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The craniofacial complex in 47,XXX females

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SUMMARY A study of the craniofacial complex in four 47,XXX Finnish females, or females with an extra X chromosome, was carried out using cephalometric analysis comprising linear and angular measurements. The lengths of the anterior and posterior cranial bases, the calvarium, mandibular ramus and posterior and upper anterior face heights were found to be significantly shorter than in female controls, while the angles between the foraminal and clival planes, the mandibular plane and cranial base, the maxillary and occlusal planes, the maxillary and mandibular planes and the foraminal and mandibular planes, and also the gonial angle, were significantly enlarged.

The present findings of reduced linear measurements, together with the results of studies on the craniofacial complex of 47,XXY and 47,XYY males, suggest dimensional variation between these groups from the promoting effect of an extra Y chromosome and the retarding effect of an extra X chromosome on craniofacial growth.

Introduction

The 47,XXX karyotype was first described by Jacobs *et al.* (1959) as the 'superfemale', although in most cases these females with an extra X chromosome were identified in hospitals for the mentally subnormal.

This triple X syndrome is estimated to occur in one in every 800 (Therman and Susman, 1993) or one in every 1002 (Nielsen and Wohlert, 1991) newborn girls. The incidence increases with maternal age, and non-disjunction apparently occurs mainly during maternal meiosis.

47,XXX girls are usually normally developed at birth, but their average birth weight is slightly lower than that of girls with normal chromosomes (Stewart *et al.*, 1982). Anthropometric studies show that the final height of triple X syndrome female usually exceeds that of controls and their leg length in proportion to their overall height increases to a significant degree (Ratcliffe *et al.*, 1994a). Studies on skeletal maturation have revealed that bone age is below normal in early childhood, at 2–4 years of age, but well within normal limits by 7–10 years of age. Adrenal androgen assays and urinary growth hormone studies (Ratcliffe, 1985) show normal values. Triple X females usually have normal fertility, and almost all their children have normal karyotypes (Miller and Therman, 2001).

Head circumference in 47,XXX infants has been shown to be smaller than for control girls (Stewart *et al.*, 1982; Ratcliffe *et al.*, 1994b) and it has been reported that the basal angle of the skull is reduced in individuals with supernumerary sex chromosomes (Rzymski and Kosowicz, 1976), and some craniofacial anomalies may occur (Simpson, 1976). The average intelligence for triple X girls seems to be slightly lower than for siblings or a population control group (Nielsen, 1991), and an interesting correlation was found between head circumference at birth and IQ at 7 years of age (Ratcliffe *et al.*, 1994b).

Regarding the oral structures of 47,XXX females, a report on permanent tooth crowns indicated significantly increased enamel thickness compared with normal females or males, whereas the thickness of dentine remained within normal female limits (Alvesalo *et al.*, 1987). By contrast, enamel was markedly reduced in thickness in 45,X females (Alvesalo and Tammisalo, 1981). It was therefore obvious that the extra X chromosome is active in amelogenesis (Alvesalo *et al.*, 1987). These studies, together with those on tooth crown size and structure in other sex chromosome anomaly groups, have demonstrated the promoting effect of the Y chromosome both on enamel and dentine growth, whereas the effect of the X chromosome on crown growth seems to be limited to enamel formation. The X chromosome would appear to exert its effect through cell secretion and the Y chromosome through cell secretion and proliferation (Alvesalo, 1997).

The aim of the present investigation was to obtain information concerning the influence of the extra X chromosome on the size and shape of the craniofacial complex in 47,XXX females.

Subjects and methods

Four Finnish 47,XXX females from 17.5 to 26 years of age at the time of examination (mean 20.48 years) were studied. Their mean height was 167.5 cm, ranging from 156 to 175 cm. The population controls were 40 normal females (mean height 163.7 cm) from 17.7 to 33.5 years of age (mean 24.79 years) and 27 normal males (mean height 177.7 cm) from 18 to 55 years of age (mean 32.66 years) taken from the

Kvantti study series. These were relatives of patients other than those of the 47,XXX females. The adult sister of one 47,XXX female was also examined.

