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Craniofacial morphology in Turner syndrome karyotypes

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ABSTRACT

Introduction: A complete or partial absence of an X chromosome in the karyotype of phenotypic females has an impact on craniofacial morphology. The aim of this study was to determine the characteristics of the craniofacial complex in patients with Turner syndrome (TS), and to evaluate the influence of various karyotypes on craniofacial morphology.

Materials and methods: The study population was comprised of 40 TS female patients, aged 9.2 to 18 years, and 40 healthy females, aged 9.3 to 18 years, as the control group. The TS patients were subdivided according to karyotype. All study participants were evaluated cephalometrically. An analysis of variance (ANOVA) and Tukey's multiple comparison test were used for analysis of the differences between the means in Turner subgroups and the control group.

Results: In general, the girls with TS were characterized by smaller dimensions and an altered morphology of the craniofacial complex compared with the unaffected girls. The curvature of the frontal bone was significantly increased, while the diameter of the head was reduced. Both the maxilla and mandible were retrognathic, posteriorly rotated, and reduced in antero-posterior length. The cranial base was shorter and flattened. Among the different karoytypes, no significant differences were determined in the dimensions of the craniofacial complex in girls with TS.

Conclusions: Our findings indicate that the karyotype has no effect on craniofacial morphology and we confirmed that a specific model of craniofacial morphology in individuals with TS is present in early childhood.

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INTRODUCTION

Turner syndrome (TS), also referred to as Ullrich - Turner syndrome, is a combination of characteristic clinical signs and complete or partial absence of an X chromosome in the karyotype of phenotypic females with gonadal dysgenesis. It affects approximately 1 in 2,000 to 5,000 live female births worldwide. [1-3] The incidence of TS in Macedonia is approximately one in 2,500 girls. [4] Several karyotypes responsible for the syndrome have been identified, the most common being monosomy X, found in about 50-60% of the girls. Less common are the mosaic and isochromosome for the long arm of the X chromosome. [5,6] Short stature, gonadal dysgenesis, pterygium colli, cubitus valgus, and low hairline at the back of the neck are the most common features of this disease. [7]

The smaller size of teeth in individuals with TS [8-12] is caused by reduced enamel thickness. [13,14] Females with TS have a tendency toward distal molar occlusion, lateral crossbite, and open bite. [8,15,16] Skeletal maturity was retarded by an average of 2.2 years [17-20] By contrast, dental maturity was accelerated, the mean difference being one year. [19,20]

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Cephalometric studies have reported retarded development of the cranial skeleton, reduced size of the craniofacial complex, retrognathic profile, increased cranial base angle, and reduced posterior cranial base in females with TS. [18,21-24] Rongen-Westerlaken et al. (1992) [25] suggested that deviations in craniofacial morphology in children with TS are probably due to a cartilage disorder. Comparative cephalometric analyses in patients with X chromosome aneuploidy [26] showed that loss of or an extra X chromosome produces opposite effects on cranial base flexion, jaw displacement, and maxillary and mandible inclination to the anterior cranial base.

Only a few studies have investigated the influence of karyotype on craniofacial morphology. [18,22,24,25] Jensen (1985) [18] found that individuals with 45,X had a more retrognathic maxilla than those in the mosaic group. Rizell et al. (2013) [27] found that the mosaic group with the presence of 46,XX cell lines exhibited less mandibular retrognathism as well as fewer significant differences from the reference group compared with those with the 45,X karyotype, while Midtbø et al. (1996), [22] Dumancic et al. (2010), [24] and Rongen - Westerlaken et al. (1992) [25] found no significant differences between 45,X and various kinds of mosaics and isochromosomes.

The aim of the present study was to determine the characteristics of the craniofacial complex in girls with TS, and to evaluate the influence of various karyotypes on craniofacial morphology.

