorders for geneticists to deal with. This is due to its bizarre inheritance and difficulties in laboratory diagnosis. In continuum to these findings, research into the nature of the fragile X mutation and improved laboratory diagnostic methods, have suddenly exploded in a series of papers from laboratories in Australia, Europe and the United States (Ledbetter, 1991[3]).

The fragile X mutation was identified by two groups (Oberle et al., 1991[83] and Yu et al.,1991[84]). They described the cloning of an unstable DNA segment which is responsible for the fragile X mutation and provides a significantly improved method for diagnosis and prenatal diagnosis of fragile X affected and carrier individuals. This accomplishment was made possible by two important resources: libraries of very large insert human DNA in Yeast Artificial chromosome (YAC) vectors and a series of human hamster somatic cell hybrids produced by Steve Warren's laboratory (Emory, Atlanta, U.S.A) containing break points at the fragile site.

Mackinnon et al.,1990,[85] micro dissected and cloned the region around the fragile site at Xq 27.3 on the human X chromosome. This microdissected library demonstrated the power of microdissection for the identification of potential coding sequences near the disease locus and provided a promising resource for the identification of the fragile X mutation.

Yu and colleagues in 1991[84] demonstrated the diagnostic value of Southern blot analysis. 65 normal males showed bands of identical size (1 Kb), while all affected fragile X males showed single or multiple bands of increased size. Phenotypically normal transmitting males (NTM) who are negative for cytogenetic expression, also showed bands of increased size, although not as large as those of affected

males. Carrier females showed one normal band, and single or multiple enlarged fragments (Ledbetter, 1991)[3].

Using different YACs which also crossed the fragile site, Jean-Louis Mandel's group in Strasbourg cloned the region around a CpG island previously shown to be highly methylated in fragile affected males but not in normal males. Probes adjacent to this CpG island detected abnormally large fragments on Southern blot in affected males and carrier females (Oberle et al.,1991)[83].

Closely following the cloning of the fragile X mutation site, an international group isolated a gene FMR-1 related to the fragile X-linked mental retardation (Verkerk et al., 1991[86] and Pieretti et al.,1991[87]). It was shown that fragile X syndrome is caused by elongation of a small DNA fragment, containing a repeat of the trinucleotide CGG located in the 5[1] exon of the FMR-1 gene (Oberle et al., 1991,[83] Yu et al., 1991;[84] Kremer et al.,1991[88] and Fu et al.,1991[89]). Most likely the increase in size is due to amplification of this repeat sequence. Normal X chromosome have between 6 and 46 copies of CGG which are stable during meiosis and a nearby CpG island which is unmethylated on active X chromosomes (Fu et al., 1991)[89].

Verkerk et al.,1991,[86] was the first to characterize the protein product of FMR-1 gene. Verkerk had raised antibodies

against synthetic peptides. These recognize a 70 KD protein, which is consistent with the FMR-1 nucleotide sequence.

The passage from premutation to full mutation status ocours only with transmission through the mother which explains the Sherman paradox, where mothers of normal transmitting males have much less risk of getting affected sons than the daughters of these normal transmitting males.

Premutation alleiles are characterized by an increase in the number of triplets to 52-100. Premutations do not cause mental retardation, the carrier males or females do not show cytogenetic expression of the fragile site and the CpG island remains unmethylated. This premutation sequence is unstable during meiosis. In the full mutation, the repeat sequence exceed the size of 200 triplets. Oberle et al., 1991, (84) in their study, observed an insertion of 150 to 200 bp in normal transmitting males while their normal daughters showed no or little apparent change in fragment size. However a much larger insertion (1000 to 3000 bp) was observed in their affected grandsons.

Rousseau et al., in 1991 (90) have devised a method of identifying carriers of mutation causing fragile X syndrome by direct DNA analysis as an efficient and reliable primary test for diagnosis of the fragile X syndrome after birth, as well as for prenatal diagnosis and genetic counselling.

Triplet repeats have been shown similarly to be the sites of mutation in two human heritable disorders other than fra XLMR: spinal and bulbar muscular dystrophy (S&MD), and myotonic dystrophy. (Caskey et al., 1992)[91].

Recently Vries et al in 1993[92] studied 52 male fragile X patients. The percentage of the cytogenetic expression of the fragile site at Xq 27.3 positively correlates with the mean size of the full mutation in the FMR-1 gene irrespective of the presence of additional premutation alleles. They also noted that the presence of a full mutation in the FMR-1 gene seemed decisive for the occurrence of mental impairment in the patient. There was no correlation observed between the degree of mental retardation and the size of the full mutation. Two families were investigated by Dennis et al., 1992,[93] and found seven males having a fragile site at Xq 27.3 but the usual insert in the FMR-1 gene was absent. The affected males had mild or no mental impairment and did not have the Martin Bell phenotype. It was not clear whether these families had unusual mutation in the FMR-1 gene or whether their fragile sites are different, but cytogenetically indistinguishable from that associated with inserts in the FMR-1 gene.

The molecular observations on the fragile X mutation are consistant with two models previously put forward to

explain the bizarre inheritance patterns of fragile X. The first model, proposed by several authors, was that the mutation occurred as a two step phenomenon rather than one or a single mutational event, with the second step always occurring in female meiosis. The second model proposed by Charles Laird (Laird et al., 1990)[94] invoked a role for "imprinting" of a mutant chromosome. The imprinting event, in this model, results from a block to reactivation of an active X chromosome prior to oogenesis (Sved and Laird, 1990)[95]. Previously Knoll et al.,1984[96], investigated 28 fra (X) heterozygotes and found one third of them mentally retarded. These had a higher frequency of fra (X) and a higher proportion of early replicating fra (X) than the normally intelligent carriers. Thus,it appeared that mental retardation in females heterozygous for the fra (X) may largely be a function of the proportion of cells with an early replicating active X chromosome possessing the fragile site.

Imprinting of the mutant fragile X allele when proposed by Laird et al., 1990[94], suggested that the mutation responsible for the fra X syndrome interferes with the process of the X chromosome reactivation in oocytes, thus blocking the transcription of loci at or near neighboring the fragile site (Xq 27.3) and producing the clinical fra X phenotype. He also suggested that the transcriptional block might result from inappropriate DNA methylation. However, Khalifa et al., in 1990,[97] observed no evidence that DNA

methylation in the vicinity of the fra X locus has a role in producing the clinical phenotype of the fra X syndrome.

Pergolizzi et al.,in 1992 [98] developed a polymerase chain reaction (PCR) method to amplify across the full mutation in affected individuals. Their results were consistent with the direct Southern blot analysis.

Linkage Studies in Fragile X Syndrome

Linkage analysis studies for DNA marker loci by specific probes, reported by many authors have been reviewed and summarized as follows:-

- Close loci proximal to Fra X A : (in that order) Cen- DX144, DX51, DX102, Fg, DX105, DX98, DX292, DX297, Fra X A (Arveiler et al., 1988, [99] Thibodeau et al., 1988, Schnur et al., 1989 [101], Dahl et al., 1989; [102] Suthers et al., 1989; [103] Suthers et al.,1991 [104] & Richards et al., 1991) [90].

- Close loci proximal to Fra X A (not in order), DX369, DX 476, DX 465 (Rousseau et al., 1991) [90].

- Close loci distal to Fra XA:(in that order) DXS296,DX304, DX52, F8, DX15, DX52, DX 115, (Arveiler et al., 1988; [99] Dahl et al., 1989; [102] Suthers et al.,1989; [103] & Suthers et al., 1991) [104].

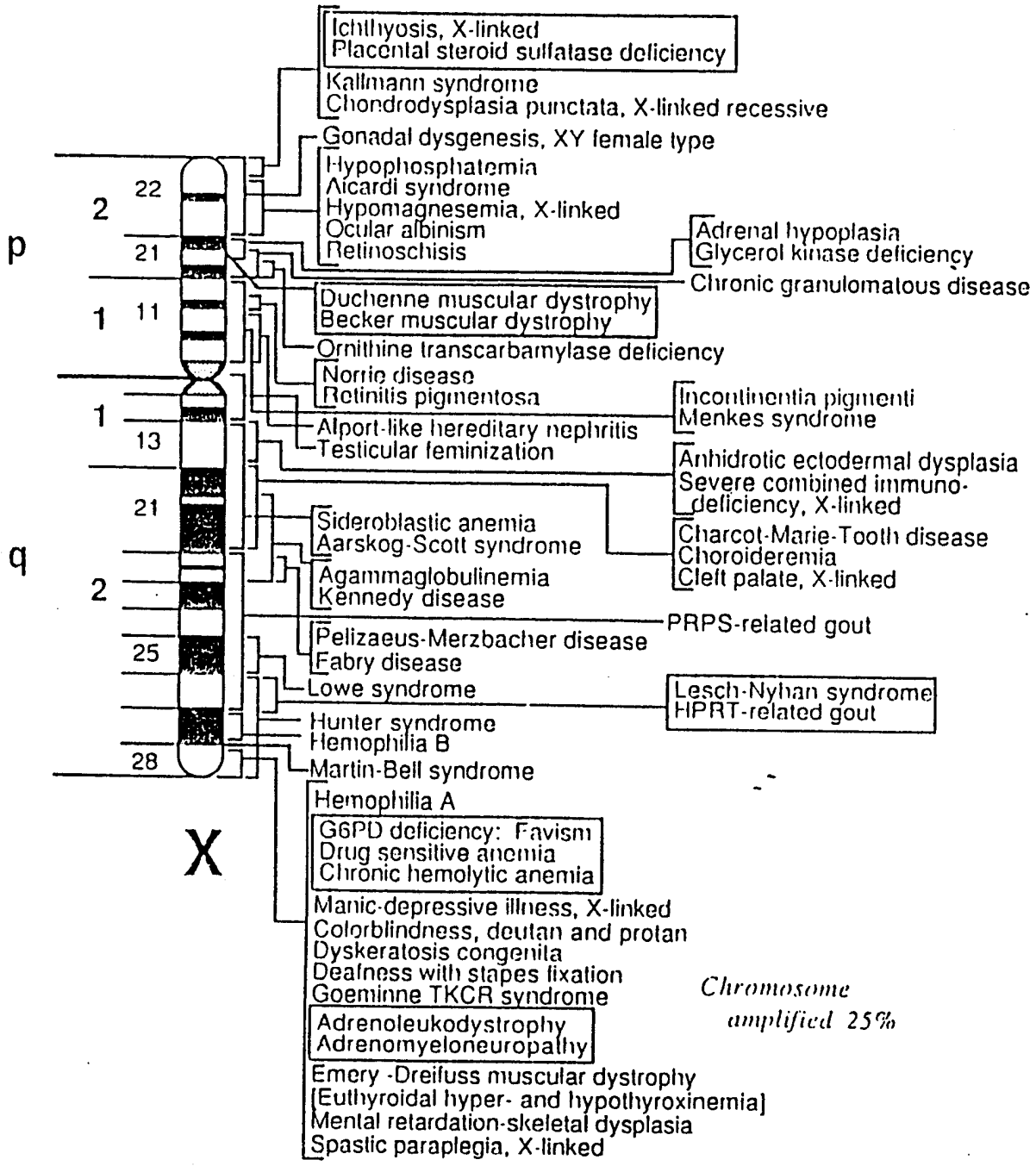


Fig. (1) X chromosomes morbid anatomy. Boxed entities = allelic disorders.

McKusick V.A.(1988): The Morbid Anatomy of the Human Genome. A review of gene mapping in clinical Medicine. Howard Hughes Medical Institute.

- Close loci related to Fra XA DXS463-DX477-DX465 (Vincent et al., 1991)[106] & Rousseau et al., 1991)[90].

The X chromosome loci are illustrated in fig (1).

D. Prenatal Diagnosis of Fragile X Syndrome

The first prenatal diagnosis of fragile X was reported in 1981 by Jenkins et al,[107] Cytogenetic methods improved rapidly since then. For the initial diagnosis of an affected male cytogenentic testing in an experienced lab has a very high accuracy. An additional important advantage of cytogenetic testing in children with unexplained developmental delay or mental retardation is that cytogenetics will detect fragile X or other chromosome abnormalities. The Southern blot assay for fragile X will obviously only detect fragile X and will require follow up cytogenetics for all negative cases (the majority). Once a positive fragile X family is identified, however, it is likely that Southern blot analysis will quickly become the primary method of analysis. This is particularly true for identification of normal transmitting males, carrier females, and for prenatal diagnosis.

Prenatal fra (X) analysis using direct DNA probes such as St B12.3 will probably become the standard of care in the near future (Rousseau et al., 1991;[90] Sutherland et al., 1991)[108].

Genetic counselling should indicate that the risks to be affected are approximately 75% when a positive female is prenatally detected. DNA testing can help determine carrier status but may not accurately predict whether a female will be mentally affected (Brown et al., 1992)[109].

The use of DNA markers and linkage analysis has gained more accuracy and this method is used as a complement to cytogentics in most laboratories (Shapiro et al., 1991)[110] (Von Koskull et al., 1992)[111].

Anthropometric Studies on Fragile X Syndrome

Metric data provided by anthropometry can help in an objective assessment of the clinician's diagnosis adding a quantitative dimension to the dysmorphologist's observational skills (Ward, 1989)[112].

Craniofacial anthropometry has an important role in the clinical diagnosis of patients through "the objective evaluation of the craniofacies" by providing fixed points of reference for comparison with "normal" populations (Salinas, 1980)[113]. Individual dysmorphic faces tend to have much greater variation from one facial area to the next than do "normal" faces (Garn, 1985)[114]. Individuals with any syndrome resemble each other clinically and the degree of craniofacial similarity is greater among syndrome affected than unaffected individuals in a single family (Saksena et al., 1987)[115].

Head anthropometry can be classified into: direct or indirect methods:

Direct methods using established techniques, landmarks and instruments providing us with true or actual measurements. Derived values e.g. indices or ratios are also true or actual and their use considerably facilitates morphologic description.

Indirect methods using palatal study models can provide true palatal measurements while radiographic cephalometry provides magnified head measurements and photoanthropometry provides reduced anthropometric measurements.

Analysis of anthropometric measurements is designed to provide a means for discrimination or classification and growth of the human body.

Anthropometry has found its way into clinical dysmorphology and cephalometry "head anthropometry". It has proven helpful in the study of malformation syndromes involving the head and neck. Here, cephalometry provides a tool that quantitaties similarities or differences between the affected individuals. Cephalometric analysis provides an objective answer to significant questions concerning the differential diagnosis of congenital anomalies of the head. For example: Does the patient have maxillary hypoplasia or

maxillary retrognathia? Is the mandible of this patient small (micrognathia) or is it positioned backwards with respect to the skull base, or both? Are the eyes of this patient widely spaced or is it an illusion?

Palatal studies with defined measurements on genetic disorders have been done by Redman et al(1966)[116] who performed measurements on normal and malformed palatal vaults. Nystrom and Ranta (1989)[117] studied the sizes of dental arches in 3 year old children with and without cleft lip and palate.

New cephalometric findings have aided in the diagnosis of different craniofacial malformations. In severe malformations such as Apert and Crouzon syndromes cephalometry has played an important role in the diagnosis and surgical management of these patients. Other craniofacial malformations where cephalometry proved useful were Achondroplasia (Cohen et al.,1985)[118], fetal alcohol syndrome and Angelman syndrome (Frias et al,1982)[119], ectodermal dysplasia (Ward, 1989)[112], Pierre-Robin syndrome and oto-palato-digital syndrome (Garn et al., 1984)[120].

Another important use of cephalometry in medical genetics relates to the identification of individuals who are mutant gene carriers but who themselves do not overtly express the trait phenotypically. This is a major problem in the delineation of malformation etiology and in counselling

individual affected families (Cohen, 1985)[121].

Quantitative evaluation of the physical phenotype in fragile X was first undertaken by Partington, in 1984,[35] who found decreased height, increased weight, ear height, head circumference and testicular volume. Later, Thake et al (1985)[122] reported 14 fragile X boys with a head circumference over the 50th percentile. This was followed by a study by Meryash et al (1984)[39] which was based on a wider range of body measurements but was performed in a small sample of 18 affected males. The average height of the individuals with the fragile (X) was less than that of published standards Seventeen of 18 subjects had absolute or relative macrocephaly and two thirds were dolicocephalic. The facial and ear length were increased, the facial breadth, hand length and foot length were decreased. These studies applied univariate methods in comparing fragile (X) individuals with normal control individuals and were limited to males.

Butler et al in 1988[123] examined 31 fragile (X) boys 1.5-12 years old. They studied 18 facial parameters to the nearest 1mm with a Vernier caliper from strict front and profile photographs, obtained from a distance of over 1.5 m from fra (X) boys compared with other facial measurements from the same face (e.g. mouth widths vs. bizygomatic diameter). This photoanthropometric analysis supports the clinical impression of a narrow face with a broad nose and broad palpebral fissures.

Loesch et al (1988)[124] applied multivariate analysis in a wide range of body (trunk, limb, head and facial) measurements in a large sample of fragile X individuals.

Loesch and Wilson in 1989,[125] transformed 34 head/face landmarks in 43 men and 72 women with the fragile X syndrome and in 99 and 103 normal men and women respectively. They also noted larger head/face shape components which may represent the mechanisms which control the breadth of the nose in relation to the intercanthic eye distance, and bigonial and bizygmatic diameters in relation to ear length and jaw length. Differences between the fragile (X) and normal individual samples were already noticeable in these components.

Meryash et al.,in 1984[39] examined 18 males with fragile (X) syndrome 18-69 years old in order to determine whether these clinical impressions are supported by actual measurements. They concluded that the characteristic appearance of a fra (X) subject is affected by relationships between the various measurements than any single measurement. This indicates that the relationship between the magnitude of the face length and face breadth is more important than absolute dimensions in defining the facial appearance of males with fragile (X). It also provides an objective basis for the impression of a long narrow face.

CHAPTER II

AIM OF THE WORK

The aim of this work is :

1. To study the dento-cranio-facial characteristics of the fragile X syndrome in an Egyptian sample of affected males and their female obligate carriers.

2. To test the efficiency of cephalometry (physical or radiographic) as an aid in the diagnosis of fragile X syndrome.

CHAPTER III

SUBJECTS AND METHODS

The studied sample consisted of 20 Egyptian male cases with fragile (X) syndrome. They were divided into three groups according to their age:

Group I : Seven cases from 6 - 10 years old.

Group II : Seven cases from 13 - 16 years old.

Group III : Six cases from 17 - 22 years old.

Those affected males were clinically and cytogenetically diagnosed at the Human Genetics Department,National Research Center Cairo and the Human Genetics Department, Medical Research Institute, Alexandria University. A fourth group, group IV, was also studied which consisted of ten obligate heterozygote female carriers.

A comparative group of forty six unaffected Egyptian males in three matching age groups as those of the fragile (X) sample was also studied. The control sample was obtained from the Pedodontics Clinic and Oral Medicine Clinic at the Faculty of Oral and Dental Medicine, Cairo University. In addition, the mothers of the fragile (X) cases were compared with a control adult female sample from the Oral Medicine Clinic, Faculty of Oral and Dental Medicine, Cairo University.

All studied cases were subjected to the following procedures:

1. Pedigree analysis

The family history for each case was evaluated and parental consanguinity was given special attention. Pedigree diagrams were constructed according to the recommendations of the editional board of the American Journal of Medical genetics as shown in fig. (2) of the pedigree symbols.

2. Clinical examination

The physical and oro-dental findings were evaluated following a special clinical chart and the oro-dental chart as shown later in text. Particular interest was given to any associated visible anomalies.

3. Cephalometric evaluation

These were divided into physical and radiographic measurements:

a- Physical measurements:

Eight measurements were taken for each case using special instruments.

b- Radiographic measurements : Thirty six linear , angular and ratio parameters were evaluated. Specific

parameterss were computed and others were manually measured. Radiographic cephalometric techniques were used to define special landmarks on the skull and face.

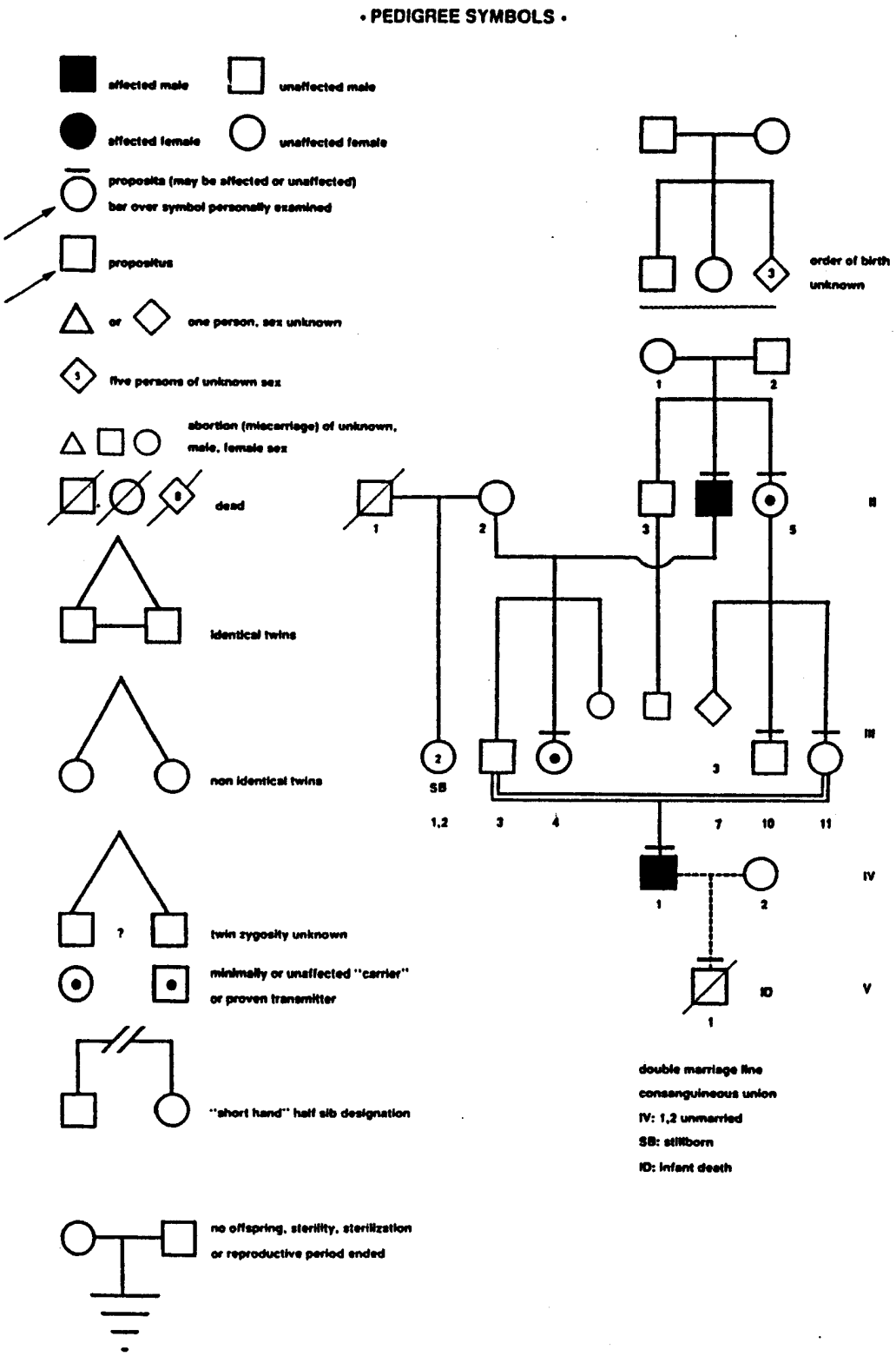


Figure 2 : Pedigree symbols

Instructions for contributors (1984) Am. J. Med. genet. 17(1): 387

Oro-dental Chart

Name

Age

HGL No.

Developmental disturbances of

1. Lips: Normal
   - Congenital lip pits and fistula
   - Enlarged, firm and everted lips
   - Attached labial fernum
   - Cleft lip
   - Hyperpigmentation around the lips
   - Multiple frenuli
   - White spongy nevus

2. Cheek biting
   - Fordyce granules

3. Gingiva: Normal
   - Hyperplasia
   - Bohn's nodules
   - Gingivitis

4. Palate: Normal
   - High arched palate
   - Cleft palate
   - Torus palatinus
   - Flat palate

5. Mouth: Microstomia
   - Macrostomia

6. Jaws: Normal
   - Macrognathia
   - Mandibular and Maxillary ridges
   - Micrognathia
   - Torus mandibularis
   - Angle of mandible

7. Relation between Mandible and Maxilla:
   - Normal relation
   - Class II (retruded mandible)
   - Deep over-bite
   - Open bite
   - Class I (edge to edge)
   - Class III (protruded mandible)
   - Wide over-jet
   - Cross-bite

8. Tongue: Normal
   - Ankylogossia (complete or partial)
   - Fissured tongue
   - Geographic tongue
   - Thyroglossal tract (cyst-hyoid
   - or infra hyoid)
   - Lingual thyroid
   - Microglossia
   - Macroglossia
   - Median rhomboid glossitis
   - Hairy tongue

9. Salivary gland : Normal
   - Aplasia (xerostomia)
   - Atresia (xerostomia and/or retention cytst)
   - Aberrancy (presence of salivary gland tissue in an anatomically abnormal position).

10. Teeth - Variation in number: Normal
   - Increase in No. of teeth
     - Supplemental teeth
     - Supernumerary teeth
       * mesiodens
       * paramolar
       * distomolar
   - Decrease in No. of teeth
     Anodontia
     - Absence of one tooth
     - Absence of group of teeth
       * False
       * True

   - Variation in size and shape of teeth : Normal
     * Macrodontia
     * Microdontia
     * Fusion
     * Hutchinson's teeth
     * Dilaceration (abnormal bend of the crown or root)
     * Peg-shaped
   - Abnormalities of structure of teeth
     * hypoplasia -- local factors
       - Trauma
       - Infection

     Flourosis or Mottled enemel
     Herditary defects

11. Others:
   - Increase caries index
   - Flared teeth
   - Premature eruption
   - Retained deciduous
   - Delayed eruption
   - Open mouth

Physical Cephalometry

The landmarks, techniques and instruments were used according to the IBP program guide to field work by Tanner et al., 1969 (126).

Head:-

Head Circumference (OFC):

Using a stainless steel non-stretchable tape, the subject seated, the maximum circumference of the head is measured with the tape passing above (but not including) the brow ridges.

Head Length:

Using a spreading caliper, the maximum length in the sagittal plane from the glabella (the most salient point between the eyebrows) to the most salient point on the occiput. Pressure is exerted to compress the tissues.

Head Breadth:

Using a spreading caliper, the maximum breadth in the transverse plane, wherever it occurs is measured. Pressure is exerted to compress the tissues.

Ear :

Ear length:

Using a sliding caliper, the maximum length of the subject's ear along its long axis is measured.

Ear breadth:

Using a sliding caliper, the maximum breadth of the ear is measured with the fixed arm of the sliding caliper parallel to the long axis of the ear.

Palate:

Palatal measurements were taken using dental study models. The measurements were performed carefully three times and averaged.