The patients and controls were radiographed and a cephalometric analysis comprising 32 linear and 12 angular measurements of the craniofacial complex was performed based on standardized lateral cephalograms. The reference points and planes used are shown in Figures 1 and 2. A sliding digital calliper (CD-15B, Mitutoyo (UK) Ltd, Andover, Hampshire, UK) was used to measure the distances between the reference points (marked in pencil on a matt acetate film) to the nearest half millimetre. Angular measurements were made to the nearest degree using a protractor. When there were two images of a structure, the reference point was placed at the midpoint. No correction was made for enlargement of the radiographs. The intra-observer method error was analysed as suggested by Bland and Altman (1986), and reliability by measuring and tracing 20 lateral cephalograms twice. The estimated error between measurements was calculated using the formula:

$$SD = \sqrt{\sum (d_1 - d_2)^2 / (2N)}$$

where ±2 *SD* are the limits within which 95 per cent of the differences between the repeated measurements are expected to lie; d_1 the first measurement; d_2 the second measurement; *n* the number of patients.

The error of the measurement, given in ±2 standard deviations of the differences between the repeated measurements, ranged between ±0.61 and ±2.34 (mean limit ±1.09) with the greatest error for linear measurements in the O–Go dimension. Angular measurements varied between ±0.89 and ±1.73 (mean limit ±1.24) with the greatest error in the For/Cliv angle. These errors were deemed to have an insignificant effect on the reliability of the results.

The craniofacial dimensions and plane angles of the four 47,XXX females were compared with those of the control females using the Mann–Whitney *U*-test. Male means for the population are quoted for reference (Table 1). All the measurements were made by one of the authors (VK).

Results

The linear measurements, dimensional ratios and angles of the craniofacial structures obtained from cephalometric analysis of the 47,XXX females and control groups of both genders are presented in Table 1.

The 47,XXX females in general demonstrated smaller linear and larger angular measurements than the control females and males. Statistically significant differences were found between the 47,XXX females and control females for nine linear and six angular measurements.

The length of the anterior (S–N; S–Fc) and posterior (Ba–Pt) cranial bases and the length of the calvarium (S–L) were significantly shorter in the 47,XXX females than in the female controls, and mandibular ramus length (Cd–Go) and posterior face height (S–Go) were significantly reduced, while the mandibular corpus (Go–Pg) demonstrated only a slight reduction.

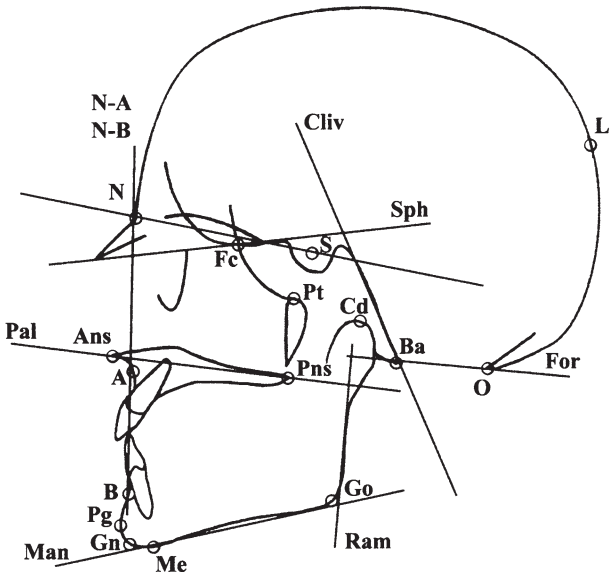

Figure 1 Reference points and planes used in the cephalometric analysis.

Points:	
S	Sella: the midpoint of sella turcica
N	Nasion: the extreme anterior point of the frontonasal suture
Ans	Anterior nasal spine: the extreme anterior point of the maxilla
Pns	Posterior nasal spine: the extreme posterior point of the maxilla
Pt	Pterygoid point: the extreme superior point of the pterygopalatine fossa
A	Point A: the deepest point in the curvature of the maxillary alveolar process
B	Point B: the deepest point in the curvature of the mandibular alveolar process
Pg	Pogonion: the extreme anterior point of the chin
Me	Menton: the extreme inferior point of the chin
Gn	Gnathion: the midpoint between pogonion and menton
Go	Gonion: the midpoint of the mandibular angle between ramus and the mandibular corpus
O	Opisthion: the posterior border of the foramen magnum
Ba	Basion: the anterior border of the foramen magnum
Cd	Condylion: the extreme superior point of the condyle
Fc	Fossa cranialis: the intersection between the sphenoidal plane and the larger wing of the sphenoid
L	Lambda: the midpoint of the lambdoid suture on the external cranial contour
Planes:	
S-N	Sella-Nasion line
Sph	Sphenoidal plane
Cliv	Clival plane
For	Foramen magnum plane
Pal	Palatal plane (Ans-Pns)
Occ	Occlusal plane (see Figure 2: from the intersection of the upper and lower incisors to the occlusal contact of the upper and lower first molars)
Man	Mandibular plane (a tangent to the lower border of the mandible)
Ram	Ramal plane (a tangent to the dorsal surface of the ramus with exclusion of the condyle)
N-A	Nasion- point A line
N-B	Nasion- point B line

