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Craniofacial morphology in young patients with Turner syndrome

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SUMMARY The craniofacial morphology of 33 Turner syndrome patients, aged 7–16.7 years, was evaluated by standard cephalometric methods. The sample was subdivided according to karyotype and 72 normal girls aged 7.1–16.1 years served as controls. The size of the calvarium and face was generally smaller in the Turner group than in the controls. The morphology was characterized by a flattened cranial base angle, a marked reduction in posterior cranial base length, facial retrognathism and short and posteriorly rotated jaws. The same morphological pattern was found in all the karyotypes, but the deviations were most pronounced in monosomy X (45X) patients. The results indicate that a deviating pattern of craniofacial size and morphology has already been established in childhood. It is suggested that the deviations originate in the fetal period, when the primary cartilages form the craniofacial skeleton.

Introduction

Turner syndrome is a genetic disorder caused by numerical and/or structural aberration of the X chromosome. X-chromosome monosomy (45X) constitutes the main karyotype, but isochromosome for the long arm of X and mosaics are also regularly observed (Connor and Ferguson-Smith, 1991). One of the most constant characteristics is reduced body height. Lyon *et al.* (1985) report a mean height of 143.2 cm for untreated women with the syndrome. The girls have gonadal dysgenesis which leads to oestrogen insufficiency and secondarily to reduction in the amount of growth hormone above the age of 9 (Albertsson-Wikland and Rosberg, 1990).

A variety of somatic abnormalities are associated with the syndrome. The classification system proposed by Lippe (1990) indicates that most of the abnormalities have their origin in disordered skeletal growth, disturbance of lymphatic development and vascular dysplasia. The pathogenesis of the growth disorder is still not understood.

The skeletal maturity shows retardation, most pronounced after the age of 13 years (Jensen, 1974; Webber *et al.*, 1982; Park *et al.*, 1983; Midtbø and Halse, 1992). Craniofacial morphology in adult women with the syndrome is characterized by an increased cranial base angle and a short posterior cranial base length. The mandible is short and the maxilla of normal anterior–posterior length. Both jaws are retrognathic and distal molar occlusion often combined with increased overjet are common findings (Jensen, 1974, 1985; Laine *et al.*, 1986; Peltomäki *et al.*, 1989; Harju *et al.*, 1989; Babić *et al.*, 1993).

Rongen-Westerlaken *et al.* (1992) have shown that similar deviations in craniofacial morphology are present in children with Turner syndrome and suggest that the deviations in the cranial base and the mandible may be explained by a disturbance in endochondral ossification.

The relation between the number of X chromosomes and craniofacial morphology has been demonstrated in studies of males with Klinefelter syndrome (47XXY karyotype) and women with Turner syndrome (45X). These investigations show that loss or addition of an X chromosome produces opposite effects on cranial base angulation and thereby on facial prognathism (Gorlin *et al.*, 1965; Jensen, 1974; 1985; Ingerslev and Kreiborg, 1978; Babić *et al.*, 1991, 1993; Brown *et al.*, 1993)

The present investigation gives a detailed description of craniofacial variables in prepu-

bertal girls with various karyotypes of Turner syndrome in order to gain further insight into the relationship between X-chromosome aberration and craniofacial morphology.

Subjects and methods

This investigation is part of a systematic study of Turner syndrome patients to evaluate growth and development before, during and after therapy with growth hormone and oestrogen. The karyotyping was undertaken by chromosome analysis of peripheral lymphocytes. The karyotyping, the hormone therapy and the study of general parameters was performed at the Department of Paediatrics, University of Bergen, Norway.

The subjects were 33 Turner syndrome patients from different parts of Norway (Table 1). Before hormone therapy the patients were examined at the Departments of Orthodontics and Oral Radiology, University of Bergen, and a lateral cephalogram was taken by a standardized technique.

From the files of screening patients at the Department of Orthodontics, 72 girls without known hormonal or genetic disorders were selected to match the Turner patients by age (Table 1). Each of them had a standardized lateral cephalogram. These patients were used as the controls.