1. Palatal width:

It is the distance between two points at the cervical aspect of the mesiolingual cusps of the upper first molars at the junction of the tooth and gingival margins. These points are designated A and B. The palatal width is measured using a Helios dial caliper graduated to one twentieth of a millimeter (fig. 3)

2. Palatal height:

It is the distance from points A and B on the

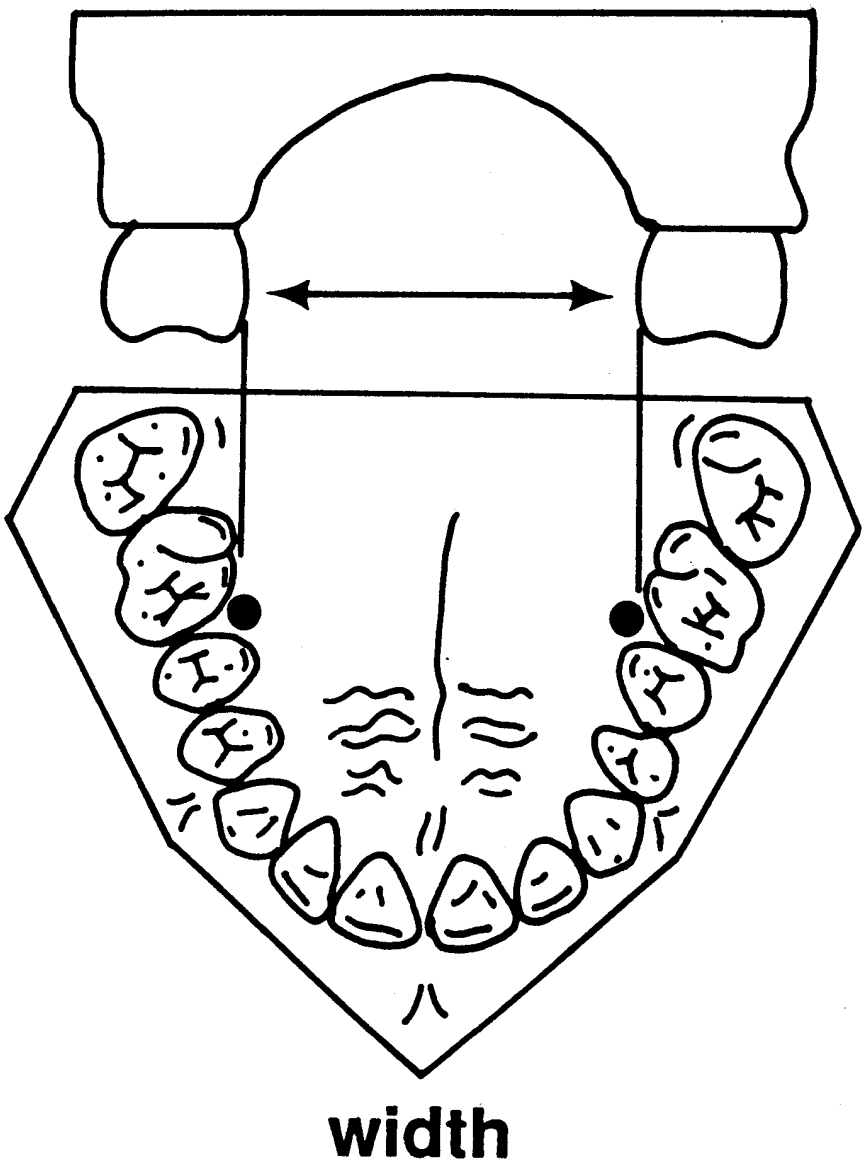


Figure No. 3: Diagram of a study model showing points used for measurement of palatal width.

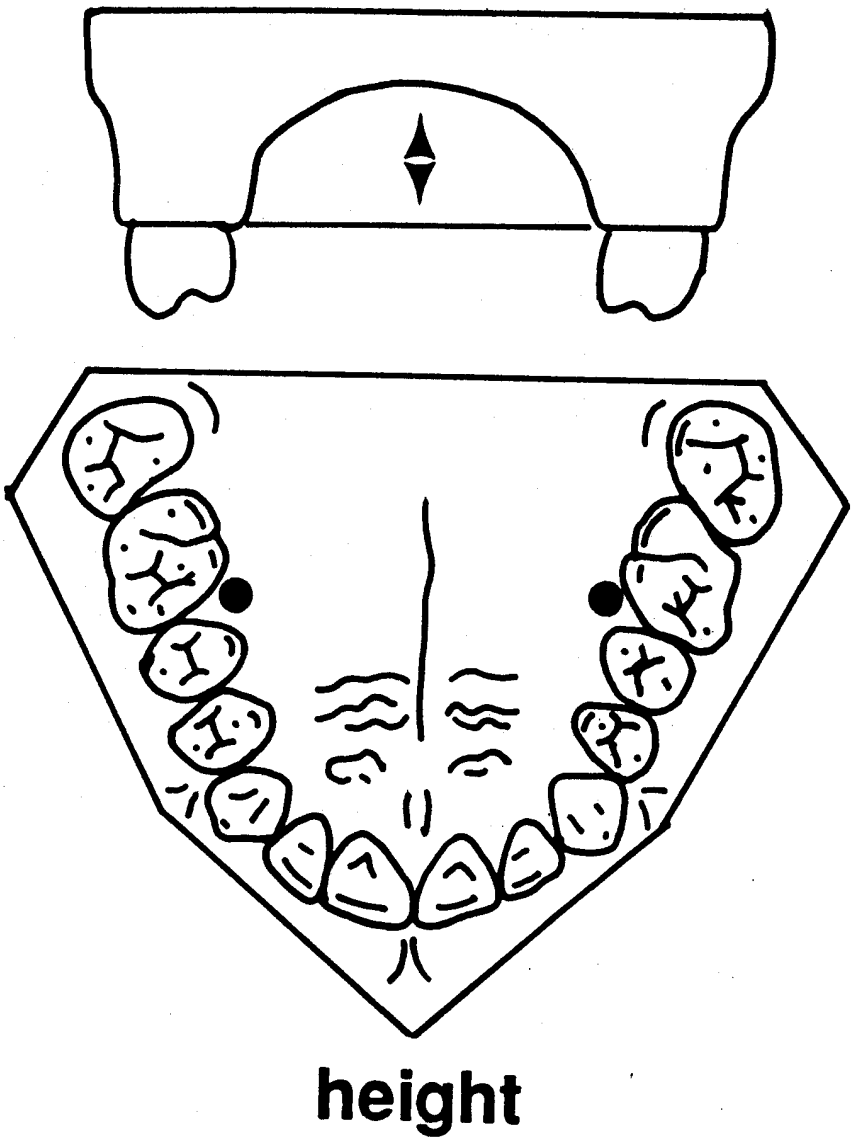


Figure No. 4 : Diagram of a study model showing points used for measurement of palatal height.

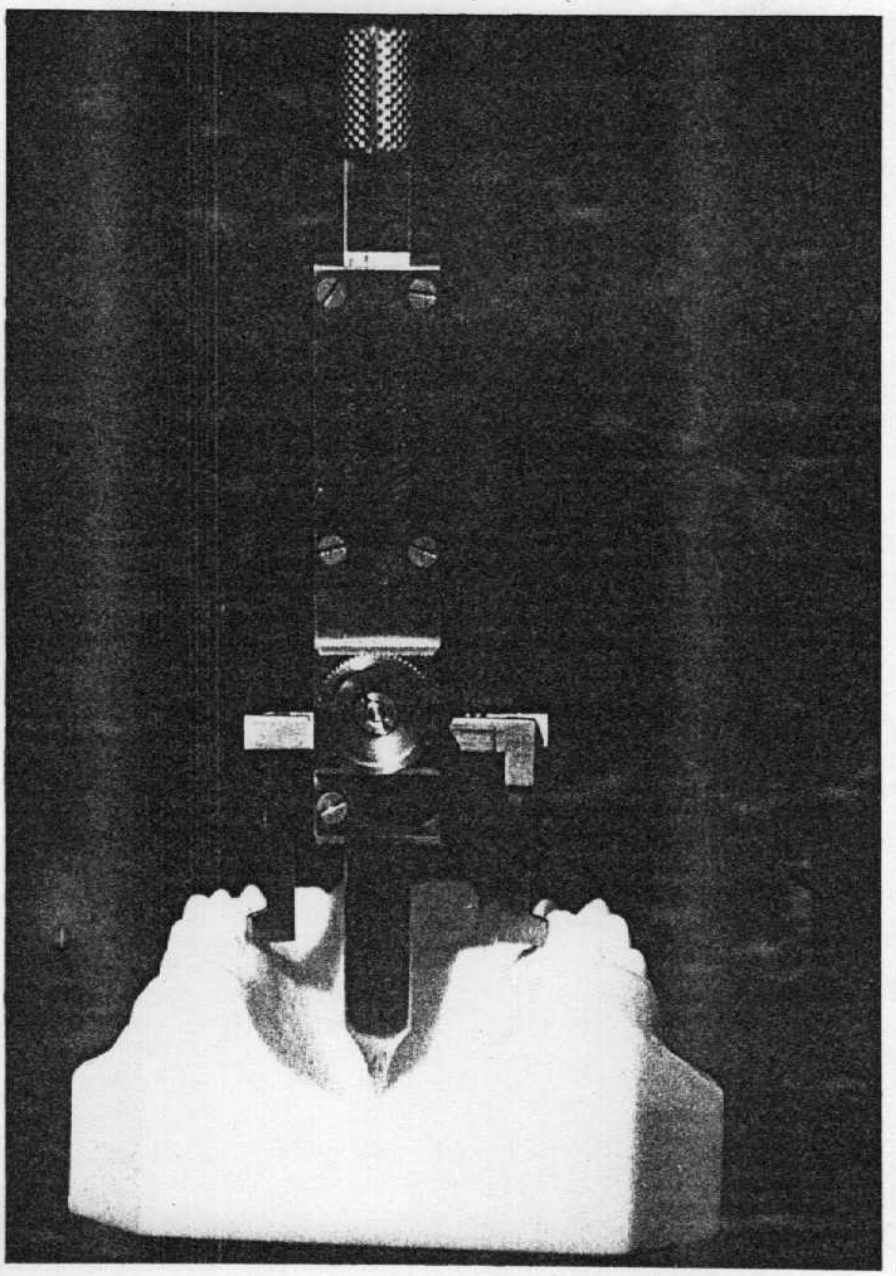


Figure No. 5 : Photograph of the palatometer used on study models for measurement of palatal height.

maxillary first permanent molars to the highest point on the palatal vault in the midline Fig. 4.

The height of the palate is measured using the palatometer manufactured by Siber Hegner & Co., New York: fig. 5.

3. Palatal length:

It is the distance from an anterior point C defined as the intersection of the midsagittal plane with a line passing over the widest point of the incisive papillae, to a posterior point D defined as the intersection of the midsagittal plane with a plane passing through the most distal points of the upper first permanent molars. The distances AC and BC were measured and the palatal length was calculated from the formula for the median of any triangle with known sides fig. 6.

$$CD = \sqrt{\frac{AC^2 + BC^2}{2} - \frac{AB^2}{4}}$$

4. Palatal Index

The ratio between the height and width X100 was also calculated.

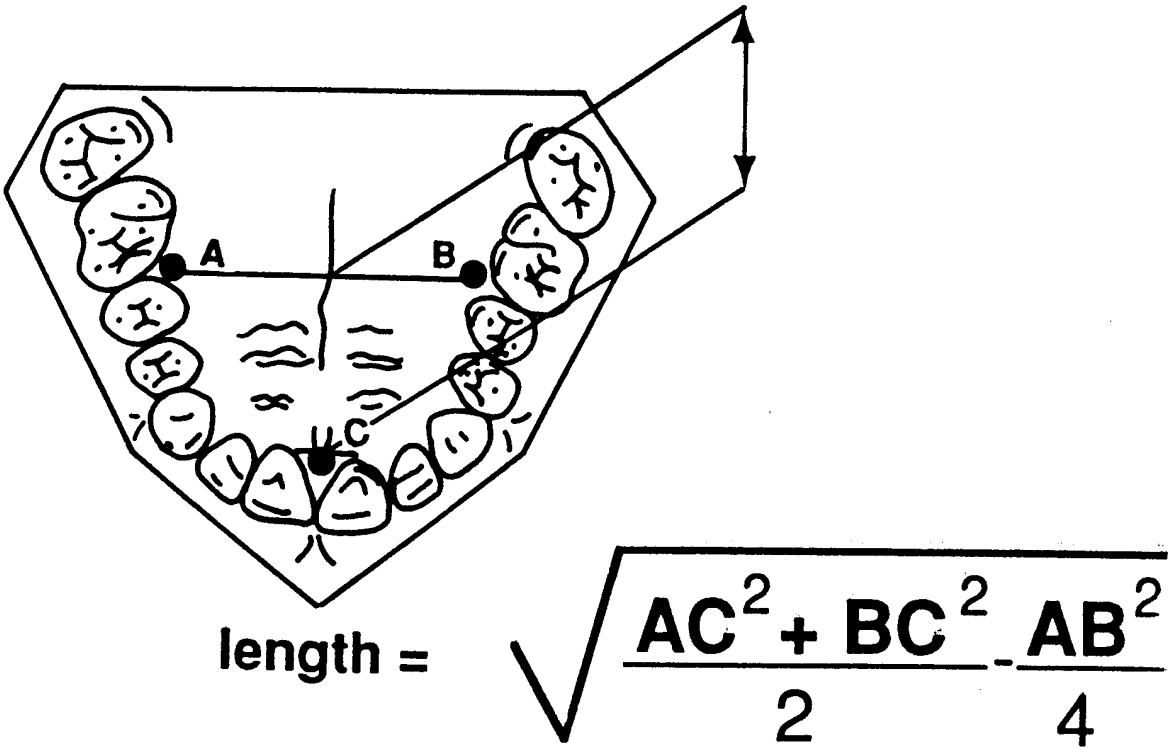


Figure No. 6 : Diagram for a study model showing the points A, B and C and the formula used for measuring palatal length

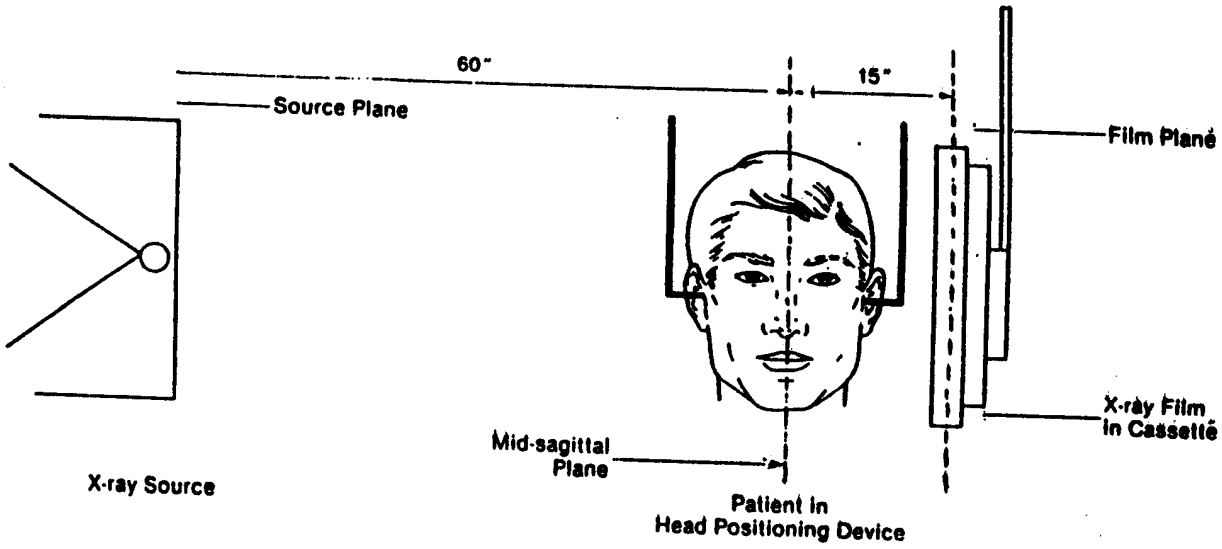


Figure No. 7 : Technique for radiographic cephalometry: diagram illustrating the position of the patient from the X-ray source and X-ray film during cephalometric radiographing.

Radiographic Cephalometry

Lateral and postero-anterior cephalograms were taken using a cephalostat at the Orthodontic Department, Faculty of Oral and Dental Medicine, Cairo University.

a. Technique for Radiographic Cephalometry:

A lateral skull radiograph was taken for each case using the standard method by Broadbent,1931. A "Siemens" cephalostat with variable output of X-rays 65 K.V. and 15 M.A. for group I (age 6-10 years) while an output of 75 K.V. and 15 M.A. was used for group II (13-16 years), group III (17-22 years) and group IV (mothers of affected males). 2.5 second exposure time was used for all groups. The tube to subject distance was five feet and the film was brought as close as possible to the head holder (fig. 7). The technical variables have been reduced to a minimum with a constant and precise positioning of the head as a pre-requisite.

8" X 10" OR-WO films were utilized in cassettes with double intensifying screens. The films were processed by the standard wet method of processing.

b. Tracing of Radiographic Films:

The tracing is a pencilled outline of the pertinent anatomic structures made on a semi transparent sheet of

tracing paper super imposed on the radiograph itself. Those structures relevant to the present study were reproduced as accurately as possible with a fine hard pencil made on the tracing.

The following tracing materials were used Tracolene or Tracofilm tracing paper (.003 translucent calk paper).
3 hard lead drawing pencils.
Transparent millimeter ruler.
Transparent protractor.
Art gum eraser.
Transparent triangle.
Sand paper pencil pointer.
Draftsman's tape or cellotape.
Radiographic Dentaurum viewing box: that box was large enough to accomodate the lateral and postero anterior films simultaneously when both were needed.

The cephalometric landmarks necessary to give the required information were identified on each radiograph according to the standards suggested by Riolo et al., (127) 1974 .

c. Measuring of Radiographic Landmarks:

Cephalometric points (fig. 8) were digitized by means of a Hipad digitizer (Houston instruments) and

specific linear, angular and ratio parameters were measured using the program of the Division of Craniofacial Genetics , Department of Pediatric Dentistry and Orthodontics, Medical University of South Carolina, Charleston, U.S.A. on an IBM-XT compatible computer.

Those parameters included in the program were computed and other relevant parameters not included in this program were manually measured.

Figure 8 : CEPHALOMETRIC LANDMARKS
LATERAL VIEW

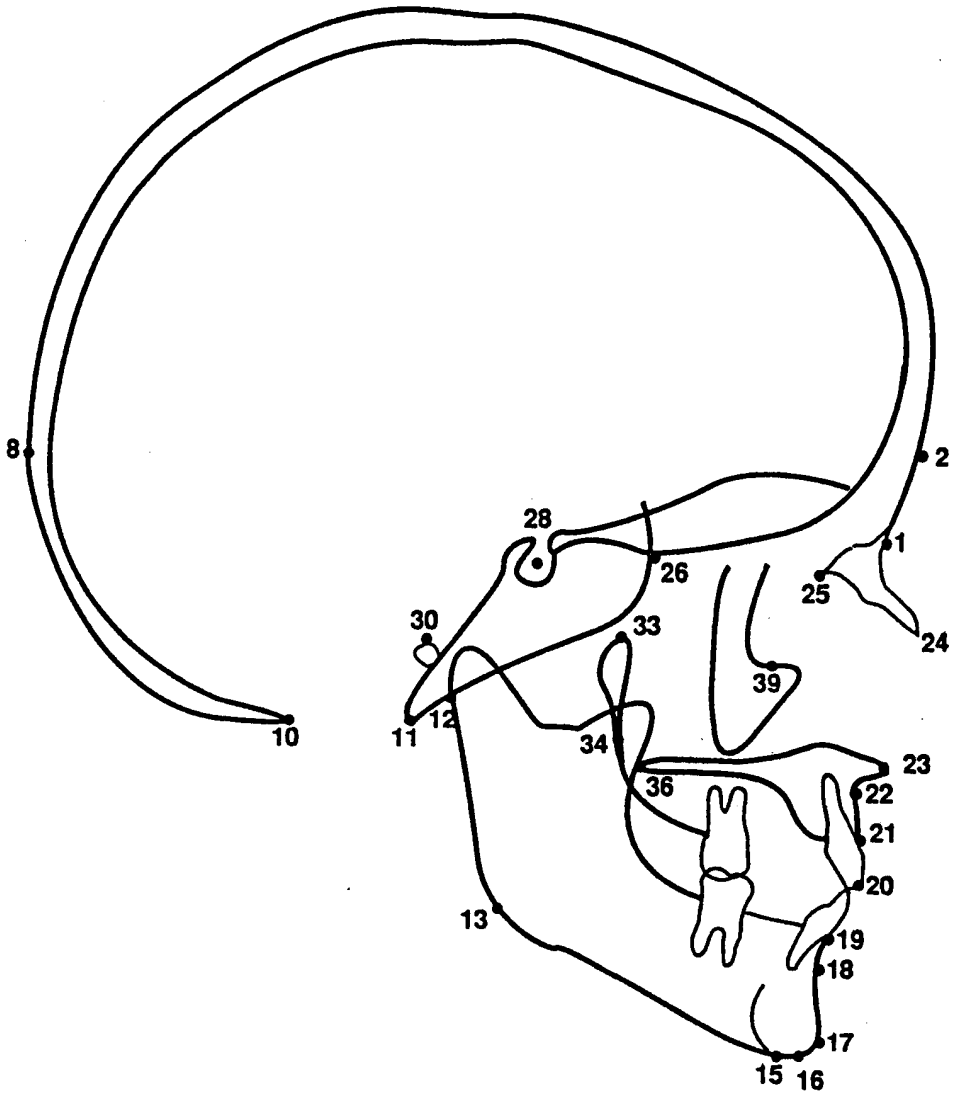


Fig. 8 : Cephalometric Landmarks (lateral view)

1. Nasion (N)
2. Glabella (Gb)
8. Opisthocranion (Oc)
10. Opisthion (Op)
11. Basion (Ba)
12. Articulare (Ar)
13. Gonion (Go)
15. Menton (Me)
16. Gnathion (Gn)
17. Pogonion (Pg)
18. B-point (B)
19. Infradentale I (Idi)
21. Infradentale S (Ids)
22. A-point (A)
23. Anterior nasal spine (ANS)
24. Rhinion (Rn)
25. Fronto maxillonasal suture (FMN)
26. Ethmoid Registration Point (SE)
28. Sella Turcica (S)
30. Porion (P)
36. Posterior Nasal Spine (PNS)
39. Orbitale (Or)

Cephalometric Points, Lines, Angles and Ratios Studied

Landmarks on Lateral Radiograms (Fig. 8) (Smahel and Skvarilova, 1988) (128)

Points:

1. Nasion (N): The most anterior point on the fronto-nasal suture intersected by the median sagittal plane.

2. Glabella(Gl): The most anterior point on the frontal bone in the midsagittal plane of the bony prominence joining the supra-orbital ridges.

3. Opisthocranion(Opc): The posterior midsagittal point of the greatest cranial length from the glabella.

4. Basion (Ba) : The most forward and lowest point on the anterior margin of foramen magnum

5. Articulare(Ar): The point of intersection of the external dorsal contour of the mandibular condyle and the temporal bone. The midpoint is used when the lateral cephalogram shows double projection of the rami.

6. Gonion (Go) : The most lateral point on the convex margin of the angle of the mandible.

7. Antigonion (Ag): The greatest concavity point on the inferior border of the mandible.

8. Menton (Me) : The lowest point on the chin from which the face height is measured. It is somewhat forward to the gnathion.

9. Gnathion (Gn): The lowest point on the median plane in the lower border of the chin palpated from below. In cephalometrics it is measured at the intersection of the mandibular base line and Nasion Pogonion line (N Pg line).

10. Pogonion(Pg): The most anterior point on the chin.

11. B-point (Supramentale): The deepest point on the contour of the mandibular alveolar process between the infradentale and pogonion.

12. Infradentale (Id): The highest interdental point on the alveolar mucosa between the mandibular central incisors.

13. Supradentale (Sp) or (Ids) (Prosthion) : The lowest most anterior point on the upper alveolar margin between the central incisors.

14. A-point (Subspinale) : The deepest point on the midiline contour of the alveolar process between the anterior nasal spine and the prosthion. The anterior limit of the maxillary basal arch as seen on the lateral radiograms.

15. Anterior nasal spine (ANS): The medial sharp bony process of the maxilla at the lower margin of the anterior nasal opening.

16. Rhinion (Rh): Most inferior point on the nasal bone

17. Posterior nasal spine (PNS): The process formed by the united projecting ends of the posterior borders of the palatine processes of the palatal bones.

18. Sella (S) : The center of the sella turcica as determined by inspection

19. Porion (Po) : A point located at the most superior point of the external auditory meatus

20. Orbitale(Or): The lowest point on the inferior margin of the orbit.

21. Sella Vertical (S.V.): A line perpendicular to Frankfurt Horizontal passing through Sella point (S).

Landmarks on postero anterior rodiograms (fig. 9) (Saksena, 1990) (129)

Points:

1. Euryon(Eu): The most lateral point at the parietal surface.
2. Temporale (Tp): The most lateral point above the level of the supramastoid crest of the temporal bone.
3. Medio orbitale (Mo): The most medial point on the medial orbital margin.
4. Latero orbitale (Lo): The lateral most point on the lateral orbital margin.
5. Zygoma (Zy): The most lateral point on the zygomatic arch.
6. Gonion (Go): The most lateral point on the convex margin of the angle of the mandible.
7. Gonial notch point (Ag): The greatest concavity point on the inferior border of the mandible.

Linear measurements on lateral radiograms:

Facial height measurements:

Total facial height N-Me.

Upper facial height N-ANS.

Lower facial height ANS-Me

Anterior mandibular height Id-Me.

Posterior mandibular height Ar-Go.

Maxillary height Sp-A-point.

Facial depth measurements:

Maxillary depth ANS-PNS.

Glabella to Sella Vertical.

Nasion to Sella Vertical.

Rhinion to Sella Vertical.

ANS to Sella Vertical.

A-point to Sella Vertical.

Supra dentale to Sella Vertical.

Infra dentale to Sella Vertical.

B-point to Sella Vertical.

Pogonion to Sella Vertical.

Cranial base measurements:

Total cranial base height (N-Ba).

Anterior cranial base height (S-N).

Posterior Cranial base height (S-Ba).

Facial profile measurements:

Angles:

<SNA : Sella Nasion A point angle determins the antero posterior relation between the maxillary basal arch and the anterior cranial base. It shows the degree of maxillary prognathism.

<SNB : Angles Sella Nasion B-point and Sella-Nasion
<SNPg Pogonion show the anterior limit of the mandibular basal arch in relation to the anterior cranial base.