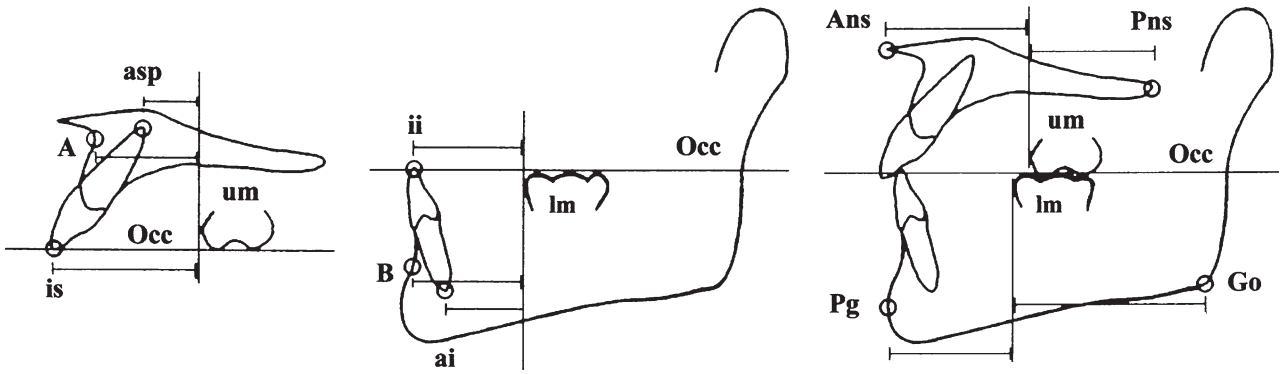

Figure 2 Occlusal analysis reference points from which measurements were made parallel to the occlusal plane.

is	Incision superius: the tip of the crown of the most anterior maxillary central incisor
asp	Apex superius: the root apex of the most anterior maxillary central incisor
um	Upper first molar: its most mesial point
ii	Incision inferius: the tip of the crown of the most anterior mandibular central incisor
ai	Apex inferius: the root apex of the most anterior mandibular central incisor
lm	Lower first molar: its most mesial point
Occ	Occlusal plane (from the intersection of the upper and lower incisors to the occlusal contact of the upper and lower first molars)
Ans	Anterior nasal spine: the extreme anterior point of the maxilla
Pns	Posterior nasal spine: the extreme posterior point of the maxilla
A	Point A: the deepest point in the curvature of the maxillary alveolar process
B	Point B: the deepest point in the curvature of the mandibular alveolar process
Pg	Pogonion: the extreme anterior point of the chin
Go	Gonion: the midpoint of the mandibular angle between ramus and the mandibular corpus

The angles between the foraminal and clival planes (For/Cliv) and between the foraminal and mandibular planes (For/Man) were greatly enlarged in the triple X female group. The gonial (Man/Ram) and SNB angles were also significantly increased. The cranial base angle (Sph/Cliv) was smaller in the syndrome group than in the control females, but the difference was not significant.

Analysing the maxillary complex, an increased maxillary plane inclination in relation to the mandibular (Pal/Man) and occlusal (Pal/Occ) planes was found and it seemed that the anterior limit of the maxilla in 47,XXX females was located closer to the sella than in the controls.

Analysis of the dental complex revealed that the apex of the upper incisor root was located closer to the upper molar (asp–um) and the tip of the lower incisor crown located closer to the lower molar (ii–lm) than in the female controls. The reductions in these measurements also affected the dimensional ratios, in that the asp–um/is–um ratio was decreased and the ai–lm/ii–lm ratio increased in the 47,XXX females. The results of the cephalometric analysis of the sister of one 47,XXX female gave similar values to the control females.

Discussion

Cephalometric analysis of 47,XXX females suggests that an extra X chromosome causes craniofacial growth reduction and changes in angular measurements compared with normal females. Certainly, because of the small sample size, the results are not necessarily representative of 47,XXX females in general.

The anterior and posterior cranial bases and calvarium dimensions were markedly reduced. A reduced head circumference has been found in 47,XXX females (Stewart *et al.*, 1982; Ratcliffe, 1985; Robinson *et al.*, 1991), a shorter anterior cranial base in 45,X/46,XX females (Grön *et al.*, 1999) and a shorter posterior cranial base in 45,X females (Peltomäki *et al.*, 1989).

