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The relationship of distinct craniofacial features between Turner syndrome females and their parents

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SUMMARY The present study aimed to assess the relationship of craniofacial features between females with Turner syndrome (TS) and their parents. Lateral cephalograms of 63 TS females and 80 family members with normal karyotype were analysed using 13 linear and eight angular cephalometric measurements. The statistical differences of the measurements between adult TS females and their mothers (n = 41) and between adult TS females and their adult sisters (n = 27) were calculated to define the distinct craniofacial features of subjects with TS. Regression models were computed to assess the association of distinct craniofacial features between TS females and their parents (n = 41 for mothers and n = 12 for fathers).

Distinct craniofacial features of the subjects with TS were an increased cranial base flexion, shortened posterior cranial base length (S–Ba), retrognathic maxilla and mandible (<SNB), shortened distance of the palate, glenoid fossa (S–Art) and gonion (S–Go) from sella, shortened body and total length (Art–Pog) of the mandible and increased vertical angles of the facial skeleton. The mothers' S–Ba (P = 0.001), <SNB (P < 0.001), S–Go (P < 0.01) and S–Art (P < 0.05) measurements predicted well the corresponding measurements of their daughters with TS. Fathers had a significant association with their TS daughters in Art–Pog (P < 0.01) measurement.

The results suggest that maternal influences contribute to the growth of a distinct cranial base and to the magnitude of mandibular retrognathism of subjects with TS.

Introduction

Turner syndrome (TS) is a sex chromosome disorder which is related to the loss of X chromosome material. The TS patients' phenotype is always female. Approximately half TS females have a karyotype 45,X. They have only one X chromosome instead of two. The other half of TS females consist of 46,XX females with one of the two X chromosomes being structurally abnormal and females with different cell line mosaicism. The clinical features of TS are thought to arise from the haploinsufficiency of non-inactivated genes on the X chromosome (Gelehrter *et al.*, 1998).

Females with TS are characterized by a short stature and gonadal dysgenesis. The growth retardation in TS starts during the intrauterine period and becomes most evident by the lack of the growth spurt during puberty (Davenport *et al.*, 1999; Andersen *et al.*, 2000). The average adult height is below 150 cm. Other skeletal features present in TS include cubitus valgus (increased angle of elbow) (77 per cent), broad chest (74 per cent), and short fourth metacarpals (55 per cent). A short (77 per cent) and webbed (42 per cent) neck is also commonly observed (Miller and Therman, 2001). Subjects with TS are often described as having a triangular-shaped face, low set ears, and micrognathia (Gorlin *et al.*, 2001). Cephalometric studies have reported an increased cranial base flexion, reduced posterior cranial base and retrognathic face (Jensen, 1985; Peltomäki *et al.*, 1989; Rongen-Westerlaken *et al.*, 1992; Babić *et al.*, 1993; Midtbø *et al.*, 1996). Females with TS have a tendency to a distal molar occlusion (50–60 per cent) (Laine *et al.*, 1986; Midtbø and Halse, 1996). Commonly observed malocclusions include a lateral crossbite (40–70 per cent), which is caused by narrow maxillary and wide and short mandibular alveolar arches (Laine *et al.*, 1985; Laine and Alvesalo, 1986; Midtbø and Halse, 1996; Szilagyi *et al.*, 2000). TS subjects have a characteristic high arched palatal form (Laine *et al.*, 1985), which might relate to a higher frequency for a cleft palate in TS (Gorlin *et al.*, 2001). The smaller size of teeth in TS (Alvesalo and Tammisalo, 1981; Townsend *et al.*, 1984; Midtbø and Halse, 1994) is caused by reduced enamel thickness (Alvesalo and Tammisalo, 1981) and is related to the haploinsufficiency of the amelogenin gene on the short arm of the X chromosome (OMIM *300391) (Lau *et al.*, 1989).