The reference points and lines used are illustrated in Figures 1A and B; the definitions according to Bjørk (1963) are listed in the figure texts. The lateral cephalograms were traced and the reference points marked directly on tracing paper in optimal illumination. With the tracing paper fixed to the radiograph the reference points were digitized with an AccuGrid digitizer (Numonics Corporation, Pennsylvania 18936, USA). The cephalometric variables were calculated by a computer program (Dentofacial Planner, 1991) and transferred to a program for statistic analysis (Minitab, 1991). In all, 43 variables (18 angular, 22 linear and 3 indices) were used to describe the craniofacial morphology (Table 2).

Table 1 Patients distributed on the basis of age and karyotype.

Karyotype	*n*	Age (years) Range	Mean
Monosomy X			
45X	24	7.0–16.7	11.6
Mosaics			
45X/46XX	3	12.5–15.3	14.3
45X/46XY	1		14.7
45X/46X,i(Xq)	1		12.8
45X/46X,r(Xq)	1		15.8
Isochromosomes			
46X,i(Xq)	3	8.7–12.8	10.7
Turner	33	7.0–16.7	12.1
Controls	72	7.1–16.1	12.5

The enlargement of the midsagittal plane differed in the two samples being 9.6% in the Turner sample and 5.6% in controls. In the statistical handling of linear measurements, the values were corrected for radiographic enlargement.

A total of 34 cephalograms were traced and digitized twice. To evaluate any systematic error, the paired *t*-test was used on the differences between the double measurements (Houston, 1983). The error of measurement τ representing the total uncertainty in tracing and digitizing procedures was calculated according to the formula $\tau^2 = \Sigma d^2/2n$ (Dahlberg, 1940), where d is the difference between the first and second measurement. The error of measurement was generally small and τ varied between 0.46 and 2.07, with the greatest value found for the interincisal angle.

Statistical analysis

In the statistical analyses the Turner patients were subdivided according to karyotype as: (i) 45X and (ii) isochromosome and mosaic patients. An analysis of variance (ANOVA) was applied to test if the three population means were equal. If the probability of significance was <0.05, Tukey's multiple comparison test was used to range the means.

Results

A comparison of the means of the craniofacial variables between 45X, mosaic and isochromosome karyotypes and normal girls are presented in Tables 3–6. Most significant differences were found between 45X patients and controls. The values for isochromosome and mosaic patients almost invariably fell between those of 45X females and controls.