Ratios:

$$\frac{\text{Upper facial height}}{\text{Lower facial height}} = \frac{\text{N-ANS}}{\text{ANS-Me}}$$

$$\frac{\text{Posterior facial height}}{\text{Anterior facial height}} = \frac{\text{S-GO}}{\text{N-Me}}$$

$$\frac{\text{Maxillary length}}{\text{Mandibular length}} = \frac{\text{PNS-ANS}}{\text{Go - Me}}$$

Figure 9 : **CEPHALOMETRIC LANDMARKS**
POSTERIO-ANTERIOR VIEW

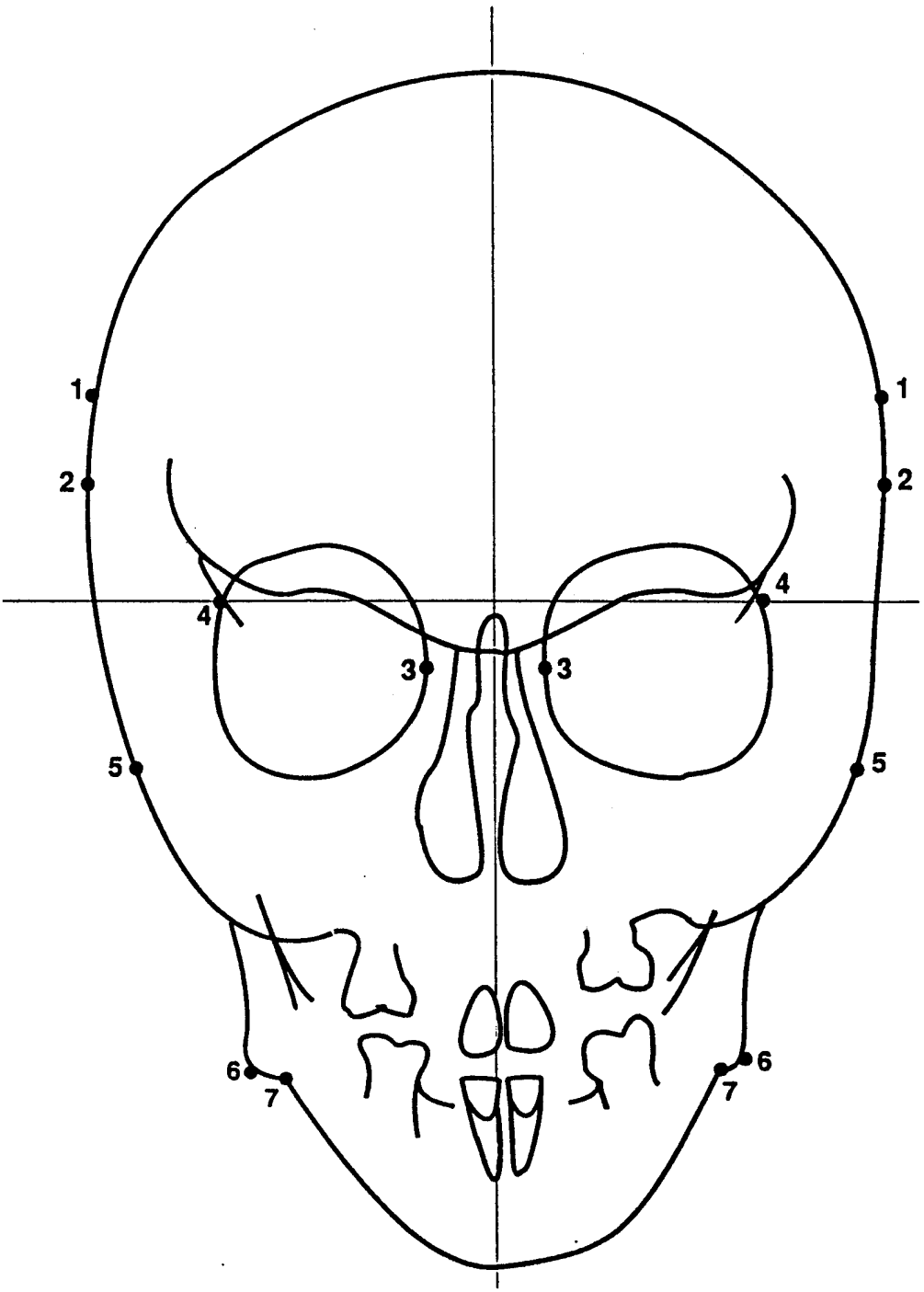


Fig. 9 : Cephalometric Landmarks (Postero-anterior view)

1. Euryon (Eu)
2. Temporale (Tp)
3. Medioorbitale (Mo)
4. Latero orbitale (Lo)
5. Zygoma (Zy)
6. Gonion (Go)
7. Antigonion (Ag)

Head measurements from postero anterior radiograms:(Fig. 9)

Facial width measurements:-

Maximum head width (Eu-$\bar{Eu}$).

Head width (Tp-$\bar{Tp}$).

Interorbital width (Mo-$\bar{Mo}$).

Face width (Zy-$\bar{Zy}$).

Mandibular width (Go-$\bar{Go}$)

(Ag-$\bar{Ag}$)

Panoramic X-Rays:

Panoramic X-ray films were done for the studied cases. The exposure begins posterior to the mandibular condyle and as the film is exposed the tube head and the film rotate around the patient's head automatically.

The anatomic landmarks as visualized on the panorex film are the orbital cavity, the nasal cavity, the inferior chonca, the maxillary sinus, palatal process of maxilla, incisive canal, zygomatic arch and malar process, angular spine of sphenoid bone, condylar process of the mandible, coronoid notch, glenoid fossa, styloid process, mastoid process, oblique ridge of mandible, mandibular foramen, mandibular and inferior border of the mandible, angle of the mandible and the teeth set.

Statistical Analysis:

The means, standard deviations and standard errors were obtained using the Minitab computer program version 7. Data were stored on a diskette in a special manner to facilitate the use of the SAS statistial program 6.03 to perform the z-score analysis and t-test analysis.

The t-test analysis was performed to compare the means of the two groups "affected" and "control" group, to test the particular null hypothesis that there is no difference between the two groups on selected cephalometric measurements.

The formula used for the t-test:

$$\frac{\text{Difference between two means}}{\text{Standard error of the difference between the means}} = \frac{\bar{X}A - \bar{X}B}{SE(\bar{X}A-\bar{X}B)}$$

Z-score analysis:

The z-score tells us how many standard deviations a particular value is away from the mean.

The standard z-score was done through the conversion of the cephalometric values to the standard scores and was

calculated by the following formula

$$(\text{Z-score}) = \frac{X - \bar{X}}{S\,d}$$

where X:represents the individual measurement,$\bar{X}$ represents the age and sex-specific mean for that measurement taken from the normal population. S.d. represents the standard deviation.

The z-score values were used in graphing the craniofacial pattern profile by using the Harvard graphics computer program. The pattern profile is based on the means of the z-scores of the different parameters. This was done to compare the fra (X) sample with the control sample age-wise and to compare the mothers of fra(X) cases with control adult females. Selection of parameters used in pattern profile were chosen according to their clinical importance and the presence of significant differences between the means. A list of abbreviations is shown at the beginning of the text.

The correlation coefficient was calculated to detect any pattern similarity or dissimilarity between the affected sibs and between the mothers and their affected offsprings. This was done using the SAS computer program.

CHAPTER IV

RESULTS

Pedigree Analysis:

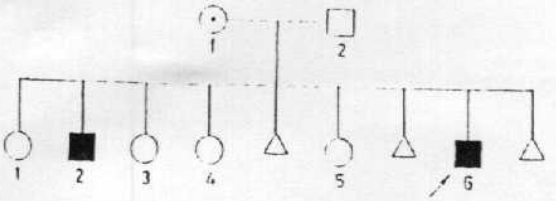
The pedigrees of the affected cases are demonstrated in pedigrees no 1-14.

The X-linked pattern of inheritance is clear in pedigrees 2, 6, 9 and 12 and it is probable in pedigrees 1, 3, 4, 11 and 14 and it is possible in pedigrees 5, 7, 8, 10 and 13.

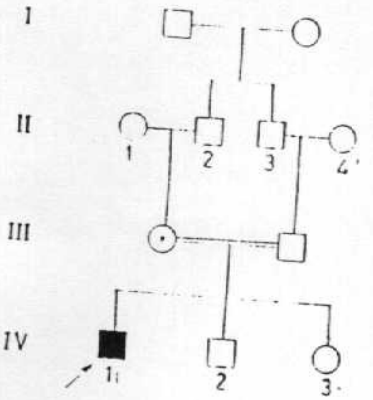
Concerning the probands 4 out of 14 families have positive consonguinity. This is evident in pedigrees no. 5, 10, 11 and 13.

Concerning all the affected family members 5 out of 14 families have positive consanguinity in pedigrees 2, 5, 10, 11 and 13.

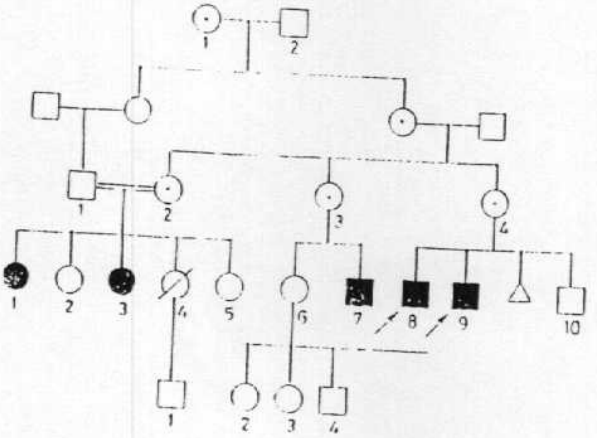
Positive maternal family history of mental retardation is found in 9 out of 14 families: pedigrees 1, 2, 3, 4, 6, 9, 11, 12, and 14.



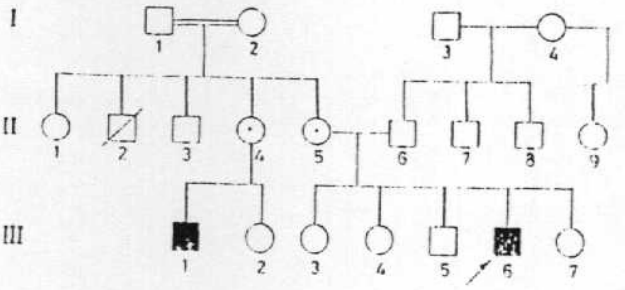
Ped. (1) P1-001



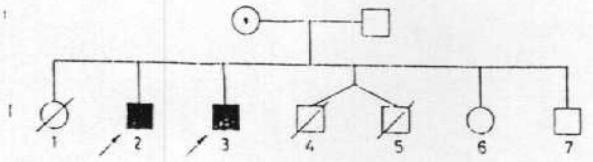
Ped.(5) P 5-015.



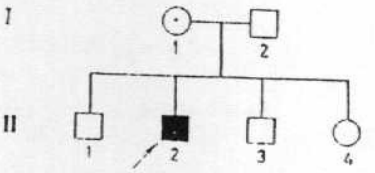
Ped.(2) P 2-004, P 2-005



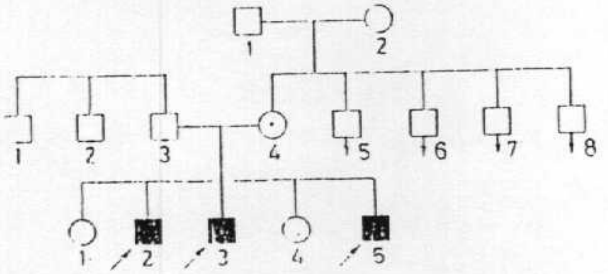
Ped.(6) P 6-019.



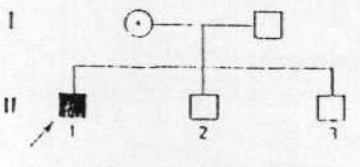
Ped.(3) P 3-007, P 3-008.



Ped.(7) P 7-022.

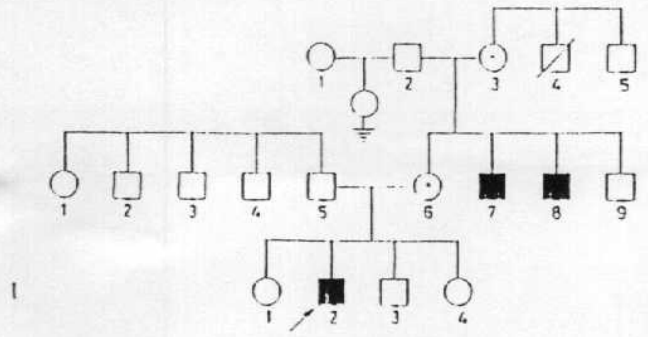


Ped.(4) P4-010, P4-010, P4-012

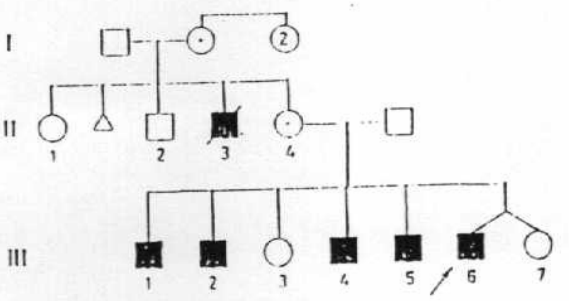


Ped .(8). P8 .-024

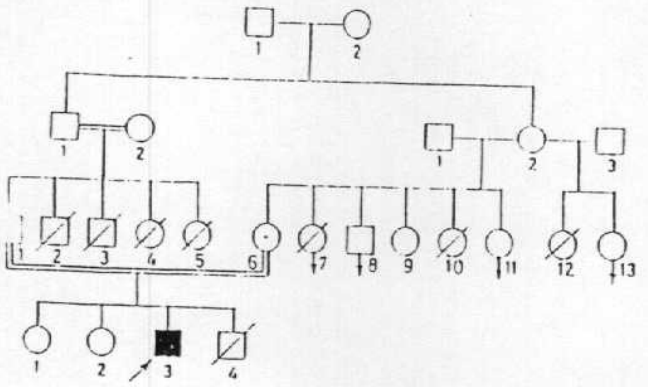
Figure 10 : Pedigrees No. 1-8



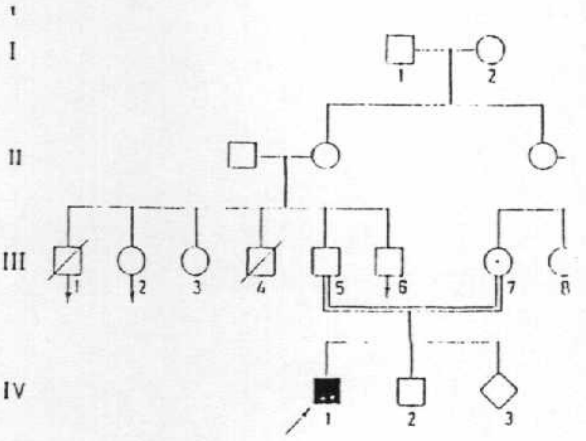
Ped. (9) P 9-026.



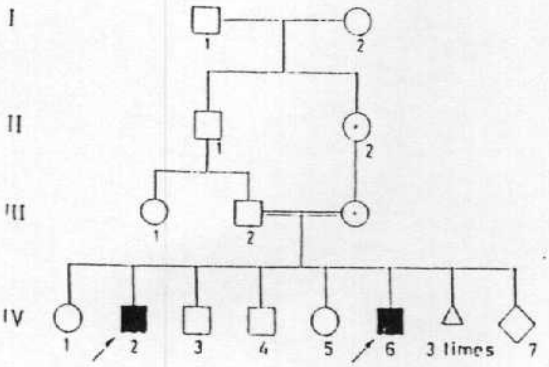
Ped. (12) P 12-035.



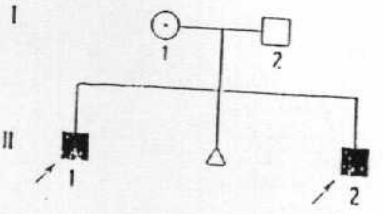
Ped. (10) P 10-028.



Ped. (13) P 20-059.



Ped. (11) P 11-030, P 11-033.



Ped. (14) P 22-063

Figure11: Pedigrees No. 9-14

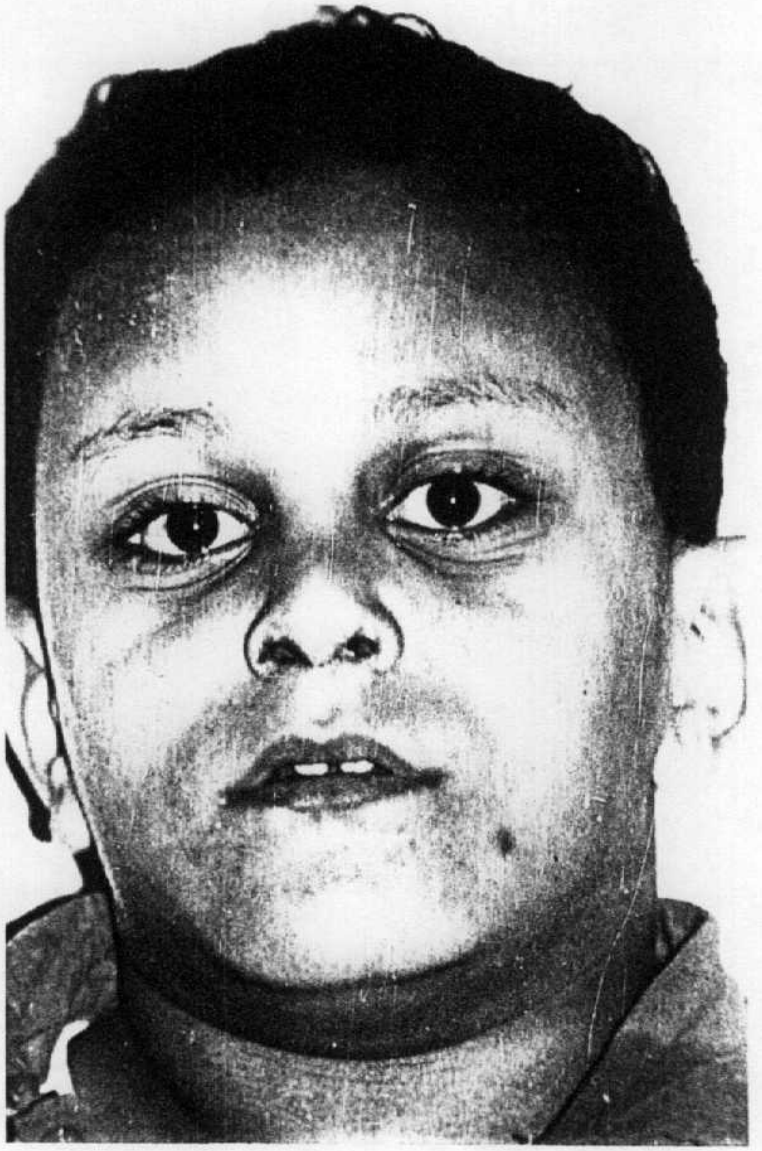


Figure No. 12 : A photograph of fragile X child (7 years old): case p4-010 with an almost normal appearance

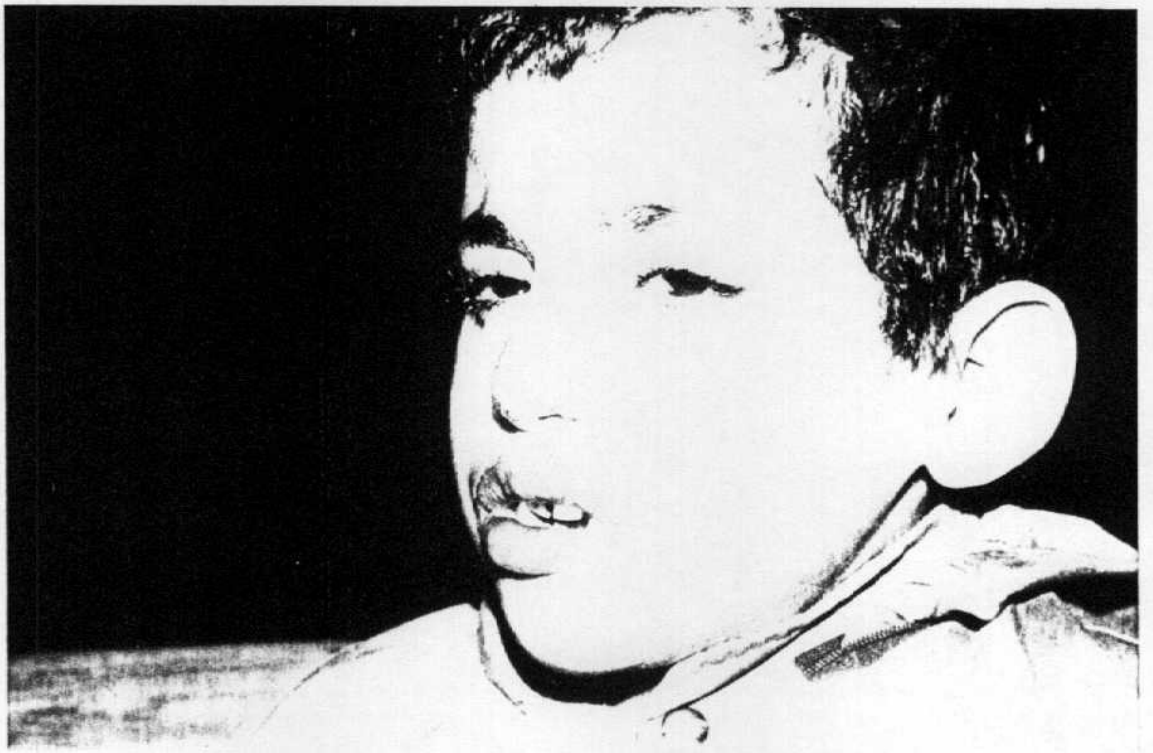


Figure No. 13 : A photograph of fragile X child (9 years old): case p10-028 showing malformed cupped ears

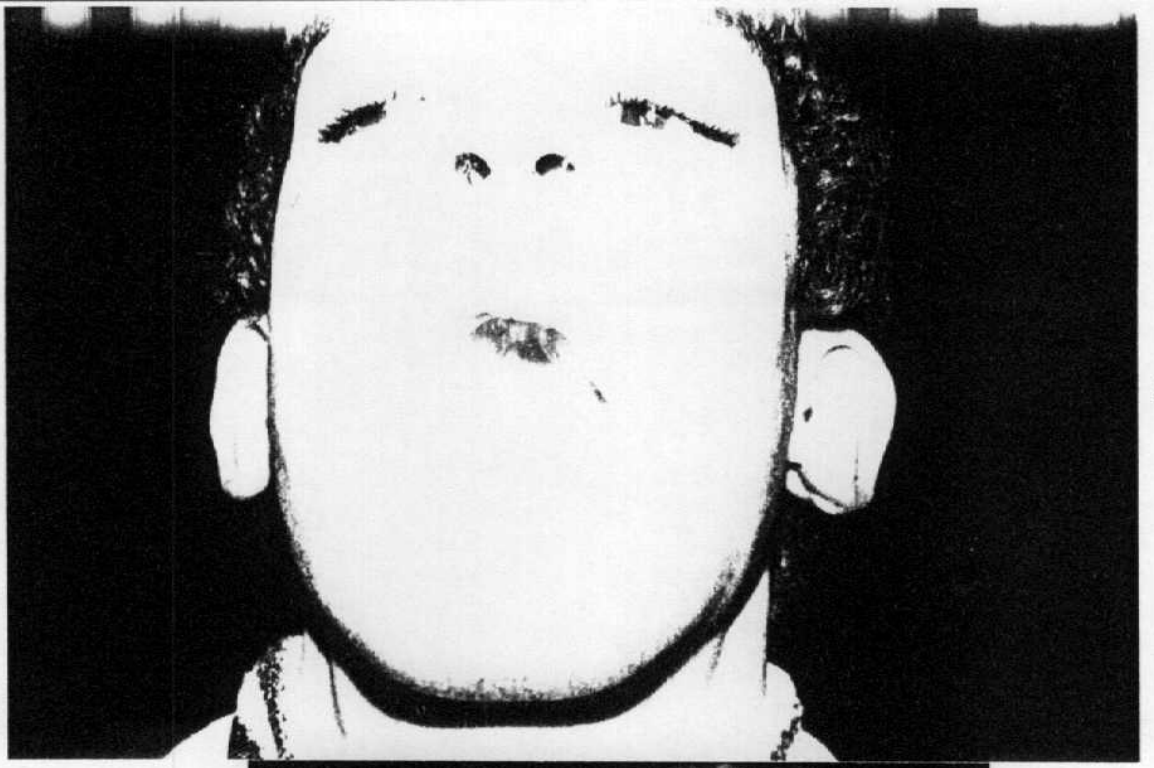


Fig. 14

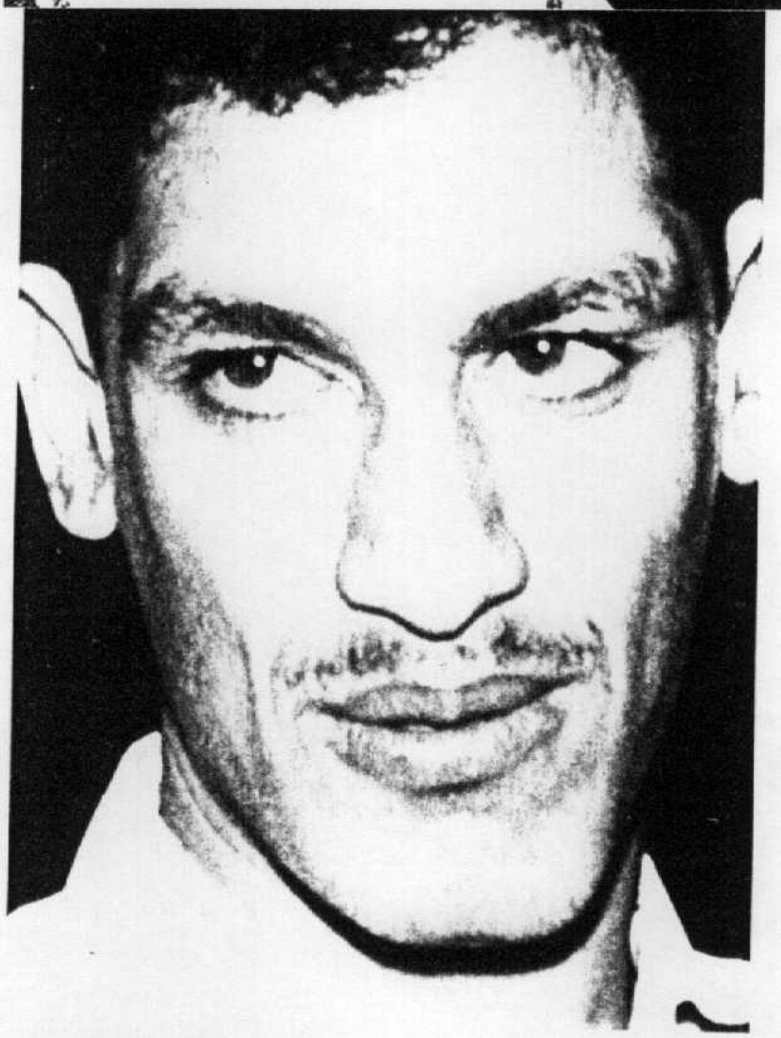


Fig. 15

Figure 14,15 : Two photographs of two affected sibs p3-008 (17 years old) showing long face, broad nose, prominent long ears and broad prominent mandible.