The genetic factors related to growth failure in TS may arise from a deficiency of X-linked gene(s) and from non-specific effects of aneuploidy on cell proliferation (Ogata and Matsuo, 1995; Haverkamp *et al.*, 1999). The short stature is suggested to be caused, at least in part, by haploinsufficiency of a short status

homeobox-containing (SHOX) gene, which is located in the terminal end of the short arm of the X chromosome and escapes the inactivation (OMIM *312865) (Rao *et al.*, 1997; Ellison *et al.*, 1997). The SHOX gene is expressed during embryogenesis, not only in the developing limb buds but also in the first and second pharyngeal arches (Clement-Jones *et al.*, 2000). However, the further influence of the SHOX gene on TS facial characteristics is not well understood.

There is a correlation for statural height between parents and their children in the general population. A similar correlation of height has been shown between parents and their children with TS, who are remarkably shorter than their parents (Brook *et al.*, 1977). This kind of relationship of stature has not been observed, e.g. between subjects with Down's syndrome and their parents. The purpose of the present study was to identify the distinct craniofacial features that characterize TS subjects and to assess the relationship of these craniofacial features between TS subjects and their parents.

Subjects and methods

Study subjects

The study population consisted of 63 TS subjects, with a karyotype 45,X, and their biological mothers ($n = 41$), fathers ($n = 12$) and sisters ($n = 27$). The mean ages and age ranges of the study groups are presented in Table 1. Approximately 10 per cent of all mothers were edentulous and 29 per cent had an edentulous maxilla. They were therefore excluded. The study subjects were part of the Kvantti Project, the material of which has been collected since the early 1970s, mainly at the University of Turku, Finland. The X chromosome monosomy of the study subjects with TS was established for medical reasons. Many of the patients with TS had received oestrogen treatment and small dose growth hormone substitutes. It can be assumed that neither the oestrogen treatment nor the growth hormone therapy had a major impact on the craniofacial morphology of the subjects with TS (Park *et al.*, 1983; Rongen-Westerlake *et al.*, 1992; Hass *et al.*, 2001).

Table 1 The mean ages (± standard deviation) and age ranges of the family member groups.

	TS subjects ($n = 63$)	Mothers ($n = 41$)	Fathers ($n = 12$)	Sisters ($n = 27$)
Age (years)	17 ± 7	39 ± 8	40 ± 11	23 ± 9
Age range (years)	6–38	24–56	30–65	15–54

TS, Turner syndrome.

Cephalometric measurements

The lateral cephalometric radiographs of each subject were analysed with a computer program (Dolphin Imaging Systems, Woodland Hills, California, USA) using 13 linear and eight angular measurements. The mandibular cephalometric measurements (Art–Go, Go–Pog, Art–Pog) were carried out by hand. Intra-observer reliability was assessed between repeated measurements for 15 subjects with a 1 week interval. An intra-class correlation coefficient (ICC) ≥ 0.9 for all measurements indicated a satisfactory level of intra-investigator reliability. The points measured are listed in Figure 1.

Statistical analyses

The distinct craniofacial characteristics of the study subjects were identified by determining the statistical