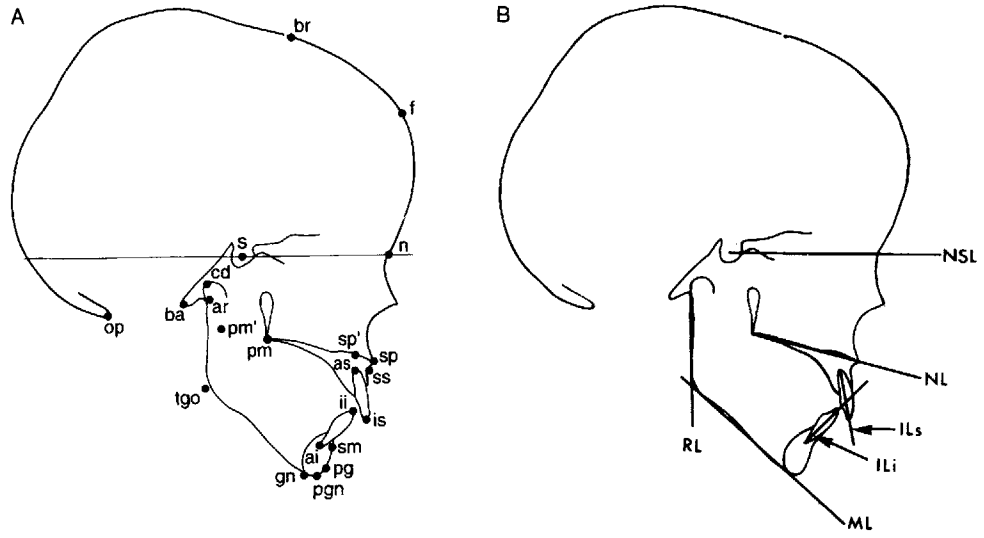

Figure 1A Cephalometric points recorded. For definitions see Bjørk (1963). br = Bregma. The intersection between the sagittal and coronal sutures on the surface of the cranial vault. f = Frontale. A point on the surface of the frontal bone defined by a line projected at right angles from the midpoint of a line connecting nasion and bregma (Bjørk, 1955). n = Nasion. The most anterior point on the frontonasal suture. s = Sella. The centre of the sella turcica. ba = Basion. The most postero-inferior point on the clivus. op = Opisthion. The most antero-inferior point on the posterior margin of foramen magnum. cd = Condylion. The most supero-posterior point on the condylar head. ar = Articulare. The intersection between the external contour of the cranial base and the dorsal contour of the condylar head or neck. tgo = Tangent-gonion. The point of intersection between the base and ramus tangents through gnathion and articulare. gn = Gnathion. The most inferior point on the mandibular symphysis. pgn = Prognathion. The point on the mandibular symphysis farthest from cd. pg = Pogonion. The most anterior point on the mandibular symphysis. sm = Supramentale. The most posterior point on the anterior contour of the lower alveolar process. ss = Subspinale. The most posterior point on the anterior contour of the upper alveolar process. sp = Spinal point. The apex of the anterior nasal spine. sp' = Spina marked. The intersection between the nasal line and a line from nasion to gnathion. pm = Pterygomaxillare. The intersection between the nasal floor and the posterior contour of the maxilla. pm' = The intersection between the nasal line and the line from sella to tangent-gonion. as = Apex superius. The apex of the root of the most prominent maxillary central incisor. is = Incision superius. The midpoint of the incisal edge of the most prominent maxillary central incisor. ii = Incision inferius. The midpoint of the incisal edge of the most prominent mandibular central incisor. ai = Apex inferius. The apex of the root of the most prominent mandibular incisor.

Figure 1B Reference lines. For definitions see Bjørk (1963). NSL = The line from nasion through sella defining the anterior part of the cranial base. NL = The line through the anterior nasal spine and the pterygomaxillary point defining the maxillary base along the nasal floor. ML = The tangent to the lower border of the mandible through gnathion. RL = The tangent to the posterior border of the mandible through articulare. Ili = The axis of the mandibular central incisor from ii to ai. Ils = The axis of the maxillary central incisor from is to as.

The differences in mean craniofacial morphology between the syndrome groups and controls are visualized in Figure 2. The tracings are based on mean values for the groups and superimposed on the Nasion–Sella line.

Craniofacial morphology in 45X patients

Calvarium

In the calvarium most dimensions differed from controls. The curvature of the frontal bone described by angle (s–n–f) was significantly increased (Table 3). The diameters of the head (op–br and ba–br) were significantly reduced but the distance (s–br) was normal. Foramen magnum (op–ba) was significantly smaller and the angle (s–ba–op) greater, which indicate altered position of the posterior point of foramen magnum relative to the posterior cranial base.

Cranial base

The flexion of the cranial base described by angle (n–s–ba) was significantly increased. The total length of the cranial base (n–ba) was significantly reduced. The reduction originated

Table 2 List of variables.