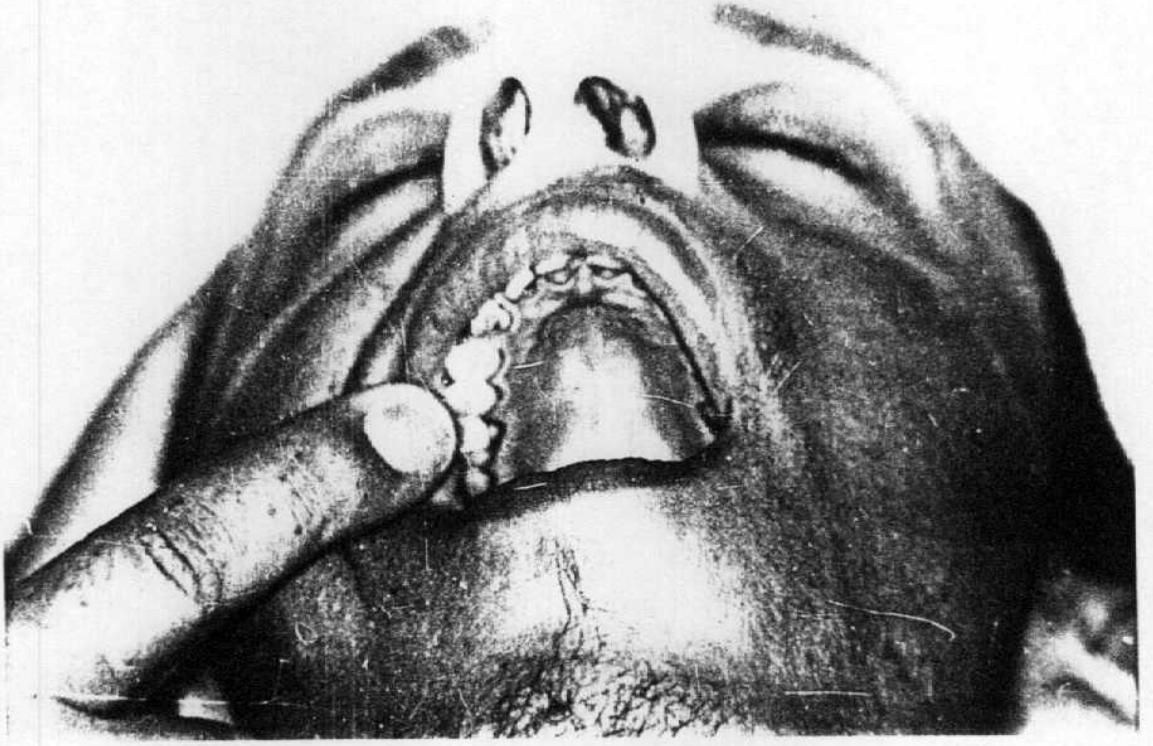


Figure No. 16 : Photograph of 18 year old fragile X male : case (P4-011) showing high palate.

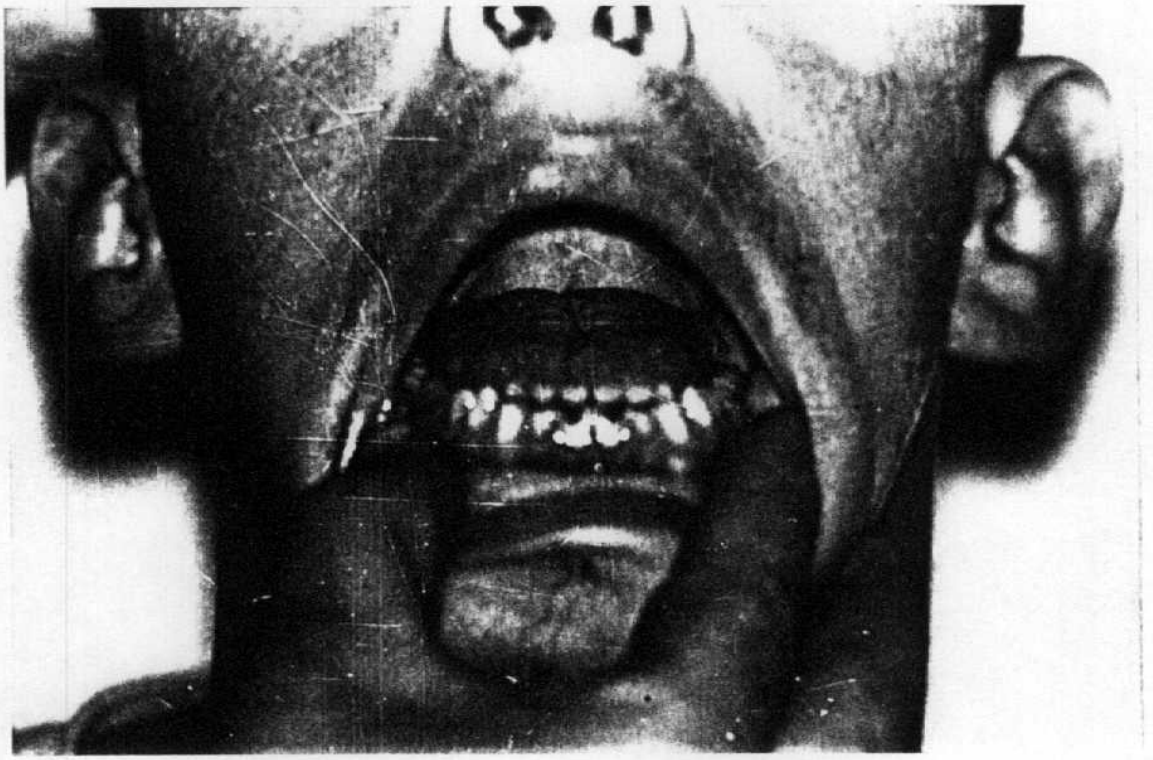


Figure No. 17 : Photograph of 18 year old fragile X male : case (P4-011) showing macroglossia and hypoplastic lower anterior teeth.

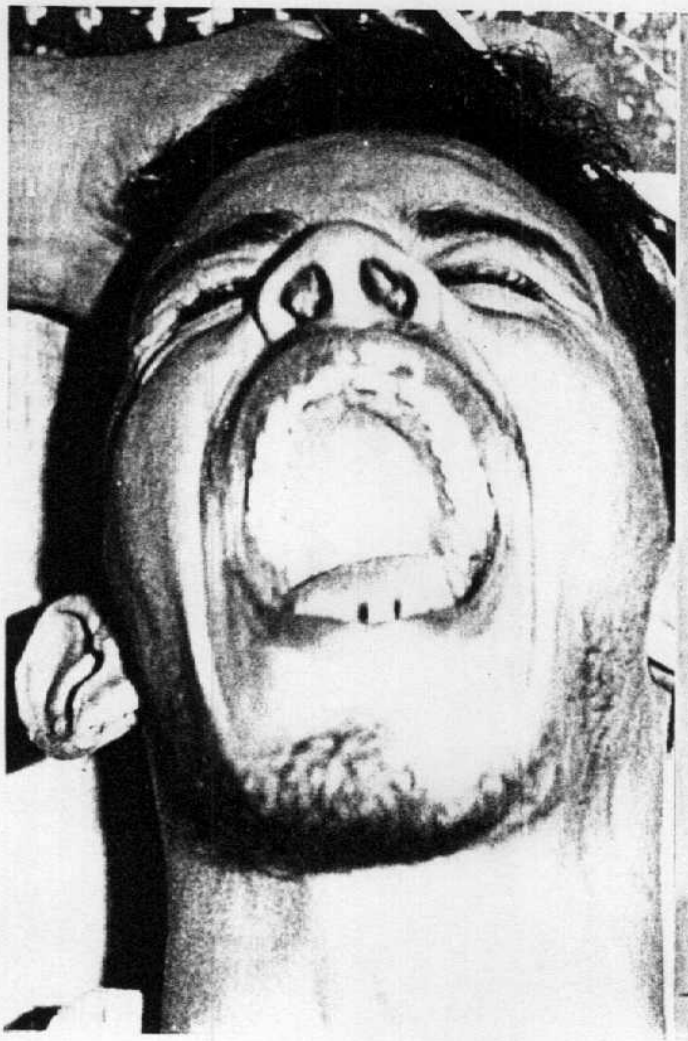


Figure 18

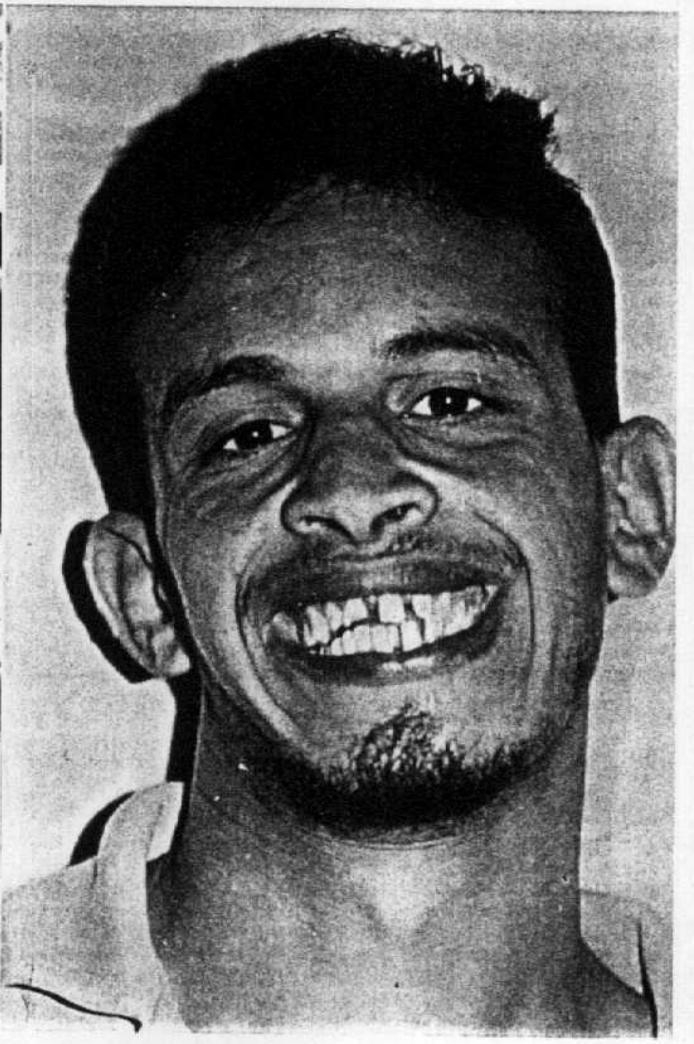


Figure 19

Figure No. 18, 19 : Two photographs of 22 year old fragile X male (P4-012) showing high arched palate long face low-set cupped ears, diastema between the teeth and malocclusion.

Figure No. 20 : A photograph of fragile X sibs P4-C10 7 years old and P4-C11(18 years old) with their mother P4-C14 showing long ears, long face and prominent mandible.

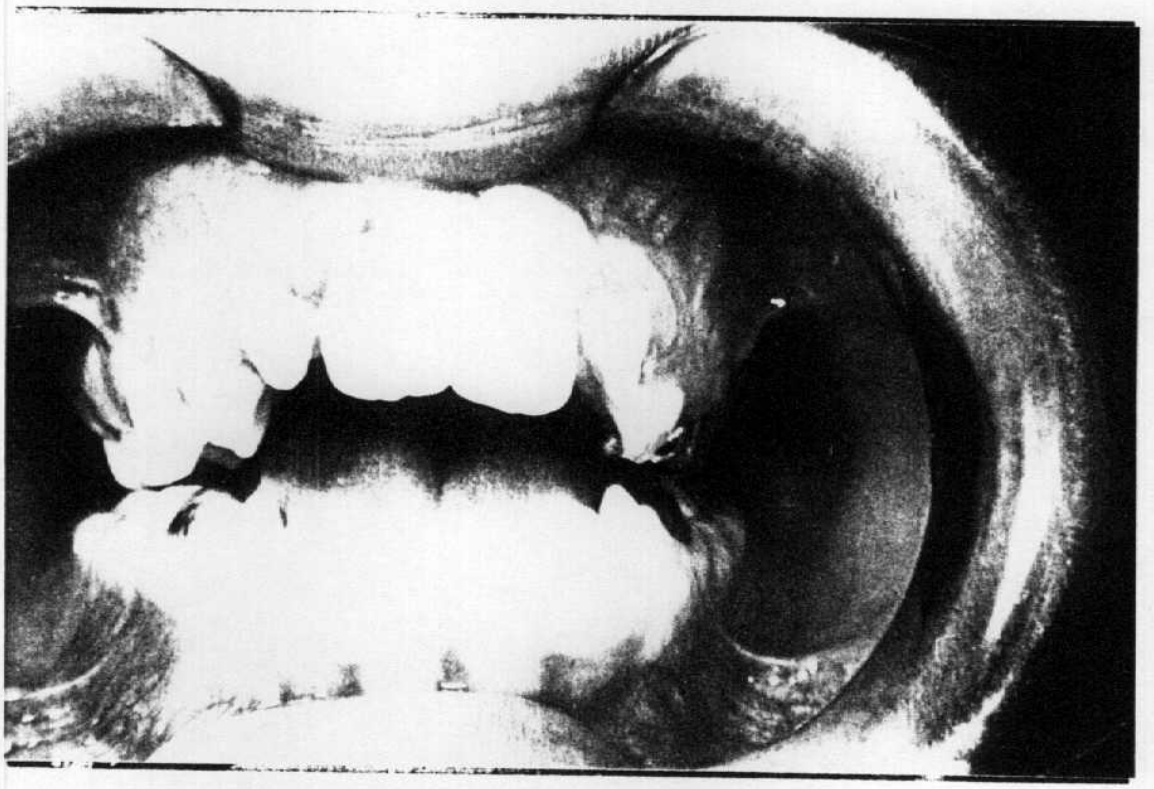


Figure No. 21: A photograph of 9-year old fragile X male (P9-026) showing open bite.

Table IV 1 : Clinical abnormalities in affected males

	Mental retardation	Delayed milestones	Long face	Long or Prominent ears	Large forehead	Flat occiput	Prominent Supercilliary arches	Light colored eyes	Nystagmus	Broad nose	Pectus excavation	Short or broad Phalanges	Flat foot	Syndactyly Clinodactyly	Hirsutism Synophris	Hyperextensible Joints	Macro Orchidism	Abnormal Speech	Hyperactive or autistic behavior
P 20 - 059 6.87 y	+		+	+															
P 11 - 033 ✱ 7.09 y	+	+	+											+	+			+	
P 4 - 010 ✱ 7.17 y	+			+			+					+			+			+	
P 10 - 028 8.57 y	+			+					+		+			+			+		+
P 8 - 024 9.70 y	+			+						+								+	+
P 9 - 026 9.01 y	+	+		+								+						+	
P 12 - 035 10.04 y	+			+								+				+			
P 22 - 064 12.02 y	+	+		+								+					+		
P 5 - 019 14.30 y	+	+	+	+			+	+		+				+	+			+	+
P 2 - 004 oo 14.46 y	+		+	+	+	+		+				+	+				+		
P 1 - 001 14.66 y	+	+			+					+		+					+		
P 22 - 063 15.15 y	+			+						+		+					+		+
P 7 - 022 15.76 y	+	+	+	+							+	+			+	+	+	+	
P 11 - 030 + 16.05 y	+	+	+						+						+			+	
P 2 - 005 oo 16.63 y	+			+	+	+		+				+	+				+		
P 3 - 008 o 17.25 y	+		+				+			+			+				+		
P 4 - 011 ✱ 18.13 y	+		+	+			+	+			+	+				+	+		
P 5 - 015 18.89 y	+	+					+	+										+	
P 3 - 007 o 21.92 y	+		+	+			+			+					+		+		
P 4 - 012 ✱ 22.60 y	+		+	+							+								
	20/20	9/20	10/20	16/20	3/20	2/20	6/20	6/20	2/20	6/20	4/20	11/20	3/20	3/20	6/20	3/20	12/20	8/20	4/20

✱, o , oo , + = Sibs

Table IV 2 : Oro-dental Abnormalities in Affected males

	Thick lips	Short Phitrum	Depressed maxilla	Prominent mandible	High arched Palate	Macroglossia	Malposed teeth retained teeth	Hypoplastic teeth	Absent teeth micro or macrodonta	Diastema	Malocclusion
P 20 - 059 6.87 y		+			+			+			+
P 11 - 033 + 7.09 y		+	+			+					+
P 4 - 010 ✱ 7.17 y	+	+							+	+	
P 10 - 028 8.57 y		+			+				+		+
P 8 - 024 9.70 y					+	+					+
P 9 - 026 9.01 y	+	+			+			+	+	+	+
P 12 - 035 10.04 y	+				+	+	+			+	
P 22 - 064 12.82 y				+	+	+					
P 6 - 019 14.30 y				+	+		+				+
P 2 - 004 oo 14.46 y					+		+				+
P 1 - 001 14.66 y				+		+	+			+	+
P 22 - 063 15.15 y	+		+			+		+	+		+
P 7 - 022 15.76 y	+		+	+	+	+	+				
P 11 - 030 + 16.05 y	+			+	+	+			+		
P 2 - 005 oo 16.63 y				+	+	+		+		+	+
P 3 - 008 o 17.25 y				+	+	+					+
P 4 - 011 ✱ 18.13 y	+		+	+	+		+	+		+	+
P 5 - 015 18.89 y	+			+		+		+		+	+
P 3 - 007 o 21.42 y		+	+	+	+	+					+
P 4 - 012 ✱ 22.60 y					+		+		+	+	+
	8/20	6/20	4/20	10/20	15/20	12/20	7/20	6/20	6/20	8/20	15/20

✱ , o , oo , + = Sibs

Table IV 3 Summary of the frequency of Clinical Abnormalities in Affected males in descending order:

Mental retardation	20/20
Long prominent ears	16/20
Macroorchidism	12/20
Short or broad phalanges	11/20
Long face	10/20
Abnormal speech	8/20
Delayed milestones	8/20
Hirsutism, synophris	6/20
Broad nose	6/20
Prominent superciliary arches	6/20
Light colored eyes	6/20
Pectus excavatum	4/20
Hyperactive or autistic behavior	4/20
Hyperextensible joints	3/20
Syndactyly, clinodactyly	3/20
Flat foot	3/20
Large forehead	3/20
Nystagmus	2/20
Flat occiput	2/20

Table IV . 4 Summary of the frequency of Oro-dental abnormalities in Affected males in descending order:

High arched palate	15/20
Malocclusion	15/20
Macroglossia	12/20
Prominent mandible	10/20
Diastema	8/20
Thick lips	8/20
Malposed or Retained teeth	7/20
Short philtrum	6/20
Hypoplastic teeth	6/20
Absent teeth, microdontia or macrodontia	6/20
Depressed maxilla	4/20

Table IV.5 The frequency of the clinical manifestations in the affected males in different age groups:

Proband #	Age	Frequency of Abnormalities	
Group I (6-10 years):			
P 20-059	6.87y	6/19	
+ P 11-033	7.09y	5/19	
* P 4-010	7.17y	6/19	36/133 = 27.06%
P 10-028	8.57y	7/19	
P 8-024	9.70y	3/19	
P 9-026	9.01y	5/19	
P 12-035	10.04y	4/19	
Group II (13-16 years):			
P 22-064	12.82y	5/19	
P 6-019	14.30y	11/19	
oo P 2-004	14.46y	9/19	53/133 = 39.84%
P 1-001	14.66y	6/19	
P 22-063	15.15y	6/19	
P 7-022	15.76y	10/19	
+ P 11-030	16.05y	6/19	
Group III (17-22 years):			
oo P 2-005	16.63y	8/19	
o P 3-008	17.25y	6/19	
* P 4-011	18.13y	9/19	41/124 = 35.96%
P 5-015	18.89y	5/19	
o P 3-007	21.92y	7/19	
* P 4-012	22.60y	6/19	

+, o, oo, * : Sibs

Table IV 5 Shows that,after exclusionof mental retardation as it was the representing complaint in all cases. 19 abnormalities were considered. The percentage of occurrence of clinical abnormalities was calculated as the percentage of the sum of positive abnormalities from the sum of features evaluated in the group.

In Group I, the percentage of occurence of clinical abnormalities is 27.06%.

In Group II, the percentage of occurrence of clinical abnormalities is 39.84%.

In Group III, the percentage of occurrence of clinical abnormalities is 35.96%.

In Group I, the percentage is considerably lower than in group II and group III.

i.e. group II and III are similar in frequency and group I was lower in frequency.

i.e. The percentages in group II and III are closer and larger than in group I.

Table IV.6 : The frequency of the Oro-dental manifestations in affected males in different age groups

Proband #	Age	Frequency of Abnormalities	
Group I (6-10 years):			
P 20-069	6.87y	4/11	
P 11-033 +	7.09y	4/11	
P 4-010 *	7.17y	4/11	
P 10-028	8.57y	5/11	
P 8-024	9.70y	3/11	32/77 = 41.55%
P 9-026	9.01y	7/11	
P 12-035	10.04y	5/11	
Group II (13-16 years):			
P 22-064 oo	12.82y	3/11	
P 6-019	14.30y	4/11	31/77 = 40.26%
P 2-004 oo	14.46y	3/11	
P 1-001	14.66y	5/11	
P 22-063	15.15y	6/11	
P 7-022	15.76y	5/11	
P 11-030 +	16.05y	5/11	
Group III (17-22 years):			
P 2-005 oo	16.63y	6/11	
P 3-008 o	17.25y	4/11	35/66 = 53.03%
P 4-011 *	18.13y	8/11	
P 5-015	18.89y	6/11	
P 3-007	21.92y	6/11	
P 4-012 *	22.60y	5/11	

Foot note o,+,oo,* : Sibs

Table IV.6 Shows that the frequency of occurrence of oro-dental abnormalities is 41.55% in Group I and 40.26% in group II while it is 53.03% in group III which shows that group I and II have close frequencies while group III is considerably larger.

Table IV.7 : Summary of the comparison between affected sibs in both clinical and oro-dental signs

	Proband #	Age	Clinical sign score	Oro-dental sign score
1	P 4-012	22.60y	6/19	5/11
	P 4-011	18.13y	9/19	8/11
	P 4-010	7.17y	6/19	4/11
2	P 11-030	16.05y	6/19	5/11
	P 11-033	7.09y	5/19	4/11
3	P 2-005	16.63y	8/19	6/11
	P 2-004	14.46y	9/19	3/11
4	P 3-007	21.92y	7/19	6/11
	P 3-008	17.25y	6/19	4/11

In the intrafamilial affected cases, the older sib has more positive clinical and oro-dental than the younger sib, (P11-030 more than P11-033, P4-011 more than P4-010 and P3-007 more than P3-008). There are, however, two exceptions (P2-004 and P2-005) and (P4-012 and P4-011).

Table No. IV.8 :The descriptive statistical results in Group I

Group I

Physical Parameter	Cases ($\bar{X}$±SE) (N= 7)	Control ($\bar{X}$±SE) (N=25)	t-test Value
OFC	53.29 ± 1.32	51.92 ± 0.342	1.00
Head Length	18.00 ± 0.59	17.28 ± 0.158	+1.18
Head Breadth	14.07 ± 0.35	13.24 ± 0.105	2.28*
Ear Length	5.635± 0.217	5.276± 0.043	1.62
Ear Breadth	3.344± 0.139	3.054± 0.595	2.44*
Palatal Height	1.32 ± 0.044	1.143± 0.08	1.94
Palatal Width	3.02 ± 0.151	3.17 ± 0.072	-0.90
Palatal Index	43.210± 0.654	36.156± 2.419	2.82*
Palatal Length	2.5 ± 0.105	2.7 ± 0.182	-0.95

Radiographic Parameter	Cases (X+SE) (N=5)	Control (X+SE) (N=19)	t-test
Maximum head width	153.5 ± 2.5	144.5 ± 1.4	2.2*
Interorbital width	23.0 ± 4.0	23.1 ± 0.6	-0.3
Face width	132.0 ± 2.0	117.5 ± 1.8	2.7**
ANS to S.V.	67.0 ± 1.5	70.4 ± 1.0	-1.6
A-pt. to S.V.	64.2 ± 0.9	67.8 ± 0.6	-2.7**
Sp to S.V.	63.7 ± 1.1	68.5 ± 1.0	-2.4*
Mandibular Length	63.3 ± 2.0	63.3 ± 1.1	-0.02
Anterior mandibular height	29.32 ± 1.3	26.04± 0.6	2.3*
Total facial height	113.8 ± 1.6	108.6 ± 1.8	1.4
Maxillary height	8.99 ± 0.7	10.13± 0.7	-0.8
Upper facial height/ Lower facial height	0.8 ± 0.03	0.8 ± 0.02	-1.1
Posterior facial height/ Anterior facial height	0.6 ± 0.02	0.6 ± 0.01	1.3
Maxillary length/ Mandibular length	0.75 ± 0.00	0.74± 0.00	0.2
Cranial flexure angle	133.0 ± 2.4	132.1 ± 1.0	0.3
Maxilla to cranial base <SNA	79.3 ± 1.8	80.2 ± 0.62	-0.6
Mandible to cranial base <SNB	75.0 ± 1.6	75.5 ± 0.7	-0.3
Mandible to cranial base <SNPg	74.8 ± 1.6	75.3 ± 0.6	-0.3
Mandibular angle	125.8 ± 1.9	127.1 ± 1.2	-0.5

* Significant at p=0.05. ** Significant at p=0.01

Table No. IV 9: The descriptive statistical results in Group II

Group II

Physical Parameter	Cases ($\bar{X}\pm SE$) (N=7)	Control ($\bar{X}\pm SE$) (N=13)	t-test value
OFC	54.5 ± 0.545	54.538 ± 0.386	0.00
Head Length	17.35 ± 0.45	17.884 ± 0.213	-1.07
Head breadth	14.08 ± 0.30	13.692 ± 0.165	+1.07
Ear Length	6.314± 0.137	5.731 ± 0.084	+1.14
Ear breadth	3.983± 0.170	3.054 ± 0.595	+1.50
Palatal height	1.6 ± 0.107	1.3 ± 0.0747	+2.30*
Palatal width	3.23 ± 0.102	3.4 ± 0.103	-1.17
Palatal index	50.039± 3.943	39.129 ± 3.372	+2.17*
Palatal length	2.5 ± 0.057	2.5 ± 0.158	0.00

Radiographic Parameter	cases (X+S.E.) (N=5)	Control cases (X+S.E.) (N=16)	t-test value
Maximum head width	153.0 ± 6.3	145.8 ± 1.6	1.7
Interorbital width	26.7 ± 0.3	25.8 ± 0.5	0.9
Face width	131.7 ± 2.3	126.7 ± 2.1	1.1
ANS to S.V.	75.1 ± 1.4	75.6 ± 1.0	-0.3
Apt to S.V.	72.0 ± 1.0	72.1 ± 1.8	-0.08
Sp to S.V.	76.0 ± 2.5	75.5 ± 1.3	0.2
Mandibular length	74.6 ± 4.7	74.1 ± 1.6	0.1
Anterior mandibular height	32.8 ± 1.8	33.0 ± 1.3	-0.1
Total facial height	125.7 ± 2.9	122.6 ± 1.6	0.9
Maxillary height	13.1 ± 2.2	12.3 ± 0.8	0.4
Upper facial height	0.8 ± 0.0	0.8 ± 0.0	0.9
Lower facial height			
Posterior facial height	0.6 ± 0.0	0.6 ± 0.0	0.3
Anterior facial height			
Maxillary length	0.7 ± 0.0	0.7 ± 0.0	-1.2
Mandibular length			
Cranial flexure angle	133.1 ± 4.9	131.2 ± 1.6	0.5
Maxilla to cranial base SNA	82.2 ± 2.5	82.2 ± 1.6	0.0
Mandible to cranial base <SNB	78.1 ± 2.0	78.8 ± 1.3	-0.3
Mandible to cranial base <SNPg	79.4 ± 1.9	80.0 ± 1.0	-0.3
Mandibular angle (gonial)	125.8 ± 1.9	127.1 ± 1.3	-0.5

* Significant at p=0.05.