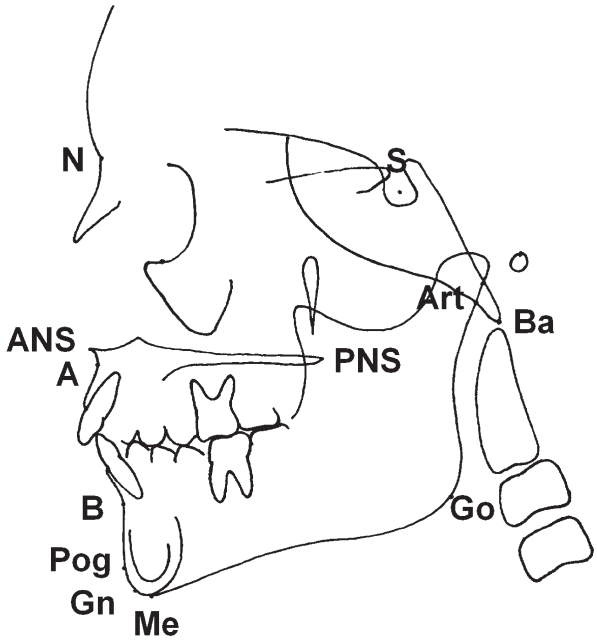

Figure 1 Cephalometric landmarks and measurements. A, point A; ANS, anterior nasal spine; Art, articulare; B, point B; Ba, basion; Gn, gnathion; Go, gonion; Me, menton; N, nasion; PNS, posterior nasal spine; Pog, pogonion; S, sella. Cephalometric planes: MP, mandibular plane; PP, palatal plane; SN, S–N plane. S–N, anterior cranial base length; N–Ba, total cranial base length; S–Ba, posterior cranial base length; S–PNS, distance between sella and posterior nasal spine; S–Go, total posterior face height; N–Me, total anterior face height; N–ANS, upper anterior face height; ANS–Me, lower anterior face height; ANS–PNS, palatal length; S–Art, upper posterior face height; Art–Go, ramus height of the mandible; Go–Pog, length of the body of the mandible; Art–Pog, total length of the mandible; <ANB, facial convexity angle; <SNA, sagittal location of the maxilla in relation to cranial base; <SNB, sagittal location of the mandible in relation to cranial base; <MP–SN, the angle of MP to SN; <N–S–Ba, cranial base flexion; <PP–MP, the angle of PP to MP; <SN–PP, the angle of SN to PP; <Art–Go–Me, the gonial angle of the mandible.

differences of the cephalometric measurements between adult subjects with TS and their mothers, and between adult subjects with TS and their adult sisters, using paired *t*-tests. $P < 0.05$ was considered statistically significant.

Multiple regression models were computed to assess to what extent the cephalometric measurements of the TS subjects could be predicted from the values of the cephalometric measurements of their parents. Age was included in the regression model to eliminate the effect of the varying age of the TS subjects. The cephalometric measurements of the subjects with TS were assigned as dependent variables, and those of their mothers and fathers and the age and age squared of the TS subjects as independent variables. As the data of the fathers were limited, the fathers' cephalometric measurements were changed to dummy variables. The fathers were divided into three groups, small (S), missing (M) and large (L), for each cephalometric measurement. The fathers belonged to the S and L groups depending on whether the cephalometric measurement was below or above the median value of all fathers. If the data of the father were missing, he was referred to the M group.

Results

Distinct craniofacial features of the subjects with TS

Females with TS differed statistically significantly both from their mothers and sisters for six linear and five angular cephalometric measurements (Tables 2 and 3). Females with TS were characterized by a shortened posterior cranial base length (S–Ba) and their palate, glenoid fossa and gonion were located closer to sella (S–PNS, S–Art, S–Go). The length of the body of the mandible (Go–Pog) and the total length of the mandible (Art–Pog) were shortened. The cranial base angle (<N–S–Ba) of TS females was increased and their face was retrognathic [mandible (<SNB) more than maxilla (<SNA)]. Their facial skeleton was also hyperdivergent (<MP–SN, <SN–PP). These 11 measurements were defined as distinct craniofacial features of the subjects with TS.

Table 2 Cephalometric measurements of adult Turner syndrome (TS) subjects and their mothers.

	TS subjects (n = 23)	Mothers (n = 23)	P
S–N	71.11 ± 3.29	71.60 ± 2.81	0.36
N–Ba	105.12 ± 6.18	105.82 ± 4.92	0.58
S–Ba	42.70 ± 3.48	45.70 ± 3.28	0.002
S–PNS	42.78 ± 2.67	49.24 ± 3.14	<0.001
S–Go	74.80 ± 6.54	79.00 ± 5.07	0.01
N–Me	117.37 ± 8.29	117.72 ± 5.54	0.86
N–ANS	52.16 ± 3.26	52.90 ± 2.74	0.36
ANS–Me	66.49 ± 7.68	65.73 ± 5.45	0.66
ANS–PNS	52.56 ± 2.85	52.54 ± 3.40	0.98
S–Art	32.56 ± 2.57	34.69 ± 3.46	0.02
Art–Go	47.17 ± 6.12	49.61 ± 4.63	0.22
Go–Pog	71.07 ± 4.81	77.37 ± 4.93	<0.001
Art–Pog	103.24 ± 6.11	112.11 ± 7.37	<0.001
<ANB	3.89 ± 2.66	1.69 ± 4.31	0.02
<SNA	78.42 ± 3.57	81.75 ± 3.48	0.001
<SNB	74.52 ± 4.12	80.10 ± 4.29	<0.001
<MP–SN	34.33 ± 8.49	29.63 ± 5.36	0.03
<N–S–Ba	134.05 ± 7.38	130.05 ± 5.82	0.01
<PP–MP	23.80 ± 8.65	22.97 ± 5.47	0.67
<SN–PP	10.60 ± 3.28	6.67 ± 2.47	<0.001
<Art–Go–Me	123.70 ± 7.77	123.95 ± 6.95	0.89