Calvarium		
Angular	s–n–f	Prominence of the frontal bone
	s–ba–op	Angle between opisthion and the posterior cranial base
Linear	op–ba	Width of the foramen magnum
	op–br	Diameter of the cranium from opisthion to bregma
	ba–br	Diameter of the cranium from basion to bregma
	s–br	Distance from sella to bregma
Cranial base		
Angular	n–s–ba	Cranial base angle
Linear	n–s	Anterior cranial base length
	s–ba	Posterior cranial base
	n–ba	Total cranial base length
Maxillary relations		
Angular	s–n–ss	Maxillary prognathism
	ba–s–pm	Angle between the posterior nasal spine and the posterior cranial base
	n–s–pm	Angle between the posterior nasal spine and the anterior cranial base
	ss–s–ba	Angle between subspinale and the posterior cranial base
	NL–NSL	Angulation of maxilla relative to the anterior cranial base
Linear	n–sp	Anterior upper face height
	s–pm	Posterior upper face height
	pm–ba	Distance from the posterior nasal spine to basion
	ss–ba	Distance from subspinale to basion
	pm–ss	Length of maxilla along the apical base
	pm–sp	Length of maxilla along the nasal floor
Mandibular relations		
Angular	s–n–sm	Mandibular prognathism
	s–n–pg	Prognathism of the chin
	n–s–ar	Angle between articulare and the anterior cranial base
	ML–NSL	Angulation of the mandible relative to the anterior cranial base
	gn–tgo–ar	Jaw angle
Linear	sp–gn	Lower anterior face height
	pm–tgo	Lower posterior face height
	ar–tgo	Height of the mandibular ramus
	gn–tgo	Length of the mandibular corpus
	cd–pgn	Mandibular length
Index	*ar–tgo* × *100* / gn–tgo	Mandibular proportion expressed as ramus height divided by corpus length
Maxillomandibular relations		
Angular	ss–n–sm	Basal sagittal jaw relationship
	ML–NL	Angle between maxillary and mandibular base lines
Linear	s–tgo	Posterior face height
	n–gn	Anterior face height
Index	*n–sp′* × *100* / sp′–gn	Anterior face height index
	s–pm′ × *100* / pm′–tgo	Posterior face height index
Dental relations		
Angular	is.as–n.ss	Proclination of the maxillary incisors
	ii.ai–n.sm	Proclination of the mandibular incisors
	is.as–ii.ai	Interincisal angle
Linear	is–n.ss	Protrusion of the maxillary central incisor relative to the NA–line
	ii–n.sm	Protrusion of the mandibular central incisor relative to the NB–line

Table 3 Analysis of variance (ANOVA) of calvarium and cranial base variables in 45X, mosaic and isochromosome patients and controls. Tukey's multiple comparison test showed no significant differences between 45X and mosaic and isochromosome karyotypes.

	45X ($n=24$)		Mosaics and isochromosomes ($n=9$)		Controls ($n=72$)		Analysis of variance		Tukey's multiple comparison test	
Variable	Mean	SD	Mean	SD	Mean	SD	F	P	45 X versus controls	Mosaics + isochromosomes versus controls
Calvarium										
s–n–f	94.5	3.25	92.9	3.74	89.9	3.57	16.47	0.000	**	*
s–ba–op	139.0	5.04	137.4	9.01	131.1	5.15	20.77	0.000	**	*
op–ba (mm)	32.4	1.78	33.9	2.50	36.6	2.24	36.52	0.000	**	**
op–br (mm)	145.8	5.09	146.4	6.93	150.7	4.89	9.99	0.000	*	*
ba–br (mm)	129.2	5.41	129.0	5.63	134.3	5.01	11.23	0.000	**	*
s–br (mm)	97.4	3.84	96.2	4.98	97.2	3.84	0.33	0.721	NS	NS
Cranial base										
n–s–ba	136.3	5.79	134.2	6.06	130.7	4.29	12.99	0.000	**	NS
n–s (mm)	63.5	2.28	63.0	4.67	64.5	2.90	1.85	0.163	NS	NS
s–ba (mm)	36.2	3.08	36.9	2.31	41.0	3.54	21.67	0.000	**	**
n–ba(mm)	93.0	4.13	92.4	3.97	96.4	4.62	7.18	0.001	**	*

*$P<0.05$; **$P<0.01$; NS = not significant.

Table 4 Maxillary relation variables in 45X, mosaic and isochromosome patients and controls. Tukey's multiple comparison test showed no significant differences between 45X and mosaic and isochromosome karyotypes.