A clear tendency for a reduction in all face heights in these 47,XXX females was found, but this was statistically significant only for posterior and upper anterior face heights. The posterior face height reduction might be caused by a shorter mandibular ramus length. A reduction in face heights and shortening of the mandibular ramus has also been noted in Klinefelter or 47,XXY syndrome males (Brown *et al.*, 1993).

Among the significant changes found in certain angular measurements of the skull in the 47,XXX females, the angle between the foraminal and clival planes (For/Cliv) was significantly increased, as also recorded in other individuals with defective karyotypes related to changes in the number of X chromosomes, e.g. 45,X females (Peltomäki *et al.*, 1989) and 45,X/46,XX females (Grön *et al*., 1999), but not in individuals with an additional Y chromosome, such as in 47,XYY males (Grön *et al.*, 1997).

Comparative analysis of increased angles between the foraminal and clival planes (For/Cliv) and between the foraminal and mandibular planes (For/Man) in 47,XXX

Table 1 Cephalometric linear measurements (mm), dimensional ratios and angles (degrees) of 47,XXX females and controls of both sexes.

	47,XXX females (n = 4)				Control females (n = 40)				Control males (n = 27)				Mann–Whitney U-Wilcoxon rank sum W-test[a]
	Mean	(SD)	Range		Mean	(SD)	Range		Mean	(SD)	Range		Two-tailed P-value
			Min	Max			Min	Max			Min	Max	
Age (years)	20.38	3.88			24.69	4.81			32.56	9.37			
Linear dimensions													
Cranial base													
S–N	68.66	1.61	67.13	70.8	73.56	3.04	67.1	80.54	76.87	4.12	65.77	83.78	0.0018**
S–Fc	23.75	2.76	20.99	26.22	27.85	1.87	23.98	31.73	29.21	2.89	20.93	36.26	0.0017**
Fc–N	45.49	3.03	41.42	47.88	46.11	3.09	40.25	53.33	47.94	3.82	38.85	53.39	0.6506
S–Ba	44.32	2.34	42.16	47.6	45.58	2.56	40.06	50.86	49	2.77	43.19	54.25	0.3948
Ba–Pt	49.47	1.78	48.39	52.11	53.47	2.93	47.24	60.59	54.49	3.25	48.76	60.11	0.0089**
Fc–Pt	17.86	3.24	14.53	22.29	17.7	2.94	11.33	23.43	20.13	3.11	13.65	26.86	0.8569
S–L	114.15	4.22	109.14	119.01	119.37	4.1	111.76	128.38	121.71	4.84	110.96	130.72	0.0358*
O–Ba	35.13	2.33	31.95	37.48	35.08	1.94	30.87	38.4	36.74	1.88	32.84	40.15	0.8314
Cranial base to maxillary complex													
S–Cd	21.03	2.9	17.43	24.47	22.28	2.62	16.77	27.01	26.45	2.78	20	32.54	0.3929
O–Cd	55.03	3.45	51.03	59.03	54.15	3.46	46.97	62.5	54	3.12	47.97	59.33	0.6224
O–Go	63.06	8.81	57.55	76.08	65.5	4.87	55.93	74.56	71.54	7.15	59.24	83.92	0.2718
S–Go	71.26	7.15	64.88	81.42	78.42	5.15	68.31	88.67	88.87	6.87	75.43	105.33	0.0362*
N–Me	114.43	5.32	106.9	118.64	120.11	5.84	108.89	134.63	131.66	5.32	120.33	145.73	0.0908
N–Ans	48.88	2.04	46.02	50.84	52.3	3.1	45.8	60.03	57.02	3.02	50.5	63.36	0.0281*
S–Ans	81.36	6.49	77.11	90.97	87.26	3.61	80.25	95.09	92.72	5.27	78.22	103.79	0.0617
S–Pns	47.82	3.95	44.51	53.53	49.32	2.6	44.27	55.96	52.87	3.12	48.37	61.99	0.2387
Maxillary complex													