Table IV 10: The descriptive statistical results in Group III

Group III

Physical Parameter	Cases Group (X±SE) (N=6)	Control (X±SE) (N=9)	t-test value
OFC	55.75 ± 0.443	56.666 ± 1.803	-1.23
Head length	18.95 ± 0.351	18.222 ± 0.223	0.92
Head beadth	13.98 ± 0.347	13.444 ± 0.1	1.50
Ear length	6.183± 0.094	5.91 ± 0.091	1.19
Ear breadth	3.666± 0.160	3.189 ± 0.087	2.82*
Palatal height	1.7 ± 0.05	1.56 ± 0.063	1.74
Palatal width	3.02 ± 0.121	3.19 ± 0.063	-1.25
Palatal index	55.897± 2.554	52.47 ± 3.92	0.732
Palatal length	2.32 ± 0.056	2.35 ± 0.109	-0.179

Radiographic Parameter	cases (X+S.E) (N=7)	Control (X+S.E.) (N=10)	t-test value
Maximum head width	152.2 ± 6.8	145.0 ± 2.8	1.1
Interorbital width	28.2 ± 2.3	26.7 ± 0.6	0.6
Face width	135.0 ± 1.3	127.5 ± 2.6	2.4*
ANS to S.V.	77.9 ± 1.0	28.2 ± 1.9	-0.1
Apt to S.V.	71.7 ± 2.0	73.8 ± 2.0	-0.7
Sp to S.V.	77.7 ± 1.4	77.5 ± 2.4	0.1
Mandibular length	79.7 ± 1.6	80.0 ± 1.7	-0.4
Anterior mandibular height	36.5 ± 1.5	33.2 ± 1.0	2.0*
Total facial height	137.5 ± 2.6	130.2 ± 3.0	1.6
Maxillary height	13.5 ± 0.1	13.5 ± 0.7	-0.1
Upper facial height/ Lower facial height	0.8 ± 0.0	0.8 ± 0.0	-1.2
Posterior facial height/ Anterior facial height	0.7 ± 0.0	0.7 ± 0.0	-0.6
Maxillary length/ Mandibular length	0.7 ± 0.0	0.7 ± 0.0	1.2
Cranial flexure angle	132.4 ± 1.7	132.1 ± 2.1	0.1
Maxilla to cranial base SNA	79.5 ± 1.4	80.5 ± 2.3	-0.3
Mandible to cranual base ‹SNB	77.0 ± 1.8	78.4 ± 1.9	-0.5
Mandible to cranual base ‹SNPg	78.3 ± 1.4	80.0 ± 1.8	-0.7
Mandibular angle	126.2 ± 2.0	121.0 ± 1.9	1.8

* Significant at p=0.05

Table IV.8, Table IV.9, Table IV.10 and Table IV.11 show the descriptive statistical results in different groups.

Group I (age 6-10 years):

Table IV 8 shows the means, standard errors, t-test values of the physical and radiographic parameters of affected cases and controls in group I.

The means of the cases are significantly higher than those of the controls except the palatal width and length which are lower than those of the controls.

The differences in head breadth , ear breadth and palatal index are statistically significant.

The means of the maximum head width, face width, anterior mandibular height of the cases are significantly larger than those of the controls. The means of the total facial height, the posterior/anterior facial height and the maxillary/mandibular length ratios and the cranial flexure angle are insignificantly larger than those of the control. The means of the cases of the remaining parameters are lower than those of the control. However, only the differences between the means of the A-point to Sella Vertical and Supradentale to Sella Vertical were significantly smaller.

Group II (age 13-16 years):

Table IV 9 shows the means and standard errors of the physical and radiographic parameters of cases and controls and the t-test values of group II.

The means of the cases are higher than those of the controls except the palatal width which is lower than that of the control. The difference in palatal height is statistically significant.

The means of the cases are insignificantly larger than those of the controls except the parameters ANS to SV, A-point to SV, anterior mandibular height, the ratio of maxillary length to mandibular length and the angles SNB, SNPg and gonial angle which are in significantly lower than those of the controls.

Group III (age 17-22 years):

Table IV 10 shows the means, standard errors and t-test values of the physical and radiographic parameters of affected cases and controls.

The means of the affected cases are higher than those of the control except the head circumference, palatal width and palatal length which are lower than those of the controls. The differences in ear breadth is statistically significantly greater.

The means of the face width and anterial mardibular height significantly larger than those of the controls. The means of the mandibular (gonial) angle, maximum head width, interorbital width, supradentale to S. V., total facial height and maxillary / mandibular length ratio are in significantly larger than those of the controls.

The means of the affected cases of, the remaining parameters are insignificantly lower than those of the controls.

Group IV (Mothers of Affected males):

Table IV 11 also shows the means, standard errors and t-test valuues of the raddiographic cephalometry of mothers of affected cases and control females.

The means of the cases are higher than those of the controls except in the head circumference, ear breadth, palatal index and palatal length which are lower than the controls. The difference in ear length is statistically significant.

The means of the ANS to S.V.,A-point to S.V., SP to SV., maxillary height, posterior/anterior facial height ratio, maxillary/mandulular length ratio, maxilla to cranial base

maxillary/mandulular length ratio, maxilla to cranial base ‹SNA, mandible to cranial base ‹SNB, & ‹SNPg and mandibular (gonial) angle are larger than those of the controls. However only the difference between the means of the maxillary height, maxillary/mandibular length ratio, maxilla to cranial base, ‹SNA, and mandible to cranial base, ‹SNB, are significant.

The means of the interorbital width, face width, mandibular length, anterior mandibular height, total facial height, upper/lower facial height and cranial flexure angle are lower than those of the controls. However only the differences between the means of the face width is significantly lower.

Table IV 11: The descriptive statistical results in Group IV

Groupt IV (Mothers)

Physical Parameter	Carrier ♀(N=10) ($\bar{X}$ ± SE)	Normal ♀(N=13) ($\bar{X}$ ± SE)	t-test
OFC	55.269 ± 0.489	55.40 ± 0.452	-0.20
Head length	17.885 ± 0.273	17.260± 0.156	+0.080
Head breadth	13.638 ± 0.213	13.520± 0.195	+0.41
Ear length	6.108 ± 0.083	5.680± 0.137	+2.70*
Ear breadth	3.285 ± 0.080	3.320± 0.083	-0.30
Palatel height	1.533 ± 0.059	1.50 ± 0.105	+0.28
Palatal width	3.40 ± 0.0788	3.35 ± 0.122	+0.06
Palatal index	46.789 ± 2.421	48.446± 4.23	-0.68
Palatal length	2.4 ± 0.105	2.55 ± 0.027	-1.39
Maximum head width	143.6 ± 1.4	146.0 ± 1.8	-0.9
Interorbital width	23.5 ± 0.9	25.9 ± 0.8	-1.9
Face width	127.3 ± 2.1	132.8 ± 1.1	-2.5*
ANS to S.V.	78.8 ± 1.1	75.3 ± 1.4	-1.9
A-pt to S.V.	74.4 ± 1.2	71.5 ± 1.5	1.5
Sp to S.V.	78.1 ± 1.6	74.5 ± 1.7	1.6
Mandibular length	76.2 ± 1.6	76.3 ± 1.5	-0.1
Anterior mandibular height	33.2 ± 0.9	33.5 ± 1.0	-0.3
Total facial height	123.8 ± 1.6	124.6 ± 1.8	-0.4
Maxillary height	16.2 ± 0.5	13.9 ± 0.7	2.7
Upper facial height/ Lower facial height	0.8 ± 0.0	0.8 ± 0.0	-1.4
Posterior facial height/ Anterior facial height	0.6 ± 0.0	0.6 ± 0.0	1.3
Maxillary length/ Mandibular length	0.7 ± 0.0	0.7 ± 0.0	2.0*
Cranial flexure angle	134.4 ± 1.8	137.3 ± 1.4	-1.3
Maxilla to cranial base <SNA	82.8 ± 0.8	77.7 ± 1.6	2.7**
Mandible to cranial base <SNB	78.6 ± 1.1	74.8 ± 1.3	2.2*
Mandible to cranial base <SNPg	78.9 ± 1.3	76.7 ± 1.3	1.2
Mandibular angle	122.1 ± 1.8	121.5 ± 1.5	0.2

* Significant at p=0.05
** Significant at p=0.01

Table IV 12 summarizing the results of cephalometry, the t-test values for all the parameters in the four groups: Group I, II and III for affected males and group IV for their mothers.

The significant parameters for physical cephalometry were:

In group I:

Head breadth, ear breadth and palatal index are significantly larger than their matchable controls.

In group II:

Palatal height and palatal index are significantly larger than their matchable controls.

In group III:

Ear breadth is significantly larger than their matchable controls.

In group IV

Ear length is significantly larger than their matchable controls.

The significant parameters for radiographic cephalometry:

In group I:

The maximum head width (Eu-Eu), and the face width (Zy-$\overline{Zy}$) and the anterior mandibular height (Id - Me) are

significantly larger than their matchable controls. The facial depths A point to Sella Vertical and Supradentale to Sella Vertical were significantly smaller than their matchable controls.

In group II:

No significant parameters.

In group III:

The face width Zy-Zy and anterior mondibular heiht are significantly larger than their matchable controls.

In group IV:

The maxillary height (Sp-A-point) and <SNA (between the maxilla and cranial base) and <SNB (between mandible and cranial base) significantly larger than their matchable controls. The face width (Zy-Zy) is significantly smaller than their matchable controls.

Table IV 12 : T-test values for Physical cephalometry in the different groups.

Parameter	Group I	Group II	Group III	Group IV
OFC	1.0	0.0	-1.23	0.20
Head length	1.18	-1.07	0.82	0.08
Head breadth	2.28*	1.07	1.5	0.41
Ear length	1.62	1.14	1.19	2.7 *
Ear breadth	2.4 *	1.50	2.82*	-0.30
Palatal height	1.94	2.3 *	1.74	-0.28
Palatal width	-0.90	-1.17	-1.25	0.06
Palatal index	2.82*	2.17*	0.73	-0.68
Palatal length	-0.95	0.00	-0.179	-1.39
Max head width	2.2 *	1.7	1.1	-0.9
Interorbital width	-0.3	0.9	0.6	-1.9
Face width	2.7 **	1.1	2.4 *	-2.5 *
ANS to S.V.	-1.6	-0.3	-0.1	1.9
Apt to S.V.	-2.7 **	-0.08	-0.7	1.5
Sp to S.V.	-2.4 *	0.2	0.1	1.6
Mandibular length	-0.2	0.1	-0.4	-0.1
Ant. mand. height	2.3 *	-0.1	2.0 *	-0.3
Total facial height	1.4	0.9	1.6	-0.4
Maxillary height	-0.8	0.4	-0.1	2.7 **
Upper/Lower facial height	-1.1	0.9	-1.2	-1.4
Posterior/Ant facial height	1.3	0.3	-0.6	1.3
Maxillary/Mand. length	0.2	-1.2	1.2	2.0 *
Cranial flexure angle	0.3	0.5	0.1	-1.3
<SNA	-0.6	0.0	-0.3	2.7 **
<SNB	-0.3	-0.3	-0.5	2.2 *
<SNPg	-0.3	-0.3	-0.7	1.2
Mandibuler angle	-0.5	-0.5	1.8	0.2

* Significant at P = 0.05
** Significant at P = 0.01

Results of Anthropometry in the Fragile X sample

One of the objectives of this study was to identify specific measurements that may help in the diagnosis of the fragile (X) syndrome. Another objective was to detect any possible similarities between the affected sons and their carrier mothers. To elucidate these objectives, statistical tests, namely t-test and comparative z-score analysis were performed.

T-test results of cephalometric measurements in the studied groups are summarized in Table IV.12.

Significant measurements in group I (6-10 years old males):

1- Head breadth increased significantly at p-value=0.05
2- Ear breadth increased significantly at p-value=0.05.
3- Palatal index increased significantly at p-value= 0.01
4- Maximum head width (HW) significantly increased at p-value = 0.05.
5- A- point to sella vertical(AS) decreased significantly at p-value=0.01
6- Face width (ZY) increased significantly at p-value =0.01
7- Sp to sella vertical (SS) significantly decreased at p-value = 0.05
8- Anterior mandibular height (AM) significantly increased at p-value=0.05

Significant measurements in group II (13-16 years old males)

1- Palatal height significantly increased at p-value =0.05

2- Palatal index significantly increased at p-value =0.05

Significant measurements in group III(17-22 years old males)

1- Ear breadth significantly increased at p-value=0.01

2- Face width(Zy) significantly increased at p-value=0.05

3- Anterior mandibular height(AM) significantly increased at p-value = 0.05

Significant measurements in group IV (adult female obligate carriers):

1- Ear length increased significantly increased at p-value=0.01

2- Maxillary height (XH) increased significantly at p-value = 0.01

3- <SNA between maxilla and cranial base (XB) increased significantly at p-value=0.01

4- Face width (ZY) decreased significantly at p-value =0.05

5- <SNB between mandible and cranial base(NB) increased significantly at p-value =0.05

6- Maxillary length to mandibular length (XN) increased significantly at p-value=0.05

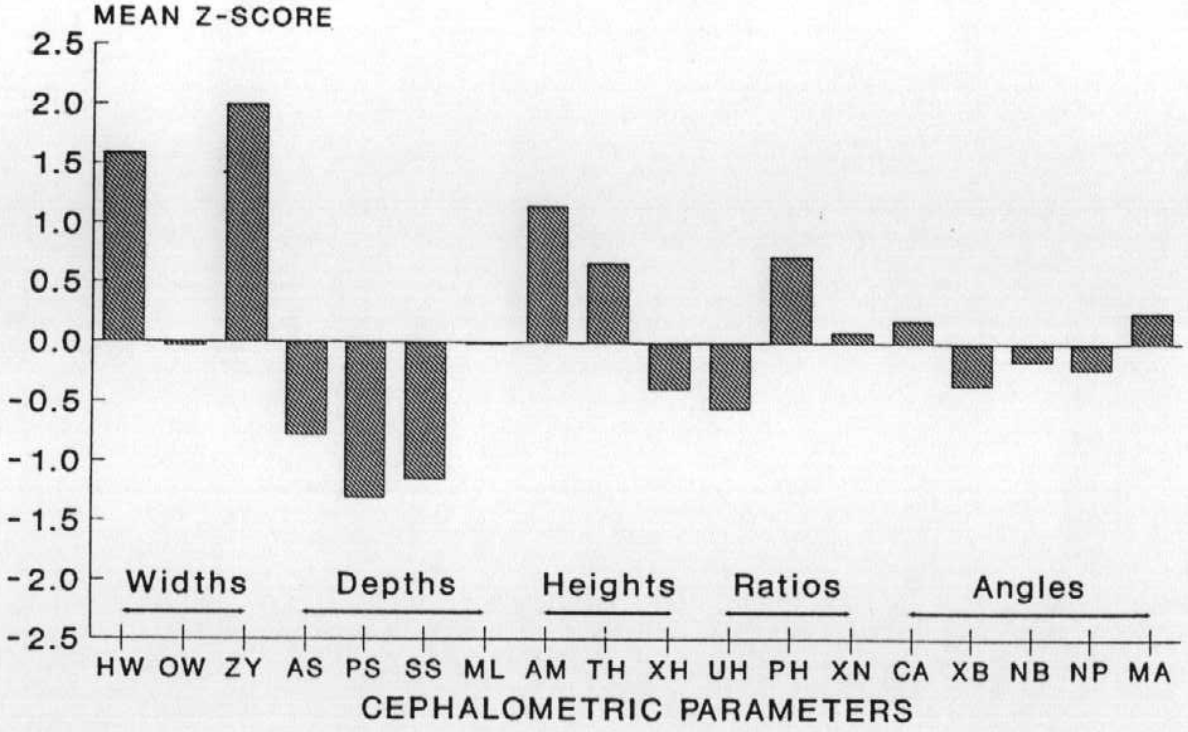
Table IV.13 : Palatal heights of the affected cases and the mean, standard deviation and range of the palatal height of the control groups.

Group I		Group II		Group III	
Case	Palatal Height	Case	Palatal Height	Case	Palatal Height
P4 - 010	1.2	P1 - 001	1.4	P4 - 011	1.6
P8 - 024	1.4*	P2 - 004	1.4	P4 - 012	1.6
P9 - 026	1.2	P2 - 005	1.9*	P5 - 015	1.7
P11- 033	1.4*	P6 - 019	1.9*	P12- 035	1.8
P20- 059	1.4*	P7 - 022	1.7*	P3 - 007	1.9
		P22- 063	1.8*	P3 - 008	1.8
		P22- 064	1.1	P11- 030	1.5
$\bar{X}$ = 1.143		$\bar{X}$ = 1.3		$\bar{X}$ = 1.56	
SD = 0.0191		SD = 0.167		SD = 0.221	
Range = 1.105-1.2		Range = 0.96-1.64		Range = 1.12-2.0	

* Denotes high arched palate
$\bar{X}$ mean of control
SD Standard deviation of control

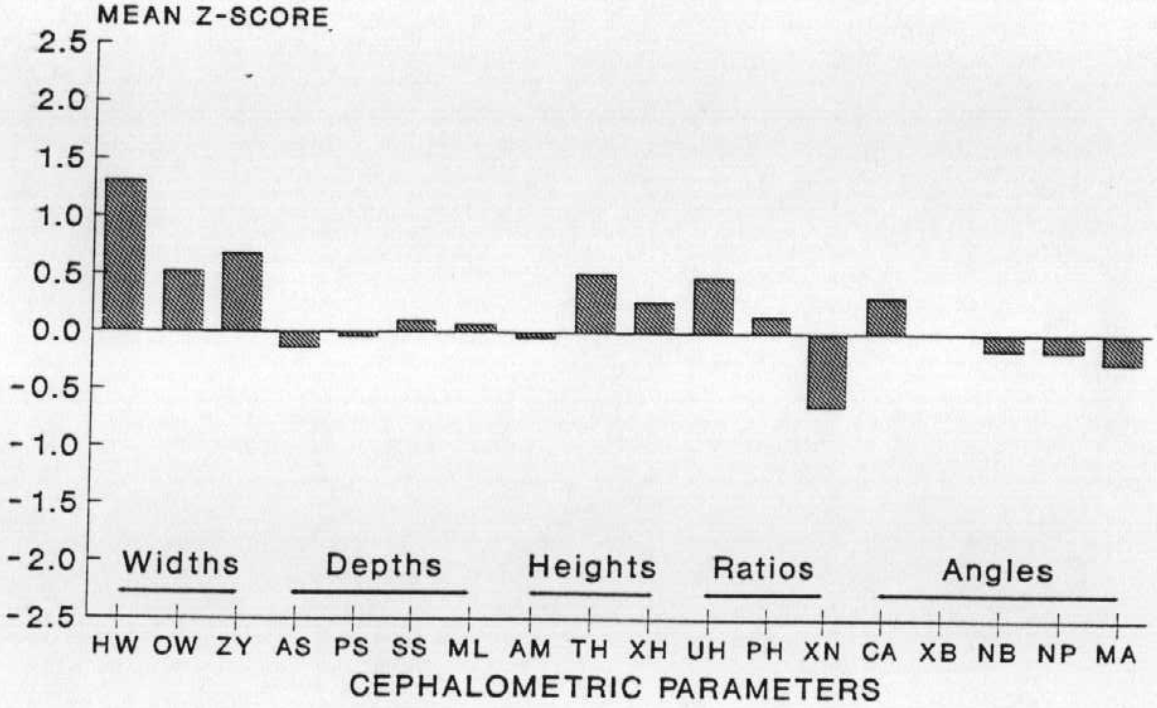
Table IV 13. Shows the values of the palatal height in c.m. Seven cases out of nineteen cases are above the upper limit of the normal range. Thus the percentage of high arched palate in the cases is 36.84 %.

Figure IV.1 Craniofacial pattern profile of group I.



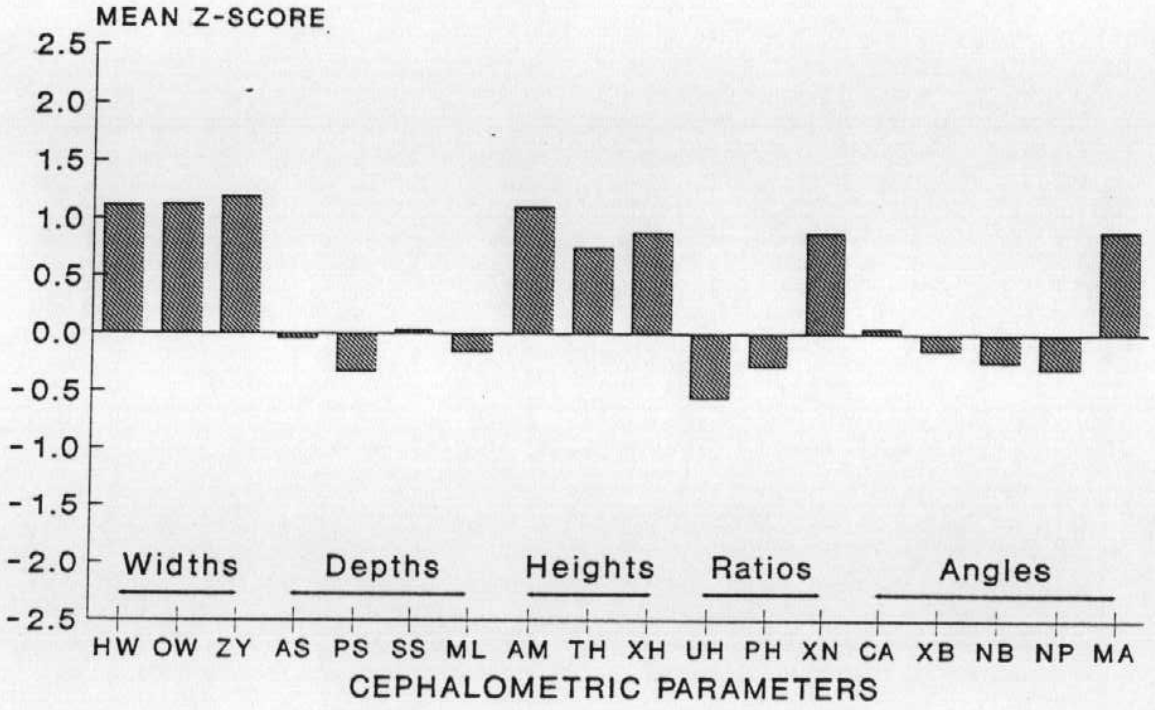
Skull:HW,CA
Mandible:ML,AM,MA
Face:OW,ZY,AS,PS,SS,TH,XH,UH,XN,XB,NB,NP

Figure IV.2 Craniofacial pattern profile of group II.



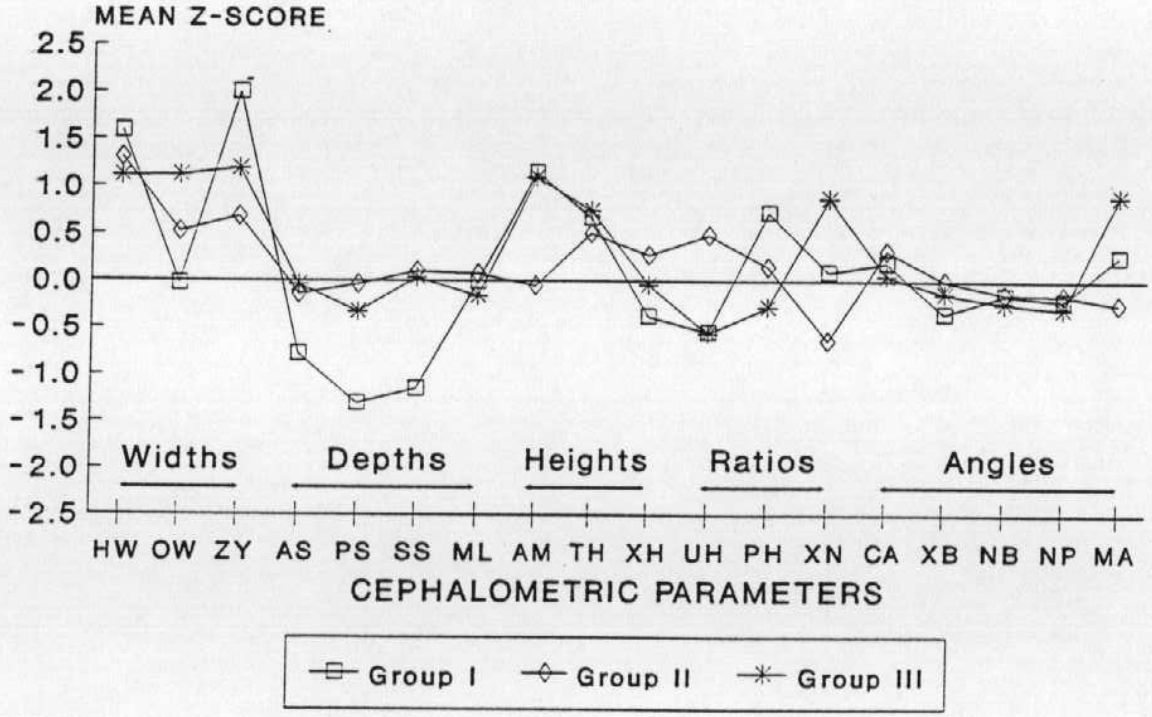
Skull:HW,CA
Mandible:ML,AM,MA
Face:OW,ZY,AS,PS,SS,TH,XH,UH,XN,XB,NB,NP

Figure IV.3 Craniofacial pattern profile of group III.