	45X ($n=24$)		Mosaics and isochromosomes ($n=9$)		Controls ($n=72$)		Analysis of variance		Tukey's multiple comparison test	
Variable	Mean	SD	Mean	SD	Mean	SD	F	P	45 X versus controls	Mosaics + isochromosomes versus controls
Maxillary realations										
s–n–ss	76.3	3.70	78.5	4.42	80.0	3.52	12.17	0.000	**	NS
ba–s–pm	63.8	4.59	61.9	5.13	59.3	3.79	11.40	0.000	**	NS
n–s–pm	72.6	3.91	72.3	4.20	71.4	3.39	0.97	0.381	NS	NS
ss–s–ba	92.2	4.75	91.5	5.04	88.1	3.78	10.57	0.000	**	NS
NL–NSL	12.0	3.55	9.4	3.14	7.4	3.53	15.62	0.000	**	NS
n–sp (mm)	45.9	3.50	45.2	3.22	47.2	3.87	1.91	0.154	NS	NS
s–pm (mm)	37.8	2.70	39.2	2.21	43.3	3.12	35.14	0.000	**	**
pm–ba (mm)	39.1	2.10	39.1	2.81	41.7	2.83	10.94	0.000	**	*
ss–ba (mm)	81.3	3.70	81.8	5.33	85.1	4.50	7.78	0.001	**	NS
pm–ss (mm)	42.3	2.56	42.7	3.36	43.4	2.38	1.78	0.174	NS	NS
pm–sp (mm)	45.3	2.73	46.1	2.91	47.2	2.93	4.12	0.019	*	NS

*$P<0.05$; **$P<0.01$; NS = not significant.

Table 5 Mandibular relation variables in 45X, mosaic and isochromosome patients and controls. Tukey's multiple comparison test showed no significant differences between 45X and mosaic and isochromosome karyotypes.

	45X ($n=24$)		Mosaics and isochromosomes ($n=9$)		Controls ($n=72$)		Analysis of variance		Tukey's multiple comparison test	
Variable	Mean	SD	Mean	SD	Mean	SD	F	P	45 X versus controls	Mosaics + isochromosomes versus controls
Mandibular relations										
s–n–sm	73.7	4.58	75.1	3.07	77.4	3.50	9.60	0.000	**	NS
s–n–pg	74.4	4.83	75.9	3.43	78.5	3.67	10.08	0.000	**	NS
n–s–ar	128.9	5.68	127.6	5.20	124.0	4.84	9.30	0.000	**	NS
ML–NSL	36.8	6.53	35.2	4.35	33.4	5.30	3.62	0.030	*	NS
gn–tgo–ar	128.5	8.17	127.5	6.62	125.2	6.35	2.23	0.113	NS	NS
sp–gn (mm)	52.1	4.25	52.8	3.86	56.5	4.22	11.39	0.000	**	*
pm–tgo	37.3	4.75	37.0	3.76	39.7	3.95	4.18	0.018	*	NS
ar–tgo (mm)	40.6	4.14	40.5	4.67	39.4	4.20	0.95	0.390	NS	NS
gn–tgo (mm)	57.9	5.53	58.5	4.87	65.0	5.32	18.51	0.000	**	**
cd–pgn (mm)	94.7	6.01	95.8	6.29	101.3	6.62	10.94	0.000	**	*
ar–tgo × 100 gn–tgo	70.3	6.47	69.5	8.58	63.1	6.09	13.73	0.000	**	*

*$P<0.05$; **$P<0.01$; NS = not significant.

Table 6 Maxillomandibular and dental relation variables in 45X, mosaic and isochromosome patients and controls. Tukey's multiple comparison test showed no significant differences between 45X and mosaic and isochromosome karyotypes.

	45X ($n=24$)		Mosaics and isochromosomes ($n=9$)		Controls ($n=72$)		Analysis of variance		Tukey's multiple comparison test	
Variable	Mean	SD	Mean	SD	Mean	SD	F	P	45 X versus controls	Mosaics + isochromosomes versus controls
Maxillomandibular relations										
ss–n–sm	2.6	2.74	3.4	2.50	3.1	2.48	0.44	0.647	NS	NS
NL–ML	24.8	6.76	25.7	5.05	26.0	4.88	0.41	0.668	NS	NS
s–tgo (mm)	63.6	5.64	64.1	4.92	68.9	6.05	8.55	0.000	**	NS
n–gn (mm)	101.4	5.56	100.5	4.90	105.7	6.78	6.06	0.003	*	NS
n–sp′ × 100 sp′–gn	85.1	8.29	83.7	7.34	82.2	6.25	1.69	0.190	NS	NS
s–pm′ × 100 pm′–tgo	109.8	16.69	123.4	23.98	135.1	21.38	13.85	0.000	**	NS
Dental relations										
is.as–n.ss	24.7	5.63	22.7	6.90	20.8	6.96	3.15	0.047	*	NS
ii.ai–n.sm	22.4	5.79	22.0	6.14	23.0	6.22	0.14	0.874	NS	NS
is.as–ii.ai	130.2	9.15	131.8	9.02	133.1	9.17	0.94	0.394	NS	NS
is–n.ss (mm)	3.8	1.85	3.5	1.86	3.6	2.67	0.09	0.915	NS	NS
ii–n.sm (mm)	3.3	1.72	3.6	1.94	3.6	2.03	0.28	0.759	NS	NS

*$P<0.05$; **$P<0.01$; NS = not significant.