Ans–Me	66.53	6.46	57.77	72.55	69.16	4.76	58.93	80.97	76.25	5.22	67.51	88.47	0.5388
Ans–Pns	52.63	5.93	46.51	60.65	54.44	2.9	47.95	59.64	59.64	3.23	51.07	65.31	0.3708
A–Pns	48.65	5.89	43.58	56.55	50.56	2.64	45.08	56.14	55.02	3.04	46.3	59.89	0.3496
Go–Pg	75.8	5.29	69.01	80.31	78.64	5.02	67.75	92.63	84.45	4.18	77.45	95.09	0.3948
Cd–Go	54.69	3.89	51.42	60.32	59.52	4.2	51.96	68.34	67.86	7.87	55.41	95.3	0.0446*
Cd–Gn	117.03	2.54	114.77	120.17	118.5	5.51	109.08	130.82	129.91	6.57	119.65	142.94	0.7084
Dental complex													
is–um	27.22	2.52	24.61	30.57	28.06	2.82	19.77	33.7	29.31	2.85	25.04	36.48	0.4613
asp–um	14.16	2.51	11.29	17.25	17.68	3.01	8.31	25.3	17.81	3.07	12.06	24.14	0.0279*
A–um	18.28	3.14	14.11	21.06	20.81	2.63	15.09	28.88	22.15	3.15	15.92	28.58	0.1173
ii–lm	19.52	4.48	15.14	25.71	24.66	3.08	18.57	32.57	23.8	2.71	17.69	31.37	0.0318*
ai–lm	16.38	1.86	14.89	19.08	15.03	3.86	10.03	25.26	14.63	2.74	8.4	18.95	0.207
B–lm	20.82	2.92	18.46	25.05	20.24	3.91	14.84	30.81	20.32	2.68	14.34	25.66	0.7058
Ans–um	21.31	3.86	16.64	25.18	24.34	3.05	19	33.05	26.4	3.54	19.13	32.9	0.1414
Pns–um	29.68	5.13	22.81	35.09	29.68	3.23	23.1	36.77	32.66	3.58	26.7	38.5	0.7952
Pg–lm	24.41	1.64	22.49	26.47	22.64	5	14.89	37	24.05	3.05	14.7	29.24	0.2748
Go–lm	49.26	5.77	41.28	54.48	53.19	6	41.02	63.4	58	5.38	46.36	70.05	0.2733
Dimensional ratios													
Ans–Pns/Go–Pg	0.7	0.13	0.5791	0.8789	0.69	0.05	0.5821	0.8006	0.71	0.05	0.6196	0.7821	0.5151
Ans–Pns/S–N	0.77	0.07	0.6928	0.8566	0.74	0.04	0.6676	0.8189	0.78	0.04	0.6654	0.8398	0.5676
Go–Pg/S–N	1.11	0.1	0.9747	1.1963	1.07	0.07	0.9083	1.1943	1.1	0.06	0.9994	1.2484	0.3307
S–Go/N–Me	0.62	0.05	0.5805	0.6863	0.65	0.05	0.5662	0.7598	0.68	0.05	0.5513	0.7401	0.2556
N–Ans/Ans–Me	0.74	0.09	0.6343	0.8574	0.76	0.069	0.5967	0.889	0.75	0.07	0.6247	0.8983	0.6224
asp–um/is–um	0.52	0.05	0.4588	0.5643	0.63	0.09	0.4203	0.8384	0.61	0.09	0.471	0.8624	0.0123*
ai–lm/ii–lm	0.86	0.1	0.7421	0.9835	0.6	0.1	0.3955	0.8503	0.62	0.1	0.4247	0.7906	0.0003***
Cd–Go/Go–Pg	0.73	0.1	0.6453	0.8741	0.76	0.07	0.6109	0.8975	0.8	0.08	0.6382	1.1112	0.2733
Angles													
Cranial base													
Sph/S-N	17.25	3.59	12	20	14.55	2.98	8	21	14.11	4.31	7	24	0.1939
Sph/Cliv	106.5	4.65	102	113	110.6	5.09	101	121	109.52	7	97	121	0.131
For/Cliv	131.25	4.65	125	136	125.68	4.58	117	136	123.11	4.73	109	131	0.0348*
Maxillary complex sagital													
SNA	81.75	6.18	78	91	81.98	3.29	77	90	82.93	4.19	75	91	0.3442
SNB	83.5	3.7	80	88	79.45	3.19	71	86	80.15	3.76	70	85	0.0359*
Maxillary complex vertical													
Pal/Occ	13	4.97	7	19	7.18	2.77	3	16	6.33	3.01	2	13	0.0111*
Pal/Man	31	5.29	26	38	25.3	4.69	13	33	23.48	5.12	15	34	0.0479*
Man/Occ	18	2.94	14	21	18.38	4.04	9	25	17.19	3.69	9	24	0.8166
Man/Ram	127.75	5.25	123	135	120.1	7.05	102	138	119.07	5.53	110	130	0.0362*
Man/S–N	33.75	3.5	32	39	30.83	5.48	19	42	29.78	5.54	22	47	0.2968
Sph/Man	16.25	7.93	11	28	16.13	5.01	5	25	15.74	6.84	4	36	0.7153
For/Man	41	5.35	35	48	30.95	5.72	16	44	29.15	6.07	17	41	0.0033**