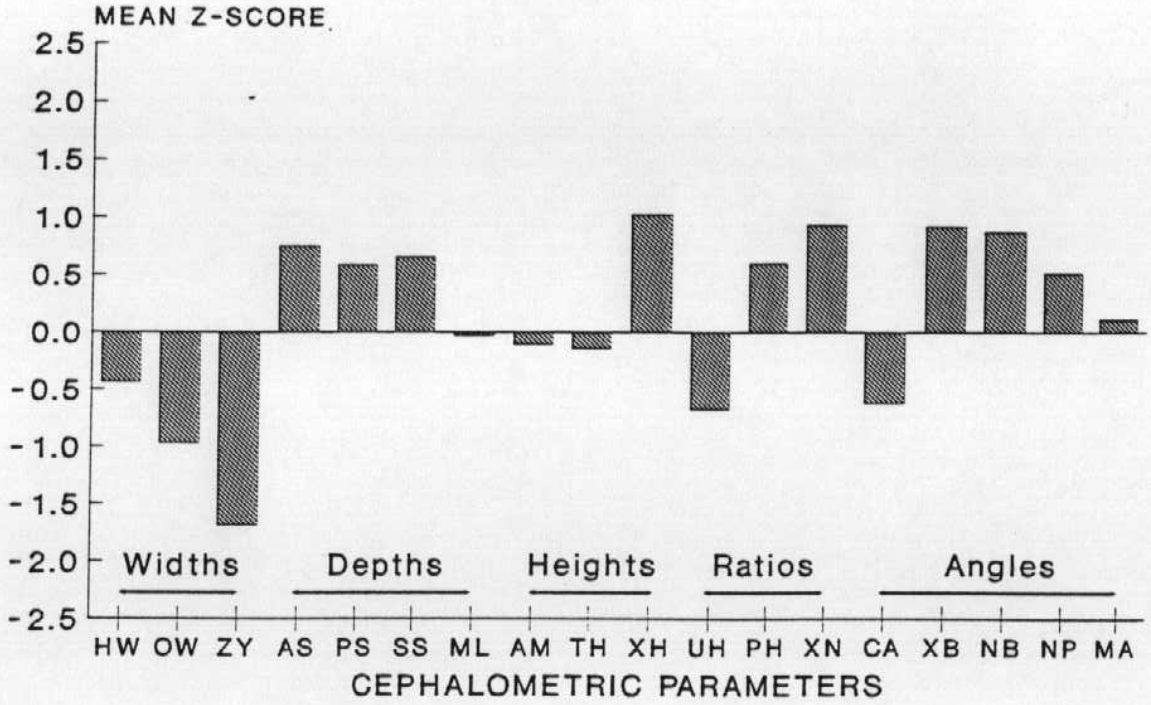
Skull:HW,CA
Mandible:ML,AM,MA
Face:OW,ZY,AS,PS,SS,TH,XH,UH,XN,XB,NB,NP

Figure IV.4 Craniofacial pattern profile by groups.



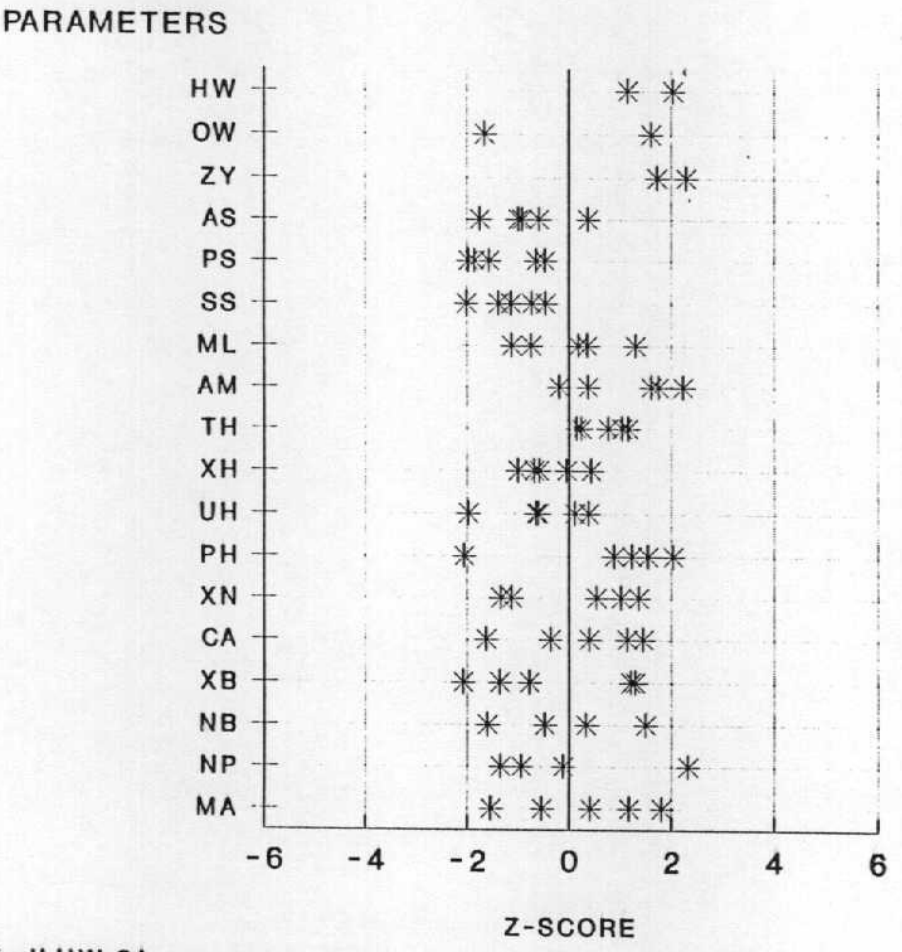
Skull:HW,CA
Mandible:ML,AM,MA
Face:OW,ZY,AS,PS,SS,TH,XH,UH,XN,XB,NB,NP

Figure IV.5 Craniofacial pattern profile of group IV.



Skull:HW,CA
Mandible:ML,AM,MA
Face:OW,ZY,AS,PS,SS,TH,XH,UH,XN,XB,NB,NP

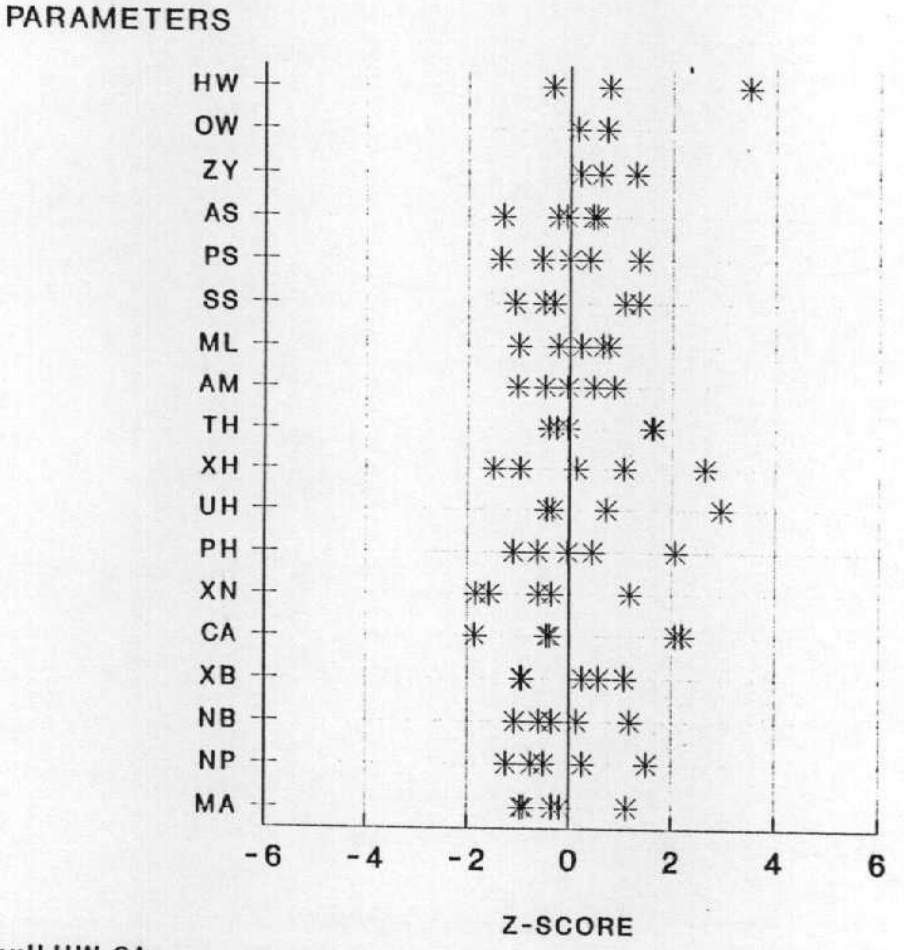
Figure IV.6 Scatter diagram of z-scores of radiographic cephalometric parameters of group I.



Skull:HW,CA
Mandible:ML,AM,MA
Face:OW,ZY,AS,PS,SS,TH,XH,UH,XN,XB,NB,NP

z-score 0 = x of controls

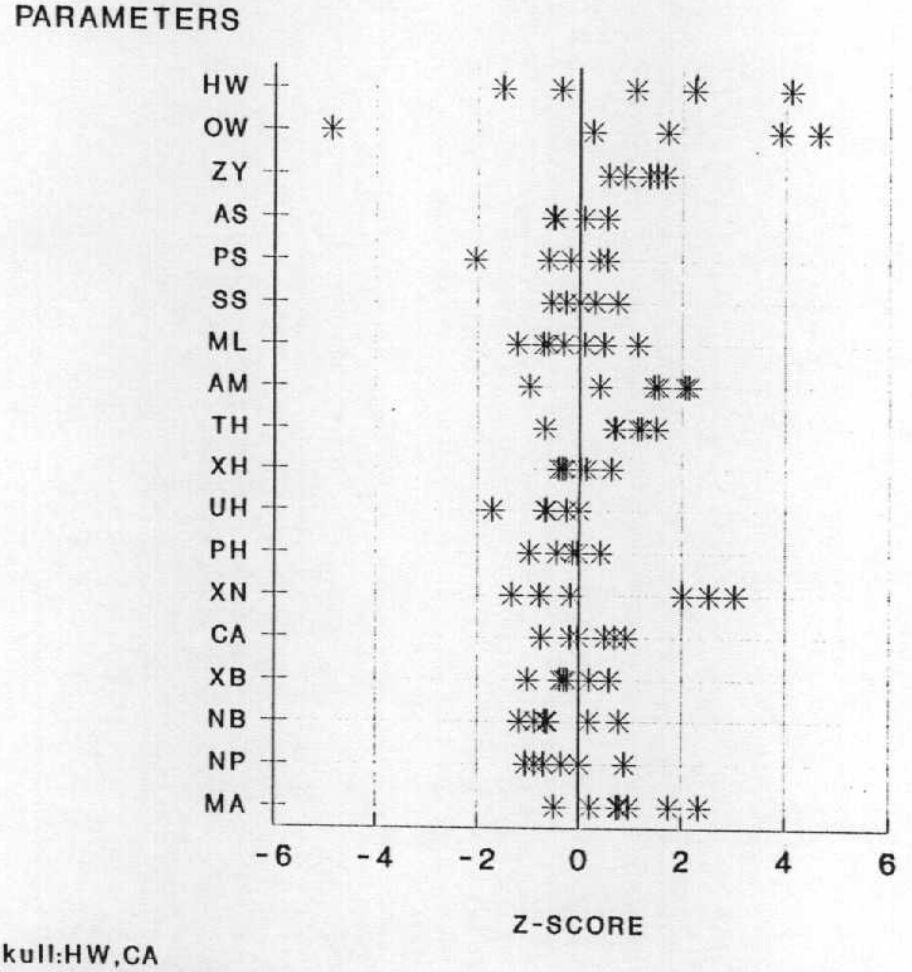
Figure IV.7 Scatter diagram of z-scores of radiographic cephalometric parameters of group II.



Skull:HW,CA
Mandible:ML,AM,MA
Face:OW,ZY,AS,PS,SS,TH,XH,UH,XN,XB,NB,NP

z-score 0 ▪ x of controls

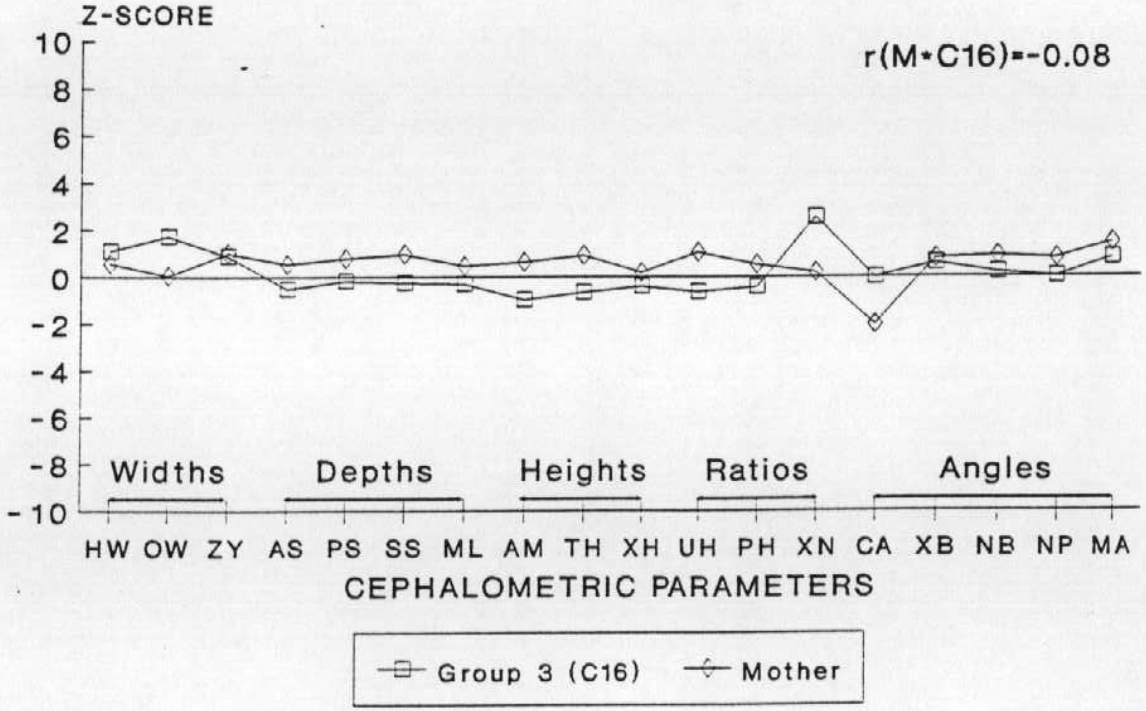
Figure IV.8 Scatter diagram of z-scores of radiographic cephalometric parameters of group III.



Skull:HW,CA
Mandible:ML,AM,MA
Face:OW,ZY,AS,PS,SS,TH,XH,UH,XN,XB,NB,NP

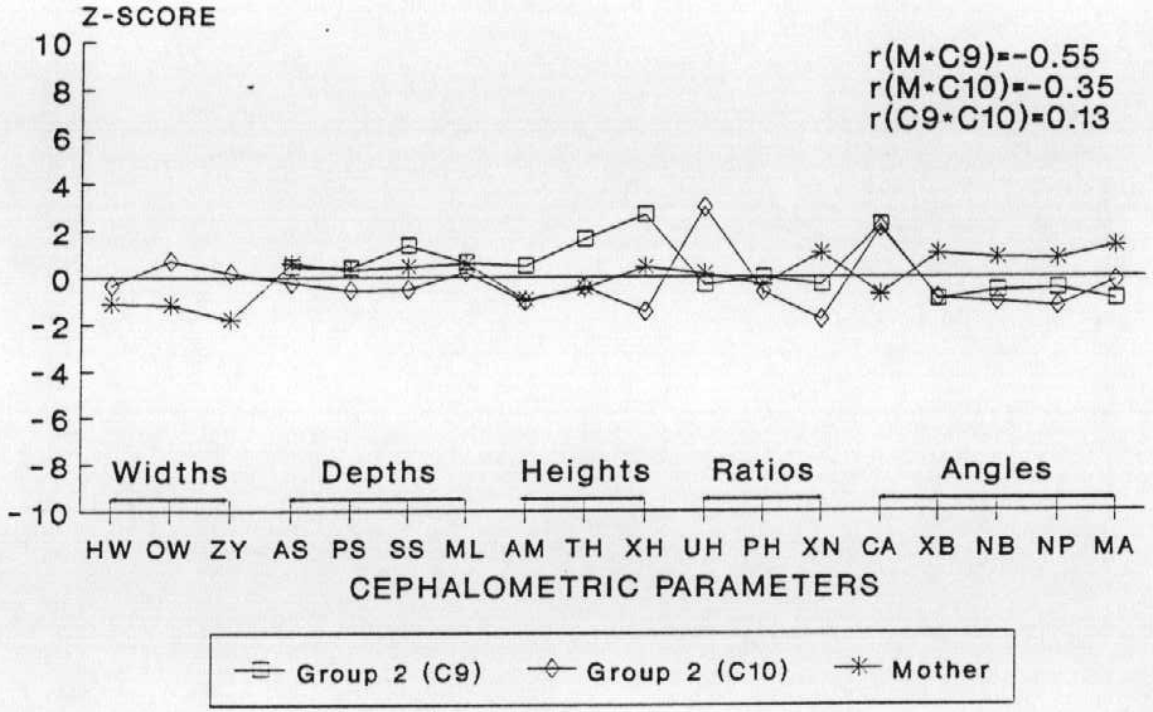
z-score 0 ▪ x of controls

Figure IV.9 Craniofacial pattern profile of mother and offsprings



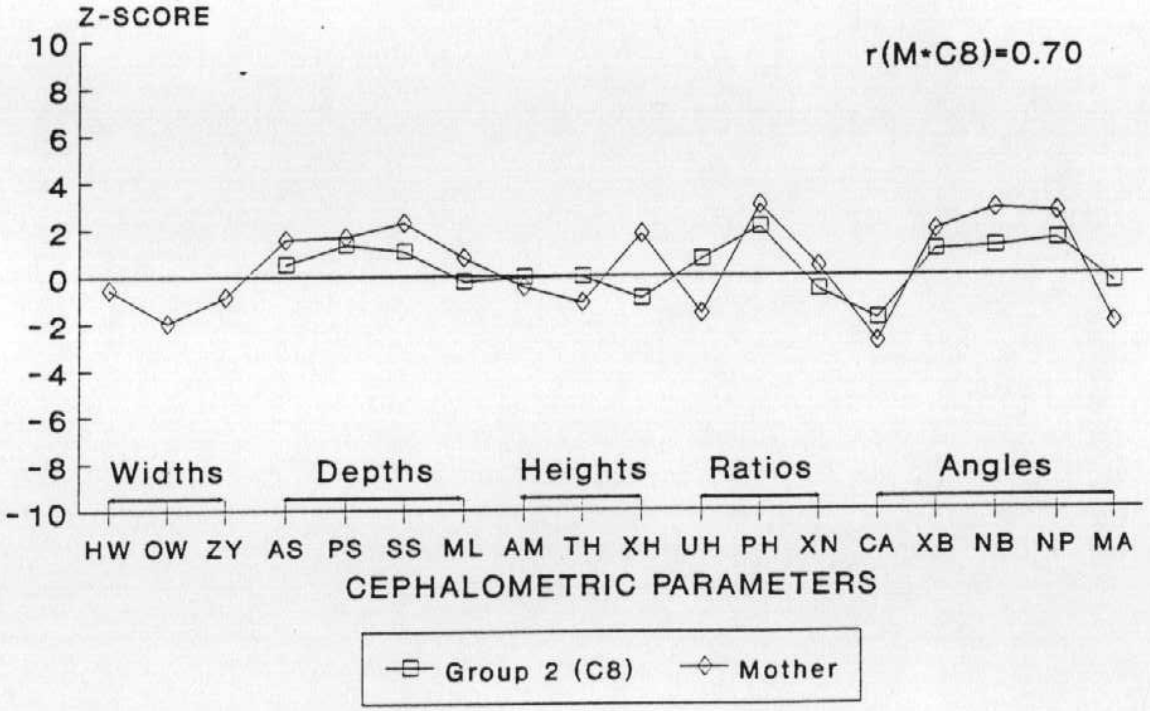
Skull:HW,CA
Mandible:ML,AM,MA
Face:OW,ZY,AS,PS,SS,TH,XH,UH,XN,XB,NB,NP

Figure IV.10 Craniofacial pattern profile of mother and offsprings



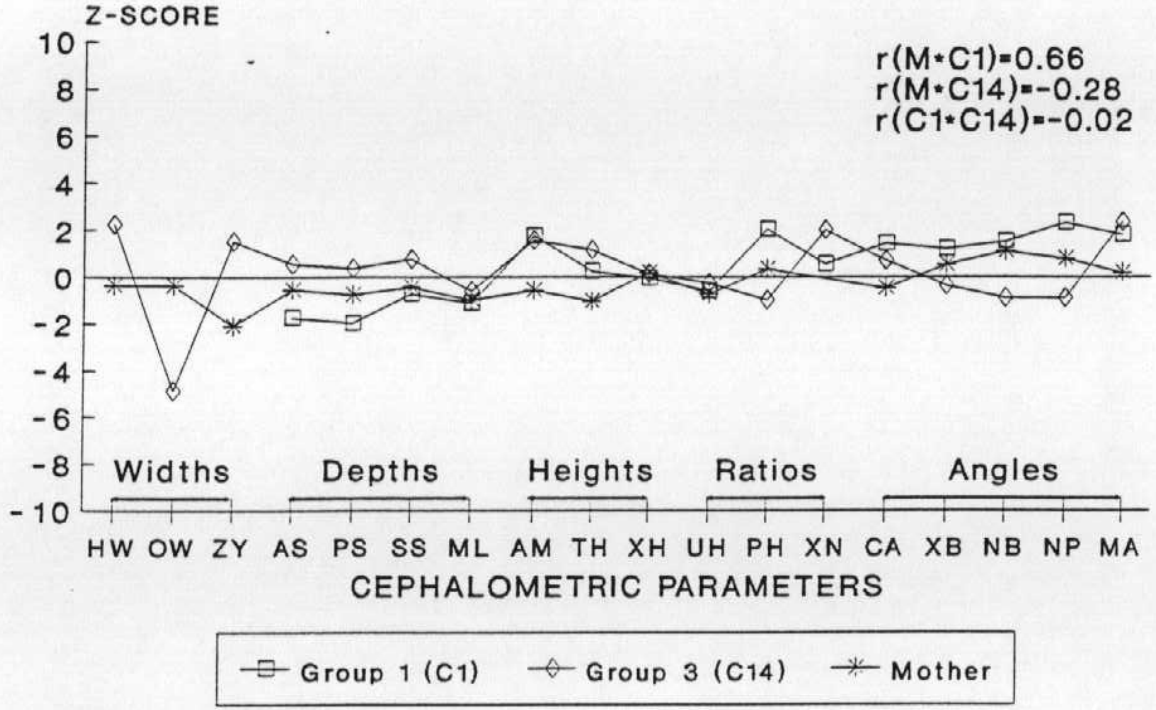
Skull:HW,CA
Mandible:ML,AM,MA
Face:OW,ZY,AS,PS,SS,TH,XH,UH,XN,XB,NB,NP

Figure IV.11 Craniofacial pattern profile of mother and offsprings



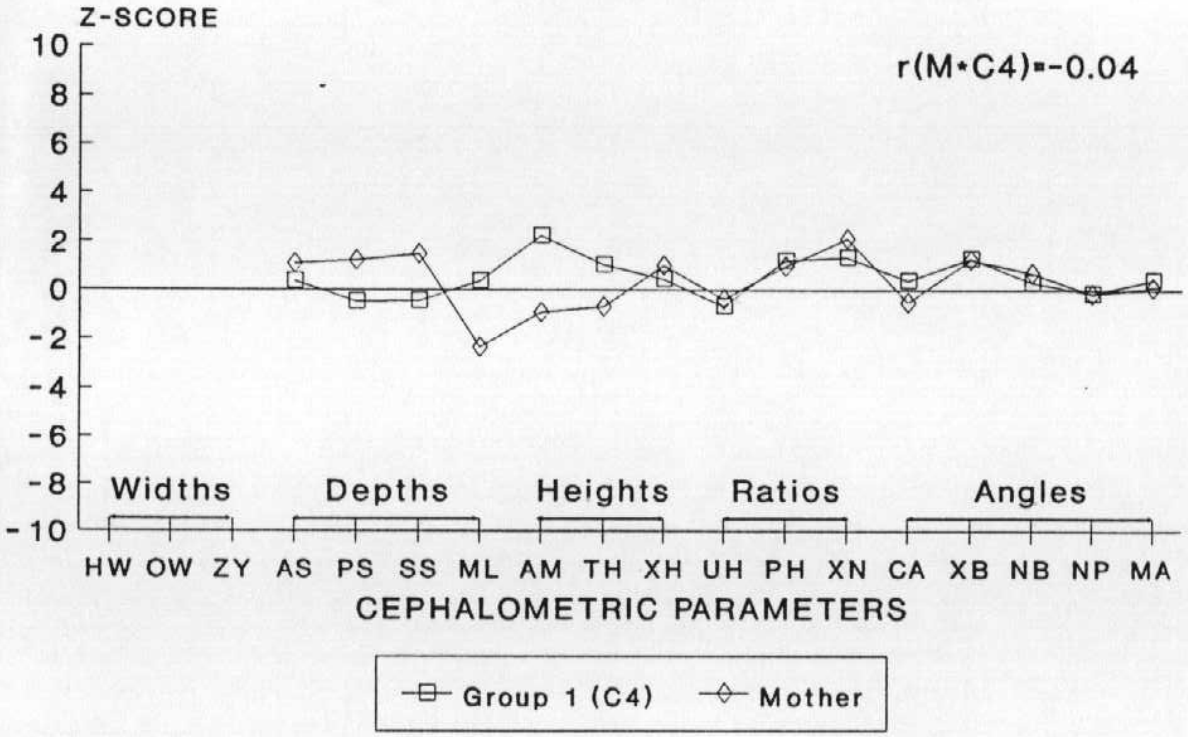
Skull:HW,CA
Mandible:ML,AM,MA
Face:OW,ZY,AS,PS,SS,TH,XH,UH,XN,XB,NB,NP