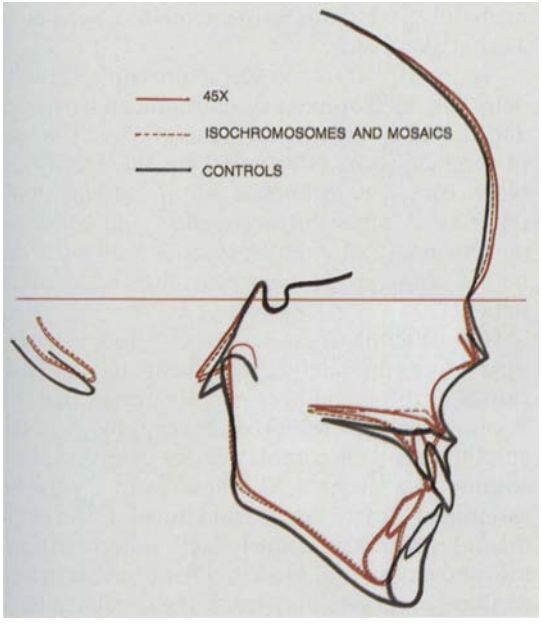

Figure 2 Tracings of the 45X, mosaic and isochromosome karyotypes and controls based on the mean cephalometric variables for each group, superimposed on the nasion–sella line (NSL) and registered at the sella point.

from a marked shortening of the posterior cranial base, (s–ba), while the anterior cranial base length (n–s) was normal.

Maxilla

The maxilla was retrognathic and posteriorly rotated shown by a significantly reduced angle (s–n–ss) and significantly Increased angle (NL–NSL) (Table 4). The angle between the posterior nasal spine and the posterior cranial base (ba–s–pm) was significantly increased which may be caused both by the posterior rotation of maxilla and the increased cranial base angle. The posterior nasal spine showed normal relation to the anterior cranial base (n–s–pm).

The upper anterior face height (n–sp) was normal while the upper posterior face height (s–pm), was significantly reduced reflecting the posterior rotation of the maxilla. Reduced distances of the linear variables (pm–ba, ss–ba) confirmed a significant retroposition of the maxilla.

The mean length of the maxilla along the nasal floor (pm–sp) was significantly reduced while the mean length of the maxilla measured from the apical base (pm–ss) was normal.

Mandible

The mandible showed deviations in sagittal and vertical position and also in size and proportion (Table 5). Significant reduction of angle (s–n–sm) and significant increase of angle (ML–NSL) demonstrated a retrognathic, posteriorly rotated mandible as did the increased angle (n–s–ar).

The anterior (sp–gn) and posterior (pm–tgo) lower face heights were significantly reduced. The vertical height of the ramus, (ar–tgo), was normal while both the length of the mandibular corpus (gn–tgo) and the total mandibular length (cd–pgn) were significantly reduced. The jaw angle (gn–tgo–ar) was normal. The proportions of the mandible expressed as the ratio between ramus height and corpus length deviated significantly, reflecting an altered mandibular shape.

Maxillomandibular relations

The basal sagittal jaw relationship (ss–n–sm) and the interbasal angle (NL–ML) were unchanged compared to normal controls (Table 6) while both the anterior (n–gn) and the posterior (s–tgo) face heights were significantly reduced.

The proportion between upper and lower face height was significantly changed for posterior face height only, reflecting the marked reduction in upper posterior face height (s–pm′).

Dental relations

The dental relations were normal except for the significantly more protruded maxillary central incisors relative to the line (n–ss).

Craniofacial morphology in mosaic and isochromosome of the long arm of X patients

The deviations in craniofacial morphology in mosaic and isochromosome patients always followed the same pattern as in 45X patients, but were less pronounced (Fig. 2). No structures showed greater deviations than those found in the monosomy (45X) group.