The values are mean ± standard deviation. The abbreviations are shown in Figure 1.

Table 3 Cephalometric measurements of adult Turner syndrome (TS) subjects and their adult sisters.

	TS subjects (n = 27)	Sisters (n = 27)	P
S–N	72.33 ± 3.28	72.30 ± 2.90	0.97
N–Ba	106.75 ± 5.12	108.57 ± 4.44	0.15
S–Ba	42.48 ± 2.64	46.23 ± 2.83	<0.001
S–PNS	44.21 ± 2.98	48.43 ± 2.78	<0.001
S–Go	74.86 ± 4.86	78.36 ± 5.70	0.003
N–Me	119.16 ± 5.75	116.98 ± 6.35	0.17
N–ANS	53.46 ± 3.08	53.03 ± 2.78	0.59
ANS–Me	67.17 ± 4.72	65.35 ± 5.36	0.12
ANS–PNS	53.23 ± 3.03	53.82 ± 2.44	0.34
S–Art	32.54 ± 3.96	34.54 ± 2.66	0.01
Art–Go	47.63 ± 3.69	48.38 ± 4.85	0.43
Go–Pog	72.21 ± 4.82	76.95 ± 3.54	<0.001
Art–Pog	105.80 ± 4.20	109.59 ± 5.26	0.003
<ANB	4.44 ± 2.61	3.76 ± 2.79	0.17
<SNA	78.06 ± 3.68	82.49 ± 3.49	<0.001
<SNB	73.63 ± 3 96	78.8 ± 4.05	<0.001
<MP–SN	35.19 ± 5.93	29.79 ± 5.48	<0.001
<N–S–Ba	135.84 ± 6.07	131.55 ± 4.74	<0.001
<PP–MP	24.95 ± 5.67	22.18 ± 5.19	0.05
<SN–PP	10.02 ± 3.46	7.60 ± 3.03	0.005
<Art–Go–Me	124.17 ± 6.14	122.05 ± 6.01	0.11

The values are mean ± standard deviation. The abbreviations are shown in Figure 1.

Association of the distinct craniofacial measurements between TS subjects and their parents

The statistical significance of the regression coefficients of the distinct cephalometric measurements between subjects with TS and their parents are shown in Table 4. The mothers' S–Ba and <SNB measurements predicted well their TS daughters' distinct S–Ba and <SNB measurements. The cephalometric measurements S–Go and S–Art also had a statistically significant association between mothers and their daughters with TS. Fathers and their daughters with TS had a significant association only for Art–Pog.

Discussion

In the general population, the height of children has a high correlation with the midparental height of their

Table 4 The association of distinct cephalometric measurements between females with Turner syndrome (TS) and their parents.

	Mothers (n = 41)			Fathers (n = 12)	
	R	P		R	P
S–Ba	0.59	0.001	L versus S	0.98	0.57
			M versus S	0.19	0.89
S–PNS	0.22	0.09	L versus S	2.41	0.12
			M versus S	1.12	0.37
S–Go	0.41	<0.01	L versus S	2.92	0.37
			M versus S	0.02	0.99
S–Art	0.24	0.03	L versus S	1.69	0.19
			M versus S	–0.21	0.83
Go–Pog	0.16	0.28	L versus S	5.12	0.08
			M versus S	1.79	0.43
Art–Pog	0.19	0.09	L versus S	7.28	0.01
			M versus S	2.00	0.34
<SNA	0.33	0.10	L versus S	0.70	0.78
			M versus S	0.18	0.93
<SNB	0.56	<0.001	L versus S	–0.25	0.91
			M versus S	0.13	0.93
<MP–SN	0.40	0.08	L versus S	–2.60	0.57
			M versus S	–1.56	0.69
<N–S–Ba	0.35	0.09	L versus S	–4.21	0.24
			M versus S	–2.67	0.33
<SN–PP	0.26	0.22	L versus S	2.35	0.23
			M versus S	2.39	0.12