Figure IV.12 Craniofacial pattern profile of mother and offsprings



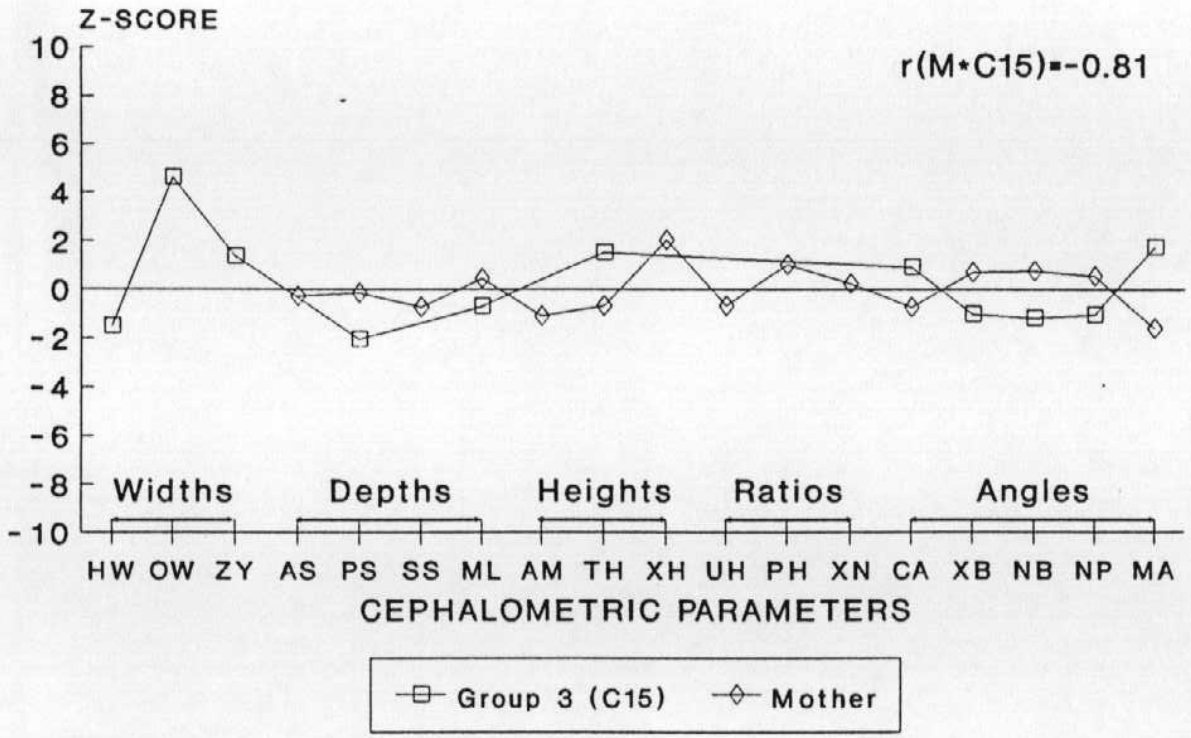
Skull:HW,CA
Mandible:ML,AM,MA
Face:OW,ZY,AS,PS,SS,TH,XH,UH,XN,XB,NB,NP

Figure IV.13 Craniofacial pattern profile of mother and offsprings



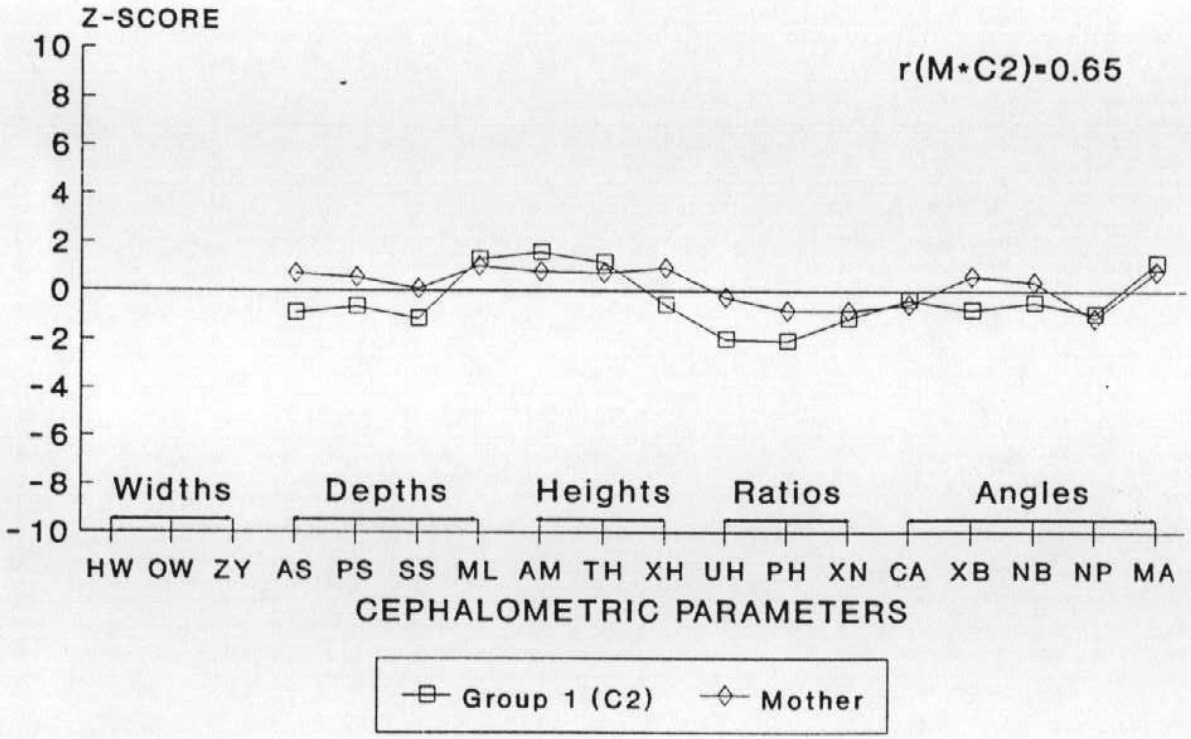
Skull:HW,CA
Mandible:ML,AM,MA
Face:OW,ZY,AS,PS,SS,TH,XH,UH,XN,XB,NB,NP

Figure IV.14 Craniofacial pattern profile of mother and offsprings



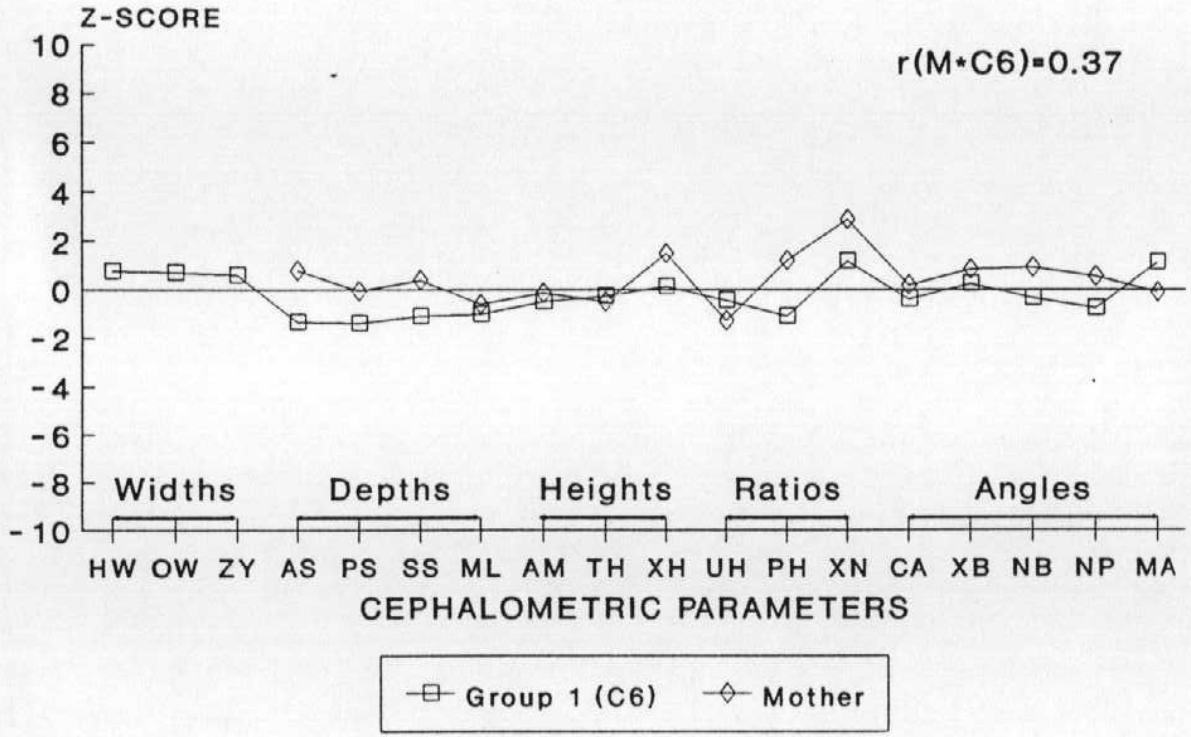
Skull:HW,CA
Mandible:ML,AM,MA
Face:OW,ZY,AS,PS,SS,TH,XH,UH,XN,XB,NB,NP

Figure IV.15 Craniofacial pattern profile of mother and offsprings



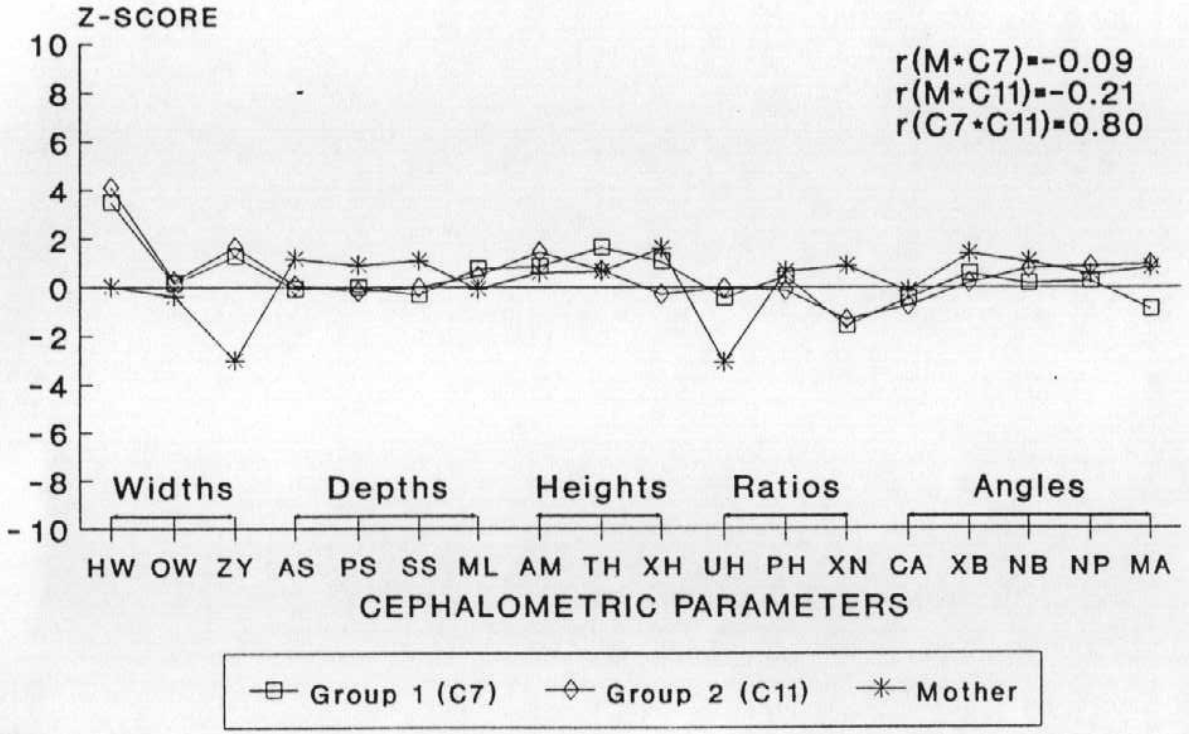
Skull:HW,CA
Mandible:ML,AM,MA
Face:OW,ZY,AS,PS,SS,TH,XH,UH,XN,XB,NB,NP

Figure IV.16 Craniofacial pattern profile of mother and offsprings



Skull:HW,CA
Mandible:ML,AM,MA
Face:OW,ZY,AS,PS,SS,TH,XH,UH,XN,XB,NB,NP

Figure IV.17 Craniofacial pattern profile of mother and offsprings



Skull:HW,CA
Mandible:ML,AM,MA
Face:OW,ZY,AS,PS,SS,TH,XH,UH,XN,XB,NB,NP

Results of Craniofacial Pattein Profile (CFPP):

CFPP in group I (6-10 years old) Fig. IV 1

The maximum head width HW and face width ZY are increased in affected ssubjects as shown by positive z-scores reaching 1.5 SD. The interorbital width OW is around the mean.

The facial depths AS, PS and SS are decreased in affected subjects than their matchable control sample as shown by negative z-score.

The mandibular length ML is around the mean.

The anterior mandibular height AM and the total facial height TM are increased in the affected subjects than their control sample as shown by positive z-scores. The maxillary height XH is around the mean.

The ratio UH between upper facial height and lower facial height are decreased as shown by negative z-score. The ratio PH between the posterior facial height and the anterior facial height is increased i.e. there is a difference in the differential growth between the upper and lower height and the posterior and anterior facial height. The ratio XN between the maxillary length to the mandibular length is around the mean.

The cranial flexure angle CA is more obtuse in the affected subjects as shown by positive z-score. The angles XB, NB and NP are decreased in affected subjects as shown by negative z-score especially in angle XB i.e. the maxilla is more retrusive in affected subjects. The mandibular angle MA is slightly increased as shown by positive z-score.

CFPP in group II (13-16 years old):

In fig IV 2, the maximum head width HW is increased in affected subjects at age group II. The face width ZY and interorbital width OW are also increased as shown by positivee z-score.

The facial depths (AS, PS and SS) are around the mean.

The mandibular length ML is also around the mean.

The anterior mandibular height AM is around the mean. The maxillary height XH is slightly increased in affected subjects as shown by positive z-score.

The ratio UH between the upper and lower facial height is increased and the ratio PH between the posterior facial height and anterior facial height is slightly increased i.e. there is a difference in the differential growth rate between the upper and lower facial height and the posterior and anterior facial height. The ratio (XN) between the maxillary and mandibular length is decreased in the affected subjects as shown by negative z-score.

The cranial flexure angle CA is more obtuse in the affected subjects than their control sample. The angles NB and NP, which measure the relative anteroposterior relation between the mandible and cranial base, are more acute in the affected subjects than the control sample. The mandibular angle MA is slightly smaller in the affected subjects.

CFPP in group III (17-22 years old):

In fig. IV 3 the affected subjects show increased maximum head width HW, face width ZY and inter orbital width OW as shown by positive z-score reaching I SD i.e. there is an increase in lateral growth direction in affected subjects of age group III than their matchable control sample.

The facial depths, AS and SS were around the mean and the facial depth PS is slightly decreased in the affected subjects than the control sample.

The mandibular length is slightly decreased also in the affected subjects.

The anterior mandibular height AM is increased in the affected subjects as shown by positive z-score. The total facial height TH is increased and the maxillary height XH is around the mean.

The ratio UH between the upper and lower facial height is decreased as shown by negative z-score and also the ratio PH between the posterior and anterior facial height which may indicate a difference in the differential growth rate between the posterior and anterior facial height and the upper and lower facial height.

The ratio XN between the maxillary length to the mandibular length is increased in the affected subjects.

The cranial flexure angle CA is positive more obtuse in the affected subjects than the control sample. The angles XB, NB and NP are smaller (i.e. more acute) in the affected subjects and the mandibular angle MA is increased in the affected subjects as shown by positive z-score.

CFPP in the 3 affected age groups

In fig. IV 4 the three previous craniofacial pattern profiles are drawn together in one figure for easy comparison

CFPP in group IV (Mothers of affected cases):

In fig. IV 5, the head width HW, face width ZY and the inter orbital width OW are more decreased in affected cases than their matchable control females.

The facial depths AS, PS and SS are increased in affected subjects as shown by positive z-score.

The mandibular length ML was around the mean.

The anterior mandibular height AM and the total facial height TM is around the mean and the maxillary height XM was increased.

The ratio UH between the upper and lower facial height is decreased as shown by negative z-score and the ratio between the posterior facial height and anterior facial height and the maxillary length to mandibular length was increased as shown by positive z-score.

The cranial flexure angle CA is slightly decreased and the angles XB, NB, and NP are increased in the affected subjects. The mandibular angle is around the mean.

Results of Scattered Diagrams

Fig. IV 6 shows the scattered diagram of the z-scores of radiographic cephalometric parameters of group I. All the parameters fall within ± 2SD with few exceptions close to +2SD namely one case in each of the zygomatic width (ZY), anterior mandibular height (AM) and <SNPg (NP).

All the affected cases of group I have positive Z-scores in the parameters head width (HW), zygomatic width (ZY) and total facial height (TH) and negative z-scores in the parameters A-point to S.V (PS) and Supradentale to S.V (SS) All the other parameters show both +ve and -ve z-scores.

Fig. IV 7 shows the scatter diagram of the z-scores of radiographic cephalometric parameters of group II. All the parameters fall within ± 2SD with few exceptions namely one case in each of head width (HW), maxillary height (XH), upper facial height (UH) and cranial flexure angle (CA).

All the affected cases of group II have positive z-scores in the parameters interorbital width(OW) and zygomatic width (ZY) All the other parameters show both +ve and -ve z-scores.

Fig. IV.8 shows the scatter diagram of the z-scores of radiographic cephalometric of group III. All the parameters

fall within ± 2SD with few exceptions namely head width (HW), interorbital width (OW), ratio between maxillary length to mandibular length (XN) and mandibular angle (MA).

All the affected cases of group III have positive z-scores in the parameter zygomatic width (ZY) only.

To conclude all the cases in the three age groups had the parameter zygomatic (ZY) with a positive z-score which denotes increased zygomatic width.

Results of Correlation Analysis on Affected males and their mothers using correlation coefficient statistical test are shown in Figs. IV.9, IV.10, IV.11, IV.12, IV.13, IV.14, IV.15, IV.16 and IV.17.

There are 12 mothers and sibs.

There are three significant positive correlation coefficients i.e. mother and sib have similar trends and two significant negative correlation coefficients i.e. mother and sib have dissimilar trends.

The three positive significant correlation coefficients are between :

mother and case #8. group II fig. IV.11 (r=0.70),

mother and case #1 group I fig. IV.12. (r=0.65)

mother and case 2 group I fig. IV.15. (r=o.65)

The two negative significant correlation coefficients are between :

mother and case # 9 group II (r=-0.55) fig IV.10

mother and case # 15 group III (r=-0.81) (fig. IV.14).

In case # 7 (group I) and # 11 (group III), the mother is dissimilar to similar sibs [r(M*c7)=0.09, r(M*c11)= -0.21 and r(c7*c11)=0.80 fig. IV.17.

In case #9 and #10 (group II), the mother is dissimilar to similar sibs [r(M*c9) = -0.55] [r(M*c10) = -0.35] and [r(c9*c10) = 0.13] fig. IV.10.

In cases #1 (group I) and 14 (group III): the mother is similar to one sib r(M*c1)= 0.66 and dissimilar to the other r(M * c14 = -0.28) and the two sibs are dissimilar r(c1 * c14) = -0.02. fig. IV.12.

There are also three pairs of sibs: one similar (r=0.80) case #7 (group I) & case #11 (group II) fig IV.17, and two dissimilar case #9 and #10 (group II) (r=0.13) fig. IV.10 and case # 1 (group I) and # 14 (group III) (r=-0.02) fig. IV.12

CHAPTER V

D I S C U S S I O N

Fragile X syndrome is the most common inherited cause of mental retardation after trisomy 21. It constitutes 20% of all mental retardation (Opitz and Sutherland, 1984)[17] and 50% of X-linked mental retardation (Opitz, 1986)[18]. It prevails among all races. Most of the affected individuals, males or females, require special education and support. In spite of intensive genetic, cytogenetic and molecular investigations there remains a lot about fragile X syndrome that is not clearly explained until now.

Many authors reported that facial features in fragile X syndrome are not diagnostic, but may be a valuable adjunct in clinical evaluation (Jennings et al., 1980; and Meryash et al., 1984[51][39].

Researchers continue to search for a quantitative measure to describe fra X affected and carrier individuals. As an attempt towards achieving this goal, cephalometry was used in this work, both physical and radiographic to quantitate the clinical observations in the fragile X syndrome.

Radiographic cephalometry proved to be effective in skeletal measurements, which are fixed bony landmarks, and can be measured more accurately than soft tissue measurements. Moreover dealing with a genetic problem as

fragile X syndrome, requires the use of genetically determined landmarks as the skeletal structures and this will decrease enviromental effects encountered when dealing with soft tissue landmarks. Errors may result due to the variation in thickness, the difference in elasticity of the soft tissues and the pressure which should be exerted during taking the measurements.

X-linked pattern of inheritance is the most commonly suggested mode of inheritance of fragile X syndrome (Mckusick, 1992 [130], Buyse, 1991 [131]).

All available cases with fragile X syndrome were included in the study. Their number was twenty and their age ranged from 6-22 years. They were divided into three groups: group I (6-10 years) or prepubertal age; group II (13-16 years) or pubertal age and group III (17-22 years) or early adulthood.

The pedigree analysis, in this study, showed that the maternal family history of mental retardation was positive in the families of four probands in pedigrees # 2 and 6 who had maternal cousins and pedigrees # 9 and 12 who had maternal uncles. The four pedigrees conform with the X-linked pattern of inheritance.

The pedigree analysis also showed that the percentage of cosanguinity in the parents of the probands was 4/14 (28.57%) and 5/19 (26.32%) when taking into consideration, all the families of the probands and their affected relatives. Hafez et al.,1983, [132] reported a close percentage (28.96%) for the general population thus showing that the consanguinity rate in this study was not higher than in the general population. This is not in favour of autosomal recessive mode of inheritance.

Meryash et al.,1984 [39], studied 18 mentally retarded adults (18-69 years) white fragile X males including 3 sib pairs and one sibship with affected brothers.

Clinical examination of the affected males in this study revealed mental retardation in 100% of the cases, with varying degrees: profound, severe, moderate and mild. Mental retardation from borderline to profound was reported to be associated with fragile X syndrome (Schwartz et al.,1988 [52]; Buyse, 1991 [131]; Mckusick, 1992 [130]).

The classic features of a long narrow face and prominent ears are often not present in the prepubertal child (Chudley and Hagerman,1987). [133] Long face was found in 50% of our studied affected males while it was reported to be 74% (60/81 studied patients) by Hagerman and Silverman,

1991, [16] at the Children's Hospital in Denver. The appearance of long ears in fragile X syndrome had the highest frequency in our cases 60% while it was 66% (76/115 studied patients) in the Denver study. Ear width is a more discriminating feature in identifying fra (X) patients than is ear length, and it can be more easily quantified than can ear prominence (Butler et al., 1991) [134]. They found that both ear length and ear width are increased in 23 of 39 fra X males. The increase in ear width exceeded 2 SD while the ear length did not exceed 2 SD. Macroorchidism was found in 60% of our cases and was reported to be 74% in the Denver study (82/111 patients). Macroorchidism, or large testicles, was present in over 80% of adult fra X males (Sutherland and Hecht, 1985) [38].

Both our study and the Denver study were drawn from Caucasian population, but the percentage of occurrence of the different features in our sample is different in order and magnitude from the Denver study. This might be attributed to the difference in the sample size and age.

The orodental features were evaluated using dental charts and confirmed by using panoramic X-rays which produce a survey of the entire maxillary and mandibular dento-alveolar region on a single film. The indication for the use of this technique and its application includes screening, diagnosis of pathological conditions, treatment planning,

evaluation of anomalies as one part of the follow - up evaluation for the patients. The frequency of the orodental features is summarized in table IV. 2.

High palate and malocclusion were found in 15/20 of our studied patients. Macroglossia in 12/20, prominent mandible in 10/20. Diastema, thick lips, malposed or retained teeth, short philtrum, hypoplastic teeth, absent teeth, micro or macrodontia and depressed maxilla were also found in smaller values.

Gingivitis and poor oral hygiene were observed in the Egyptian fragile X cases but this may be due to the low socio-economic status of some families and the burden of having a mentally retarded child that usually neglects the minimum oro-dental needs. The above findings together with the presence of diastemas, rotated or infra erupted teeth and reduced mesio-distal diameter are interpreted as new associations that merit further studies.

Few reports on oro-dental findings in fragile - X syndrome in Caucasian samples included malocclusion (cross-bite and openbite), high palate, occlusal wear, low caries rate, minimal hard and soft tissue disease and prominent mandible(Shellhart et al.,1986[56]; Cassamassimo et al.,1986[135]; Hagerman and Silverman, 1991[17]). Tooth crown assymetry was reported by Peretz et al.,1988[57]. High palate was reported by

many authors (Brown et al.,1986;[59] Hagerman et al., 1983;[34] Carpenter et al.,1982;[136] Jennings et al.,1980;[51] and Davids et al.,1990).[40] Cleft palate was found in 5/61 by Partington in 1984.[35]

By clinical examination high arched palate was reported in 48% of the cases (Hagerman and Silverman,1991)[16] and 65% of cases by Davids et al., 1990.[40] In our study high arched palate was found in 75% of the affected cases.

The palatal height was measured in our sample using a palatometer on study models of affected individuals and the results were compared with the corresponding controls. This is an accurate objective ascertainment of the palatal height. To our knowledge, this method was not applied before in measurement in fra X individuale.

An interesting finding was the discrepancy between the percentage of occurrence of high arched palate: 48% by clinical examination and 36.84% by measurement. This discrepancy might be due to the false impression or optical illusion of a high palate when it is only narrow. This may give an overestimation to the frequency of palatal height. This explanation was confirmed by finding that the palatal width of the probands was narrower than that of the control

cases in the three affected age groups, although the differences were not significant (table IV. 12). The age of the patients was not a factor affecting the expression of high palate.

The frequency of clinical abnormalities in each studied group, was calculated as the percentage of the sum of positive abnormalities from the sum of positive clinically examined features in all the affected males.

After exclusion of mental retardation as the presenting abnormality in all cases, 19 features were scored and summarized in table IV. 5. The frequency of abnormalities ranged from 3-7 per individual in group I, from 5-11 in group II and from 5-9 in group III. The percentage of occurrence of clinical abnormalities was 27.06%, 39.84% and 35.96% in group I, II and III respectively.

The percentage of occurrence of oro-dental abnormalities was 41.55%, 40.26% and 53.03% in group I, group II and group III respectively.

It is interesting to note that there is a marked shift in the percentage of occurrence of clinical abnormalities from group I to group II and III, while this shift in the oro-dental abnormalities is from group I and II to group III. The studied clinical abnormalities manifest at a younger age than the oro-dental findings. Partington in 1984 [35] reported that the characteristic facial appearance was recognizable under 18 years old. Nielson, in 1983, [55] reported that the characteristic facial appearance emerge at 8-12 years (at or prior to puberty).

The description of a craniofacial syndrome should utilize anthropometric measurements as a simple technical tool for clinical diagnosis. Anthropometry is a more objective method of defining the degree and type of physical abnormalities than the subjective clinical inspection. Craniofacial anthropometry has an important role in the diagnosis of patients. Salinas (1980)[113] discussed its application as the "objective evaluation of the craniofacies" and it serves to provide fixed points of reference for comparison with normal populations. Clinicians must keep in mind that small errors in measurement techniques or landmark identification can move a measurement from the "normal" to the "abnormal" range. This problem stresses the need for measurement accuracy and utilizing one or two isolated measurements in the physical exam (Ward, 1989)[112].

Metric data provided by anthropometry together with cephalometic analysis and analysis of photographs can help an objective assessment of the clinician's diagnosis adding a quantitative dimension to the dysmorphologist's observational skills (Ward, 1989)[112].