Also in mosaic and isochromosome karyotypes the most severe changes were observed in

the calvarium and the cranial base (Table 3), in maxillary position (Table 4) and in mandibular size and shape (Table 5). Maxillomandibular and dental relations variables did not differ significantly from controls (Table 6).

Among the 43 variables (linear, angular and indices) investigated, 13 differed significantly comparing mosaic and isochromosome karyotypes with controls, while 29 deviated significantly for the 45X karyotype (Tables 3–6). No significant differences were found comparing mosaic and isochromosome karyotypes with 45X patients.

Discussion

In the present study, young patients with Turner syndrome differed from normal girls both in craniofacial size and morphology; most linear dimensions were smaller. The face was retrognathic with marked deviations in cranial base length and flexion, and in mandibular size and shape. The deviations followed the same specific pattern for all the karyotypes, but were most pronounced in the monosomy X (45X) patients. The results are in accordance with Rongen-Westerlaken *et al.* (1992) and indicate that from childhood craniofacial morphology is already changed in a pattern characteristic for this syndrome.

The most pronounced deviations were found in structures derived from the chondrocranium and a cartilage disorder has been proposed as a possible aetiology (Rongen-Westerlaken *et al.*, 1992). The development of the craniofacial skeleton occurs as a result of two processes, endochondral and intramembranous ossification. In the fetal period the chondrocranium forms the craniofacial skeleton. During development most of the primary cartilages are replaced by bone. The cranial base grows by endochondral ossification in the synchondrosis, the mandible by intramembranous ossification and by appositional growth of the secondary cartilage of the mandibular condyle. The other bones are formed by intramembranous ossification, and growth occurs mainly in the sutures and by surface remodelling. Growth is controlled through a variety of mechanisms including circulating hormones, locally generated growth factors, vascularity and innervation (Nilsson *et al.*, 1986; Ranke *et al.*, 1987; Horton, 1990). One or more disturbances of this processes probably contribute to the growth deficiency in Turner syndrome.

An interrelationship seems probable between defective development of craniofacial cartilages and impaired growth of the epiphyses. Growth of long bones is effectuated by the epiphyseal plate cartilage. Stänescu *et al.* (1965) have reported changes in the chemical and enzymologic structure of chondrocytes as well as in the matrix of the growing cartilage in Turner patients.

Hall (1988b) discusses the complex mechanisms of craniofacial development and possible causes of dysmorphogenesis. He argues that the development of craniofacial morphology is the culmination of a complex series of diverse and overlapping events. All these events may be assembled into three fundamental developmental processes, namely cell differentiation, morphogenesis and growth. Disturbances in any of these processes may cause irreversible effects on craniofacial morphology.

Disturbances in these fundamental processes have been considered contributory to the pathogenesis in Turner syndrome. Some of the mechanisms discussed are: timing and level of X-chromosome inactivation (Therman *et al.*, 1980; Therman, 1983; Lyon, 1983; Shapiro, 1990; Epstein, 1990), alteration in cell generation time of 45X cells (Barlow, 1973; Simpson and Le Beau, 1981; Frias and Carnevale, 1983; Verp *et al.*, 1988; Varrela and Larjava, 1989), defective growth control due to abnormal hormonal regulation (Ranke *et al.*, 1987) and restricted mesenchymal tissue growth (Lippe, 1990).

The cartilage of the head is derived both from the neural crest cells and the mesoderm (Noden, 1986). It seems that the basic shape of craniofacial elements, especially those of of the mandibular skeleton, represents intrinsic properties of the mesenchyme producing the structures (Noden, 1984; Hall, 1984, 1988b). The size of the mesenchymal condensations also seems important (Hall, 1988b). Several of the abovementioned mechanisms may contribute to deviations in the mesenchymal condensations in Turner syndrome patients and thus to the dysmorphogenesis.