*P < 0.05; **P < 0.01; ***P < 0.001. [a]47,XXX females versus control females.

females probably indicates that an additional X chromosome mainly affects the foraminal plane, because the inclination of the mandibular plane does not vary significantly relative to other cranial base planes.

The cranial base flexure has an influence on general face morphology. Rzymski and Kosowicz (1976) reported that a reduced number of sex chromosomes was associated with an increased basal angle, whereas a reduction in this angle appears in patients with supernumerary sex chromosomes. This statement is endorsed by the results of an increased basal angle from studies of individuals with 45,X (Peltomäki *et al.*, 1989) and 45,X/46,XX (Grön *et al*., 1999) karyotypes. Although only an insignificant reduction in the cranial base angle (Sph/Cliv) was found in 47,XXX females, it expressed a clear trend.

Gorlin *et al.* (1965), summarizing their descriptions of the facial appearance in various chromosomal aneuploidies, pointed out that in the case of additional X chromosomes the mandible is more prognathic in relation to the maxilla and cranial base. The findings in the present study of a significantly increased SNB angle in these 47,XXX females may be related to the significant decrease in anterior and posterior cranial base dimensions, because the mandibular corpus (Go–Pg) demonstrated only a slight reduction and the substantial reduction in ramus height (Cd–Go) was compensated by a flattened gonial angle.

Analysis of angular relationships of the mid face in this triple X female group demonstrated some changes compared with the control groups in that the palatal plane was canted upwards, as was obvious from the significantly increased angles between the palatal and occlusal planes and between the palatal and mandibular planes. Due to the altered inclination of the palatal plane and shorter anterior cranial base, the anterior limit of the maxilla (S–Ans) was located closer to sella. The slightly retruded maxilla in 47,XXX females could also enhance mandibular prognathism.

The mandibular and maxillary skeletal Class III growth pattern in 47,XXX females may lead to compensatory changes in the dento-alveolar complex, in the form of a reduction of the proclination of the upper incisors (asp–um) and retroclination of the lower incisors (ii–lm).

The results of the present and other studies have shown that X chromosome aneuploidy can influence skull dimensions, although the underlying mechanisms are not clear. Lyon (1974) pointed out that each somatic cell has one active X chromosome, and any additional X chromosome is inactivated early in embryonic development. Evidence has accumulated during the last decade, however, to suggest that parts of the second (or third) X chromosome may remain active for a longer period. X-specific genes escaping inactivation could affect the phenotype in individuals with X chromosome aberrations because of the dosage effect. These genes are isolated in various parts of the X chromosome (Ogata and Matsuo, 1993). Babić *et al.* (1991), in their study of the effect of an extra X chromosome on craniofacial morphology in men with Klinefelter syndrome or 47,XXY males, hypothesized that their craniofacial dimensions were probably associated with a reduced expression of the genes on the long arm of the Y chromosome, due to the presence of the double dose of the X chromosome genes.

Previous studies of 47,XXY males, or males with an extra X chromosome, indicate that their craniofacial linear growth was somewhat reduced relative to that of normal males, but was still greater than in females (Babić *et al.*, 1991; Brown *et al.*, 1993) and they also showed increased height (Varrela, 1984). By contrast, the extra Y chromosome in 47,XYY males definitely increases craniofacial growth (Grön *et al.*, 1997) and their height is also remarkably increased relative to normal males or 47,XXY males (Varrela and Alvesalo, 1985). Conceivably, the variation in craniofacial linear dimensions between these groups results from the promoting effect of an extra Y chromosome and a retarding effect of an extra X chromosome on growth within the craniofacial complex.

Conclusions

The results of this study indicate that the presence of an extra X chromosome causes a reduction in craniofacial growth and reflects on the overall length of the calvaria, the anterior and posterior carnial bases and the facial complex.

The unbalanced chromosome constitution in 47,XXX females creates some characteristic phenotypic features, e.g. an increase in height due to an increased leg length, small head circumference, increased tooth enamel thickness, and, as reported here, reduced linear growth and increased angles within the craniofacial complex.

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