Our findings were compared to those anthropometric findings available in the literature. However the comparison of certain parameters was possible only with group III as those parameters were studied on adults.

Ward in 1989,[112] cited an example from a study on hypohydrotic ectodermal dysplasia (HED) in which anthropometry reveals details of facial morphology e.g. reduced facial height and other facial features in spite of the fact that facial widths are comparatively normal.

Individual dysmorphic faces tend to have much greater variation from one facial area to the next than do "normal" faces(Garn et al,1985[114]). Individuals with any syndrome resemble each other clinically and the degree of cranio-facial similarity is greater among syndrome affected than unaffected individuals in a single family. Gene carriers showed similar though non-identical pattern of defects (Saksena et al., 1987)[115].

Selected measurements, when expressed as z-scores (standard deviation units) relative to standards for age and sex, show if affected subjects are above or below the mean for their age by one or two standard deviations or more for a certain measurement. Anthropometric measurements describing craniofacial morphology transferred to z-scores and compared with normal databases lend themselves to mutivariate analysis.

Z-score analysis of individuals of different ages can be pooled so as to provide a single z-score pattern profile that may be characteristic or diagnostic of a syndrome. Once a number of patients have been identified and measured, their z-score pattern profile drawn, the resulting

craniofacial pattern profile can be used for evaluation, description and comparative diagnosis of the syndrome (Garn et al.,1984)[120]. Garn's approach indicates that a dimension characterized by a low z-score or a high z-score is of immediate diagnostic or developmental significance. Also the pattern profile reduces the extraordinary complex interdimensional relationships of the head and face to form an easily visualized comparison. Taken together the z-scored measurements, the graphic representation and the numerical measures provide the opportunity to identify borderline syndromes, to describe and identify "syndromatic" familial conditions not known to have a craniofacial component. Two facial profiles which might prove similar by pattern profile approach, might be deemed different by discriminant analysis simply because of differences in size.

Craniofacial pattern profile proved useful, like the metacarpo-phalangeal pattern profile, in identifying high deviations from normal pattern and it allowed comparison of the craniofacial pattern profile of individuals with different age and sex (Garn et al., 1984)[120].

Garn et al., in 1984,[120] quantitatively described similarities between patients, family resemblances, or differences in pattern or configuration through craniofacial pattern profile in a sample of the oto-palato-digital syndrome and a number of cleft palate syndromes.

Allanson and Farkas (1991)[137] effectively highlighted the value of anthropometric craniofacial pattern profile in 199 individuals with trisomy 21 aged 6 months to 60 years. Using anthropometric craniofacial pattern profile, he identified dysharmonic craniofacial growth and documented abnormal dimension e.g. reduced ear length and relatively reduced maxillary growth compared to mandibular growth with age. Saksena et al.[115], in 1987, similarly proved similarities between sibs and between sibs and their mother of a family with unusual facial morphology using craniofacial pattern profile. They suggested accordingly that the two sibs and their mother are the carriers of the same genetic syndrome.

Cohen et al.,in 1985[118] also used profile patterns for 25 adult males and 26 adult females with achondroplasia and came up with significant findings in achondroplasia e.g. enlarged calvaria, frontal bossing, large frontal sinuses, occipital prominence, normal anterior cranial base length, strikingly shortened posterior cranial base length, an acute cranial base angle, a short deformed and depressed nasal bone, short upper facial height, recessed maxilla, posterior tilt of nasal floor and a prognathic mandible, anteriorly displaced but of abnormal size with a normal gonial angle and a high coronoid process.

Frias et al., in 1982 [119], analyzed cephalometric measurements of 3 series of patients, one with the tricho rhino phalangeal syndrome type 1 (TRPS-1) another with fetal alcohol syndrome (FAS) and third one with Angelman syndrome (Happy Puppet syndrome AHPS). They converted 40 linear and angular measurements to standard scores to represent the number of standard deviations with a particular observation from the norm or average for that observation. They concluded that the craniofacial abnormalities observed in the cephalometric analysis of patients with TRPS-1 appear to be directly related to the underlying defect in endochondral ossification present in the disorder, those observed in FAS and AHPS suggest that they may be secondary to abnormal growth and development of the CNS.

Lavelle, in 1989 [138], emphasized that the technique whereby cephalometric parameters of anomalous craniofacial dimensions are compared with normative controls on the basis of their scores (Garn et al., 1985 [114]) has probably the most obvious clinical application in cases of hydrocephaly, cleft palate, cleft lip and microcephaly.

Quantitative evaluation of the physical phenotype in fragile X syndrome was first undertaken by Partington, 1984, [35] in a sample of 61 fragile X subjects from 30 families in

Ontario, Canada. Their age ranged from 2-59 years. The measurements evaluated by Partington were: weight, stature, testicular volume, head circumference and ear height. His comments on affected children were drawn from 39 subjects younger than 18 years.

A study by Meryash et al., 1984,[39] was performed on a sample of 18 affected males (18-69 years) and was based on a wider range of body measurements.

Later Thake et al.,1987,[139] reported on 10 fragile X boys Butler et al.,in 1988,[134] examined 31 fragile X boys (1.5-12 years old). They studied 18 facial parameters from strict front and profile photographs obtained from a distance of 1.5 m from fra X boys compared separately with other facial measurements from the same face (e.g. mouth width vs bizygomatic diameter).

Loesch et al.,1988,[124] applied multivariate analysis in a large sample of fragile X individuals, 147 adult males (56 men and 91 women), compared with 111 men and 108 women. The facial parameters evaluated in males and females were ear length, ear breadth, bizygomatic diameter, bigonial length, upper facial height, total facial height and jaw length. Loesch and Wilson,1989,[125] studied a sample of 43 men and 72 women (17-75 years) and used physical examination of human body shape measurements in discriminant analysis in order to

obtain unbiased classification of individuals having fragile X or being normal. Loesch and Wilson evaluated 16 head/face measurements and 18 trunk/limb measurements. Loesch and Scott, 1989,[140] generated a method for estimating the likelihood ratio and the risk of an individual being affected with fragile X syndrome based on the study of Loesch et al., 1988[124].

Butler et al., 1991,[129] used multivariate discriminant analysis on 39 fra (X) affected males (2.5-75.6 years).

In the present work, cephalometry applied in fragile X sample used physical measurements and study models together with radiographic measurements.

The use of study models for palatal measurements is not only convenient to both the probands and the observer but also gives accurate results. The palatal measurements thus taken are accurate. The study models are an exact replica of the oral cavity and therefore they were included with the other physical measurements.

Radiographic cephalometry does not produce exact measurements as there is a magnification factor which is inherent in all radiographic measurements. When the film-tube distance is constant in radiographing the probands and the control cases, even the linear measurements based on

radiographic films are comparable due to the constant magnification.

According to the method applied, cephalometry (head anthropometry) may be either direct or indirect. Indirect methods are numerous. The indirect methods used in our study are study models and radiographic cephalometry.

T-test and z-score statistical analyses were done on cephalometric measurements in the studied groups of fragile X males and their mothers.

The head circumference was around the normal range in our four studied groups. Butler et al.,1991 [134] found an average z-score of less than +2SD which is also within the normal range. Partington, in 1984, [35] found an increased head circumference in a sample of 61 fragile X subjects. The overgrowth of the head was evident in childhood. Meryash et al., 1984 [39] found that 17 of 18 subjects had macrocephaly and two thirds were dolicocephalic. Meryash study confirmed that males with fragile X had an increased head circumference. There was absolute macrocephaly (head circumference more than 2SD above the normal mean) in more than one fifth of the subjects i.e. 4 of 18 patients. Thake et al.,1987, [139] reported 10 fragile X boys with a head circumference over the 50th percentile. The head circumference in our study had a mean of 55.75± 1.1 cm in the affected adult males as compared to

Meryash study (mean=58 ± 2.1cm). The mean of head length was 18.95 + 0.9 cm. as compared to Meryash study that was 19.9 + 0.8 cm. The mean of head breadth was 13.98 ± 0.8 cm compared to Meryash study that was 15.6 ± 0.8cm. The head breadth, measured physically, and the maximum head width, measured radiographically, were both larger than normal in the adult affected group in our study, although the increase is not significant. The t-test value for head breadth was greater than head length, in adult fra X males thus the dolicocephalic appearance which was reported by Meryash et al., 1984, [39] in two thirds of the studied males, was not evident in our studied younger or adult fra X cases. Butler et al., 1991, [134] found an average z-score around the normal range for both head breadth and head length.

Long face was found in 10 of 20 affected males and broad nose was found in 6 of 20 males, which confirms the finding of Butler et al., 1988 [123], of a narrow face with a broad nose, by photo anthropometric analysis. The z-score of face height in affected adult males in our study was from 0.5 SD to 1.5 SD compared to Meryash study (z-score of face height from -1.4 SD to 4.25 SD and the mean z-score was 1.1 SD). Loesch et al., 1988 [124], found a z-score of total face height 0.50 SD. The facial length was increased and the facial breadth was decreased in 10 fragile X boys reported by Thake et al., 1987 [139]. The upper facial height had a z-score of -0.50 SD in our studied affected males and -1 SD in the studied adult males by Loesch et al., 1988 [124].

The bizygomatic diameter was increased with a z-score from 0to + 2 SD compared to Meryash study [38] (z-score of bizygmatic diameter from -7.2 S.D. to 2.2 S.D. and the mean z-score was -3 S D. Loesch et al., 1988 [124], found the mean z-score around -0.25 SD. and Butler et al., 1991 [127], found an average z-score of -2 SD for bizygomatic diameter and -1 SD for bigonial diameter.

Our results showed an increased bizygmatic diameter in contrast to decreased bizygomatic diameter in other studies on fragile X syndrome by 1cm (Buyse, 1990) [131].

The mandibular length, in our study, had a z-score around the normal range compared to Loesch et al., 1988, which was +0.25SD in affected males.

The ear length was insignificantly increased in our three studied groups of affected males. The mean ear length in group III was 6.2 + 0.2 cm compared to that in Meryash study which was 7 + 0.4 cm. The ear breadth was larger in affected males than females. Loesch et al.,1988, [124] found an increased ear length and ear breadth in the affected males. Partington, 1984, [35] found an increased ear length with increasing age in adults with the fragile X syndrome. Butler et al., 1991, [134] found an average z-score for ear length and

ear width higher than +2SD. Thake et al.,1987,(139) reported an increased ear length in 10 fragile X boys. They concluded that the characteristic appearance of a fra X subject is affected by relationships between the various measurements than any single measurement. This indicates that the relationship between the magnitude of face length and face breadth is more important than absolute measurements in defining the facial appearance of fra X males. This provides an objective basis for the impression of a long face.

Loesch et al., 1988,(124) found that facial abnormalities were more frequent than body abnormalities. Loesch and Wilson, 1989,(125) found a decreased upper face height/face measurements in 77 % fragile X men and the trunk/limb measurements were found in 70% fragile X men.

Loesch and Scott, 1989,(140) suggested that the number of abnormal cases studied should be increased and they recommended the addition of dental and palatal measurements to aid in the classification of normal and abnormal individuals and correct the previous rate of misclassification.

The mothers of the studied affected males had a head circumference around the normal range. In contrast to the affected sons, the mothers had a decreased head width (H.W)

as revealed by t-test and z-score analysis. Loesch et al., 1988, [124] found that the men had more abnormalities than the women. The upper facial height was decreased in adult females and the mandibular length was around the normal range. In our study, the face width ZY and the interorbital width OW are decreased, the facial depth AS is increased and the maxillary height XH is increased significantly as revealed by t-test and z-score analysis. Fryns, 1980, [66] reported a large face and a prognathic mandible in 28% of 144 obligate female carriers. Gorlin et al.,1990, [141] reported a long narrow face in 60% of post pubertal heterozygotes and Buyse,1991 [131] ,also reported a long face in fragile X female carriers. Loesch et al., 1988, [124] showed a z-score of mandibular length of +0.75 SD and a z-score of upper facial height of -1 SD in the studied females. Loesch and Wilson, 1989, [125] analyzed 16 head/face measurements, using physical examination in 72% fragile X women and 18 trunk/limb measurements in 65% fragile X women. They found increased bigonial length and an equal ear size in both sexes.

In our study, the ratio XN between maxillary/mandibular length was increased, the cranial flexure angle CA was decreased and the angles SNA, SNB and SNPg were increased in the carrier mothers than the control sample i.e. the mothers of fra X males do not necessarily have similar skeletal facial relationships as their affected sons.

The t-test analysis used in our study showed significant differences in many parameters at a p-value less than 0.05. Also a dimension that is characterized by a low z-score or a high z-score is of immediate diagnostic or developmental significance , and the pattern profile presented in graphic forms, lines or bars, benefits in constructing a form that is easily visualized and easily compared (Garn et al., 1984)[120] .

Craniofacial pattern profile was based on radiographic cephalometry. The studied measurements were chosen according to the pattern profiles reported in the literature and suspected to show significance from the clinical examination of our studied cases. The craniofacial pattern profile is more clear in group I (6-10 years), less evident in group III (17-22 years) and least in group II (13-16 years) which might indicate that the characteristic facial appearance is more evident in childhood.

In group I, the head width HW and the face width ZY of the affected males were significantly increased as revealed by t-test values at p-value 0.05 and 0.01 respectively and the z-score analysis using craniofacial pattern profile.

In group III, the face width ZY was significantly increased at p-value < 0.05 and the head width HW and the

interorbital width OW were also increased as shown by z-score analysis.

The facial depths (AS and PS) were significantly decreased by t-test analysis at p-value 0.01 and 0.02 respectively). This was confirmed by a smaller <SNA in the affected males than the controls. The facial depths AS, PS and SS were decreased as shown by negative z-score in the craniofacial pattern profile.

The anterior mandibular height (AM) was significantly increased at p-value < 0.05. This might be due to over eruption of the mandibular teeth as a compensatory mechanism for the open bite tendency found in the affected subjects (75%). On the contrary, the mandibular length is similar in both affected and control samples. The increase in the anterior mandibular height in the affected cases gave the impression of a clinically larger mandible, as reported by Loesch and Hay,1988 [57], Schwartz et al.,1988 [52] and Buyse,1990 [131].

Shellhart et al.,1986 [56], Casamassimo et al.,1986 [135] and Gorlin et al.,1990 [141] reported a long face with large jaws and open bite in the fragile X syndrome patients. The total facial height (TH) was increased while the maxillary height (XH) was decreased. The significant increase in the anterior mandibular height(AM) and the slight decrease in the maxillary height (XH) resulted in insignificant increase in the total facial height.

The ratio (UH) between the upper and lower facial height was decreased and the ratio (PH) between the posterior and anterior facial height was increased. This might indicate a difference in the differential growth rate between the upper and lower facial heights. There might also be a tendency towards more vertical growth than horizontal growth direction. Angles SNA and SNB were decreased indicating that the growth pattern may be more vertical than horizontal thus leading to a long face and a retrusive maxilla as was previously reported by many authors (Loesch and Hay, 1988[57]; Lachiewicz et al., 1988[48]; Schwartz et al., 1988[52] and Gorlin et al., 1990[141]). The retrusive maxilla was confirmed before by decreased facial depths (AS and PS). The smaller angles SNA, SNB and SNPg resulted in increased vertical facial growth than horizontal, similar to group I.

The mandibular (gonial) angle (MA) and the cranial flexure angle (CA) were slightly increased leading to slight backward position of the mandible and a small < SNB. This is revealed clinically as a retrognathic mandible in fra X cases in spite of similar mandibular lengths in both affected and normal subjects.

In group II there were no significant differences between the affected males of this age group and their matchable control males concerning cephalometric measurements.

In general, the cephalometric measurements in the fragile X sample indicate the presence of over-eruption of mandibular teeth as a compensatory mechanism of open bite tendency and more vertical than horizontal growth direction.

Scatter diagrams of the craniofacial pattern profiles were carried out searching for trends in selected parameters. The findings showed that the only parameter with a uni-directional trend is the bizygomatic width which had a positive z-score in every studied case in the three age groups.

The correlation coefficient, as a measure of association, was calculated to detect any pattern similarity or dissimilarity between the affected sibs and their mothers or between the affected sibs and each other. Correlation analysis showed that there is no rule regarding the similarity or dissimilarity in the craniofacial pattern profile between the sibs together and the mothers and their offsprings. It revealed that the mother may be dissimilar to similar sibs (Fig. IV. 10 and IV. 17) or the mother may be similar to one sib and dissimilar to his sib (Fig IV.12).

According to the literature available, no cephalometric measurements on fragile X was mentioned before our work to help compare with our findings. A larger number of affected cases in the different age groups may enable us to perform

mutivariate analysis to confirm the presence or absence of any significant craniofacial measurements associated with the fragile X syndrome.

Concerning the results obtained on the carrier population, the mothers were inconsistantly similar or different from their affected sons. This may be due to the differental lyonization of the X chromosome and this can produce a wide range of variation in the expression of disease - related traits among carriers. Carriers can be expected to have a range from normal to fully affected in appearance.

Quantitative measurement of the dento-cranio-facial abnormalities in fragile X syndrome confirmed the results of the previous clinical studies which reported variability of expression and genetic heterogeneity in this syndrome. We used physical and radiographic cephalometry and analysed the results statistically,and found that accurate anthropometric measurement are more important than clinical impression in the diagnosis of the syndrome. Molecular studies on the positive fragile site may be the only accurate diagnostic test with the aid of accurate anthropometric measurements, cytogenetic and clinical studies.

CHAPTER VI

SUMMARY AND CONCLUSION

Fragile X syndrome is one of the most common forms of heritable mental retardation. It constitutes a major health problem as it affects all ethnic groups and most of the affected individuals require education and support.

The present study aimed at the quantitative evaluation of the dento-cranio-facial characteristics of the fragile X syndrome, as an aid in te diagnosis of the syndrome.

The studied sample consisted of twenty Egyptian male cases with fragile (X) syndrome. They were divided into three age groups:

Group I : Seven cases from 6-10 years old.

Group II : Seven cases from 13-16 years old.

Group III : Six cases from 17-22 years old.

Those affected males clinically and cytogenetically diagnosed at the Human Genetics Departments at the National Research Center, Cairo and the Medical Research Institute, Alexandria.

A fourth group, group IV, was also studied which consisted of the obligate heterozygote female carriers.

A comparable group of forty six unaffected Egyptian males matched to the three affected age groups was also

studied. This control sample was obtained from the Pedodontics Clinics and the Oral Medicine Clinic at the Faculty of Oral and Dental Medicine, Cairo University. The mothers of the fragile (X) cases were compared with control adult female sample from the Oral Medicine Clinic, Faculty of Oral and Dental Medicine, Cairo University.

All the studied cases were subjected to pedigree analysis, clinical examination, and cephalometric evaluation using physical, study models, and radiographic techniques: Panoramic X-rays were also done to visualize the different anatomic landmarks. Statistical analysis was performed in the form of t-test and z-score analyses. The z-score values were used in drawing the craniofacial profile using the Harvard Graphics program. These tests were used to compare the affected males and females with the corresponding control subjects. Correlation coefficient was also calculated to detect similarity/dissimilarity between mothers and affected offspring or between two or more affected sibs.

Clinical examination revealed mental retardation in 100% of the affected male cases, long face in 50%, long ears in 80% and marco-orchidism in 60% of the affected studied males. Oro-dental abnormalities as high palate and malocclusion were found in 75%, macroglossia in 60% and prominent mandible in 50% of the affected studied males

Diastemas, thick lips, absent teeth, micro or macrodontia rotated or infraerupted and depressed maxilla were also found at lower rates. Carrier females ranged from normal to fully affected in appearance. The palatal height was measured using a palatometer on study models and this is an accurate method for objective ascertainment of palatal height. Seven out of nineteen cases had high arched palate (36.84%).

The percentage of occurrence of the clinical abnormalities was 27.06%, 39.84% and 35.96% in group I, II and III respectively while the percentage of occurrence of oro-dental abnormalities was 41.55%, 40.26% and 53.03% in group I, II and III respectively. This showed a marked shift in clinical abnormalities from group I to group II and III while this shift in the oro-dental abnormalities was from group I and II to group III. The studied clinical abnormalities manifest at a younger age than the oro-dental ones.

The physical anthropometric measurements studied in our subjects were head circumference, head length and breadth, ear length and breadth and palatal height and width.

The radiographic cephalometric measurements studied were maximum head width, interorbital width, face width, facial depth (ANS to Sella Vertical, A-point to Sella

vertical and supradentale to sella vertical) mandibular length, anterior mandibular height, total facial height, maxillary height, upper facial height/lower facial height, ratio, posterior facial height/anterier facial height ratio, maxillary/mandibular length ratio, cranial flexure angle, maxilla to cranial base < SNA, mandible to cranial base < SNB and <SNPg and mandibular angle.

The significantly larger parameters in group I were head breadth, ear breadth, palatal index, maximum head width (Eu-Eu), face width (Zy-Zy) and anterior mandibular height (Id-Me). The significantly smaller parameters in group I were the facial depths (A-point to Sella Vertical and Supradentale to Sella Vertical).

In group II, the significantly larger parameters were palatal height and palatal index. There were no significant radiographic parameters in group II.

In group III, the ear breadth, face width Zy-Zy were significantly larger than their matchable controls. In group IV, the ear length the maxillary height (Sp-A-Point) and <SNA (between the maxilla and the cranial base) were significantly larger while the face width (Zy-Zy) was significantly smaller.

Craniofacial pattern profile was based on radiographic cephalometry and the measurements chosen were based on those reported in the literature and suspected to show significance from the clinical examonation of our studied cases. The craniofacial pattern profile was more clear in group I, followed by group III and lastly group II i.e. more evident characteristic facial appearance in childhood.

The scatter diagrams drawn on the Z-score of cephalometric parameters showed that the only parameter with a uni-directional trend is the bizygomatic width which had a positive Z-score in every studied case in the three male groups. Correlation coefficient analysis showed that there was no rule regarding similarity or dissimilarity in the craniofacial pattern profiles between the sibs together and the mothers and their offsprings.

The cephalometric analysis in the fragile X males in general indicated the presence of over eruption of mandibular teeth and more vertical than horizontal growth direction.

In conclusion quantitative analysis of the dento-cranio facial abnormalities in fragile-X syndrome confirmed variability of expression which might indicate genetic heterogeneity in this syndrome as was reported in other populations.

There were no dento-cranio-facial feature to be considered of minimum diagnostic value in the fragile-X syndrome except the bizygomatic diameter which had a uni-directional trend in all cases.

Molecular studies on the positive fragile site may be the only accurate and reliable diagnostic test in many affected cases.

CHAPTER VII

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CHAPTER VIII

ARABIC SUMMARY

ملخص البحث

متلازمة الصبغة X الهشة هى أحد أهم صور التخلف العقلى الوراثى ولذلك فهى تشغل أحد المراكز الهامة فى مشاكل الصحة لأنها تصيب المجموعات السكانية المختلفة كما يحتاج المصابون لتعليم ومساندة خاصة.

هدف هذه الدراسة هو تقييم الصفات الجمجمية - الفمية - الوجهية فى متلازمة الصبغة X الهشة فى المصريين باستخدام قياسات الرأس للوصول إلى تشخيص دقيق لهذه المتلازمة.

لقد تكونت العينة من عشرين ذكر مصرى مصاب بهذه المتلازمة وتم تقسيمهم إلى ثلاث مجموعات تبعاً للعمر:

المجموعة الأولى: سبعة ذكور يتراوح أعمارهم من ٦-١٠ سنوات.
المجموعة الثانية: سبعة ذكور يتراوح أعمارهم من ١٣-١٦ سنة.
المجموعة الثالثة: ستة ذكور يتراوح أعمارهم من ١٧-٢٢ سنة.
وتوجد مجموعة رابعة: تكونت من عشر أمهات حاملات المرض.

وقد تم الكشف الإكلينيكى الدقيق والدراسة الوراثية الخلوية للمصابين فى قسم الوراثة البشرية بالمركز القومى للبحوث وقسم الوراثة الإنسانية بمعهد البحوث الطبية بجامعة الاسكندرية.

كذلك شملت الدراسة على ٤٦ ذكر مصرى غير مصاب قسموا كذلك إلى ثلاث مجموعات من نفس الأعمار للمقارنة وقد تم الحصول على عينة المقارنة من عيادة قسم الأطفال بكلية طب الفم والأسنان - جامعة القاهرة. وقد تم مقارنة الأمهات حاملى المرض مع عشر سيدات غير حاملات للمرض تم الحصول عليهم من قسم طب الفم والأسنان بكلية طب الفم والأسنان - جامعة القاهرة.

وقد تعرضت جميع الحالات للدراسات الآتية:

١- تحليل شجرة العائلة.
٢- الفحص الاكلينيكى الدقيق.
٣- قياسات الرأس عن طريق القياس السطحى وبالأشعة عن طريق النماذج الجبسية.
٤- عمل أشعة بانورامية للفكين.

٥- التحاليل الإحصائية لقياسات الرأس مثل إختبار T لمعنوية الفروق بين عينات المصابين والعينات الضابطة وعمل رسم بيانى لنمط الرأس الجمجمى للمصابين، ومعامل الارتباط لحساب التشابه أو عدمه بين الأمهات وأبنائهم المصابين والغير مصابين.

وقد أوضح الفحص الإكلينيكى أن ١٠٠٪ من الذكور المصابين بتخلف عقلى، و ٥٠٪ منهم لهم وجه طويل، و ٨٠٪ لهم أذن طويلة و ٦٠٪ منهم مصابون بكبر حجم الخصيتين و ٧٥٪ منهم يعانون من عدم تطابق الفكين وارتفاع فى سقف الحلق و ٦٠٪ منهم لسانهم كبير الحجم و ٥٠٪ بهم بروز للفك السفلى.

وقد اختلفت أعراض هذه المتلازمة إختلافاً يتراوح بين الطبيعى والاصابة التامة فى الأمهات حاملات المرض وذلك يرجع لاختلاف ظهور الصور الاكلينيكية للمرض.

وقد أوضحت قياسات الرأس عن طريق الاشعة والقياسات السطحية أنه يوجد بالمصابين زيادة للنمو الجانبى للرأس وزيادة فى ارتفاع الأسنان بالفك السفلى.

أكد التحليل الكمى وجود الاختلال الجمجمى - الفمى - الوجهى والتفاوت فى الأعراض الظاهرة وعدم التجانس الوراثى فى متلازمة X الهشة كما ورد فى التقارير المسجلة عن مجموعات سكانية أخرى.

فى هذه الدراسة لم نحصل على أى صفة أو قياس معين للأسنان والجمجمة والوجه يمكن تشخيص هذه المتلازمة عن طريقه/وتشير هذه الدراسة إلى ضرورة استخدام وسائل الهندسة الوراثية والتكنولوجيا الحيوية الجزئية لمحاولة الوصول إلى تشخيص دقيق لهذه المتلازمة.

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دراسة نمط الرأس والوجه والأسنان
في مرض التخلف العقلي
المرتبط بكروموسوم X الهش

رسالة مقدمة إلى

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إيفاء جزئياً للحصول على درجة الدكتوراه
في الوراثة الإنسانية

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