Alteration of morphogenesis has been demonstrated in tooth development (Midtbø and Halse, 1994a, b). An important step in tooth morphogenesis and also in the initiation of the

differentiation of craniofacial cartilages is epithelial–mesenchymal interactions (Kollar, 1981, 1983; Slavkin *et al.*, 1984, 1988; Hall, 1983a, b, 1988a). Their importance in morphogenesis of teeth is established but their role in craniofacial dysmorphogenesis is less well documented. However, much of the epigenetic control of differentiation and morphogenesis is effected by epithelial mesenchymal interactions (Hall, 1984, 1988b). It may be speculated that the abnormal amount of X-chromosome material in Turner syndrome may influence these interactions.

The investigations of Diewert (1982, 1985) of early craniofacial development suggest that differences in craniofacial morphology may be established much earlier than previously recognized. She explored the contribution of differential growth of cartilages to changes in craniofacial morphology by cephalometric methods adapted for histological material. The most evident feature of human facial growth during the embryonic period is the predominance of growth in the sagittal plane and at 10 weeks post-conception the face already has a typically human appearance. Both the mean cranial base angulation and maxillary position were similar to the angulation observed later, pre- and post-natally (Wisth and Bøe, 1974; Diewert, 1985). Rapid directional growth of the primary cartilages is important to the development of normal human facial morphology. Inhibition during this critical period, may have irreversible effects on the face that cannot be changed after replacement of the primary skeleton by the bony skeleton (Diewert, 1982)

Bishara and Jakobsen (1985) conclude after a longitudinal investigation of changes in growth pattern from 5–25.5 years, in three normal facial types, that there is a strong tendency to maintain the original facial type with age. Is this so also in Turner syndrome patients? Our findings and those of Rongen-Westerlaken *et al.* (1992) in children and young girls with Turner syndrome show that a retrognathic facial type with increased cranial base angle, reduced posterior cranial base length and a short posteriorly rotated mandible is already present from 3.5 years of age. Jensen (1974, 1985) and Peltomäki *et al.* (1989) observed a retrognathic facial type with the same specific deviations in adults with the syndrome, which indicates that the original facial type is also maintained with growth in Turner patients. The nature of the deviations and their localization are consistent with the theories of Diewert (1982, 1985). We suggest therefore, on the basis of these findings, that defective growth of the primary cartilages in the late embryonic and early fetal periods may contribute to the observed changes in craniofacial morphology, which further indicates that these changes may already be present from the tenth week.

Several common features are observed when comparing Turner syndrome patients with achondroplasia patients. Achondroplasia is a genetic disorder occurring either sporadically or inherited as an autosomal dominant trait (Gorlin *et al.*, 1990). In these patients endochondral ossification is disturbed causing reduced growth of long bones. The posterior cranial base is reduced in length while the anterior cranial base is normal, the size of foramen magnum is reduced and frontal bossing is a predominant feature (Eteson and Stewart, 1984). We have observed all these features in milder forms in our investigation of Turner patients, which may indicate some interrelationship in timing and aetiology of the defects. The altered shape of the calvarium and the frontal bossing observed in Turner syndrome patients could be interpreted as secondary to the restricted growth of the cranial base.

Several investigations have confirmed the connection between the number of X chromosomes and facial prognathism (Gorlin *et al.*, 1965; Jensen, 1974, 1985; Ingerslev and Kreiborg, 1978; Rongen-Westerlaken *et al.*, 1992; Babić *et al.*, 1993; Brown *et al.*, 1993). Jensen (1974) suggests that the differences in facial prognathism are secondary to the cranial base flexion which is increased in patients with X-chromosome monosomy (45X) and reduced in Klinefelter (47 XXY) syndrome patients (Ingerslev and Kreiborg, 1978). It seems generally accepted that loss or addition of an X chromosome influences the shape of the cranial base and thereby the degree of prognathism.

This investigation of Turner syndrome patients shows that a specific pattern of craniofacial morphology is already established in childhood. Earlier investigations have shown that the pattern is maintained with growth and a retrognathic facial type with deviations of specific structures can thus be obseved from infancy to adulthood, supporting the hypothesis that the deviating craniofacial morphology

develops in the fetal period when the primary cartilages form the craniofacial skeleton. The abnormal X-chromosome constitution may through various mechanisms influence differentiation, morphogenesis and growth of cartilage, which probably contribute to the dysmorphogenesis.

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