The regression coefficients with P values for parents' measurements are shown. The fathers were divided into three groups: small (S), missing (M) or large (L), using a dummy variable for each cephalometric measurement. The intercept, linear and quadratic effect of the TS subjects' age are not included in the table. The abbreviations for the measurements are shown in Figure 1.

parents (Tanner *et al.*, 1970). Unlike in some other syndromes, this pattern of correlation is preserved between daughters with TS and their parents (Brook *et al.*, 1977; Massa *et al.*, 1990). Anthropometric studies have shown weaker associations of head dimensions than of body and limb dimensions between TS daughters and their mothers (Varrela *et al.*, 1984). The present study aimed to assess if the distinct craniofacial features of TS females were related to the normal craniofacial features of their parents. A similar type of association of S–Ba and <SNB measurements between mothers and their daughters with TS was observed, as previously been reported for stature between parents and their daughters with TS. A tendency for paternal influence in the size of the TS daughters' mandibles was observed.

The females with TS and their mothers had a relatively strong association in posterior cranial base length. Aberrant skeletal features of TS subjects are present in early foetal development during the period of bone ossification (Andersen *et al.*, 2000). Both the long bones and the cranial base develop through endochondral ossification and the growth in cranial base synchondroses and in the epiphyseal plates of the limbs proceeds through cartilage formation, maturation, calcification and bone replacement (Enlow, 1990). The sphenoccipital synchondrosis, which is located in the posterior cranial base area, is the main growth site of the cranial base as the intersphenoidal synchondroses cease to grow around the time of birth (Enlow, 1990). It has been reported that haploinsufficiency of some gene(s) on the X chromosome that escape inactivation in normal subjects and have a Y homologue are at least partially responsible for statural growth retardation in TS (Rao *et al.*, 1997; Ellison *et al.*, 1997, Zinn *et al.*, 1998). The results of the present study suggest that similar mechanisms could be involved in the deficient growth of the posterior cranial base of subjects with TS.

In normal individuals, the lateral parts of the cranial base grow parallel with the elongation of the clivus, even though their growth increments are due to sutural growth (Björk, 1955). In TS, growth of both the clivus and the lateral parts of the cranial base is retarded. The glenoid fossa is located closer to sella, thus resulting in mandibular retrognathism. Several earlier studies have reported that <SNB is influenced by the addition to or loss of one X chromosome in the human karyotype (Babić *et al.*, 1991, 1993; Brown *et al.*, 1993). The X chromosome monosomy causes retrognathism of the mandible of TS females. The association of <SNB, S–Art and S–Go between mothers and their daughters with TS supports the concept that maternal factors influence the degree of mandibular retrognathism of their TS daughters.

The total length of the mandible and the mandibular body length are reduced in TS subjects. Art–Pog showed a significant association between fathers and their TS daughters. The low association of Go–Pog between parents and TS subjects can imply that the length of the ramus and corpus of the mandible are more influenced by external factors than the total length of the mandible (Dibbets *et al.*, 1987). One of the external factors in TS is that the TS subject's mandible must adjust to a frequently observed narrow maxillary alveolar arch. Lymphatics and lymphoedema, which are commonly observed in newborns with TS, can also contribute to their facial characteristics (Horowitz and Morishima, 1974; Ogata *et al.*, 2002). In the present investigation, the paternal influence in the craniofacial morphology of females with TS should be interpreted with caution, because of the limited number of fathers attending the study.

Both genetic and non-genetic aetiological factors have been suggested to influence craniofacial features in TS (Ogata *et al.*, 2002). The lack of one X chromosome causes shortening of the posterior cranial base and a retrognathic position of the mandible of females with TS. The present results support the concept that maternal influences contribute to the degree of deficiency of the posterior cranial base and to the magnitude of mandibular retrognathism of females with TS.

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