MATERIALS AND METHODS

This investigation was part of a systematic study whose purpose was to track development specific to children with TS and determine the influence of various karyotypes on the study variables. Study was approved by Teaching and Science Research Council of Ss. Cyril and Methodius University of Skopje. The karyotyping was done by chromosome analysis of peripheral lymphocytes. The study population was comprised of 40 TS female patients, aged 9.2 to 18 years, who were patients at the Pediatric Clinic, Medical Faculty, University of Skopje. Most of the individuals had been treated with growth hormone and estrogen. Forty healthy females, aged 9.3 to 18 years, patients at the Department of Orthodontics, Faculty of Dentistry,

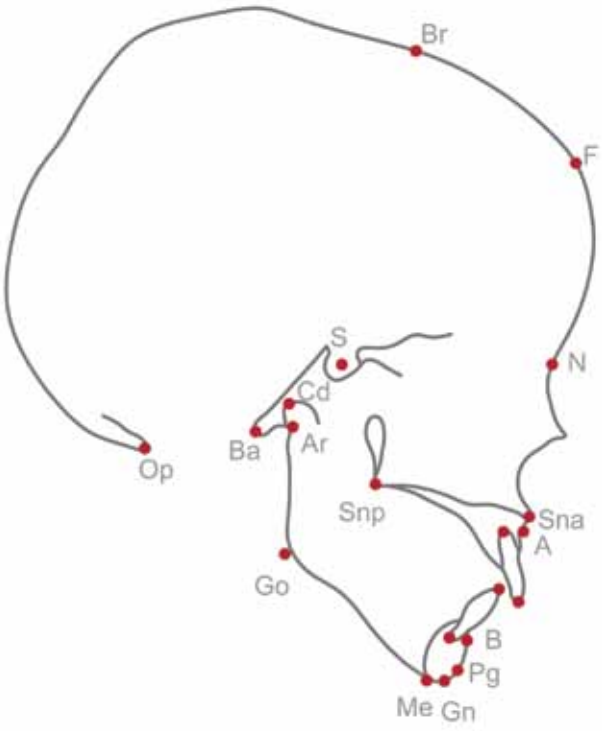
Table 1. *Patients distributed on the basis of age and karyotype*

Karyotype	Sample Size (n)	Age (years) Range	Mean
Monosomy X 45,X	26	9.2-18	14.7
Mosaic 45,X/46,XX	11	9.3-18	15.1
Isochromosome 46,X, i (Xq)	3	9.8-18	14.1
Turner syndrome (total)	40	9.2-18	14.8
Control group	40	9.3-18	14.9

Table 2. *The angular and linear measurements and their descriptions*

Angular measurements	
S-N-F	Prominence of the frontal bone
S-Ba-Op	Angle between opisthion and the posterior cranial base
N-S-Ba	Cranial base angle
S-N-A	Maxillary prognathism
N-S/SpPl	Angulation of maxilla relative to the anterior cranial base
S-N-B	Mandibular prognathism
S-N-Pg	Prognathism of the chin
N-S-Ar	Angle between articulare and the anterior cranial base
Ar-Go-Me	Jaw angle
N-S/MPl	Angulation of the mandible relative to the anterior cranial base
A-N-B	Basal sagittal jaw relationship
B	Angle between maxillary and mandibular baselines
11/N-A	Proclination of the maxillary incisors
41/N-B	Proclination of the mandibular incisors
11/41	Interincisal angle
Linear measurements	
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
N-S	Anterior cranial base length
S-Ba	Posterior cranial base length
N-Ba	Total cranial base length
N-Sna	Upper anterior face height
S-Snp	Upper posterior face height
Snp-A	Length of maxilla along the apical base
Sna-Snp	Length of maxilla along the nasal floor
Sna-Me	Lower anterior face height
Snp-Go	Lower posterior face height
Ar-Go	Height of the mandibular ramus
Go-Me	Length of the mandibular corpus
Cd-Gn	Mandibular length
N-Me	Anterior face height
S-Go	Posterior face height
11→N-A	Protrusion of the maxillary central incisor relative to the N-A line
41→N-B	Protrusion of the mandibular central incisor relative to the N-B line

Figure 1. *Cephalometric points: Br, Bregma; F, Frontale; N, Nasion; S, Sella; Ba, Basion; Op, Opisthion; Sna, Anterior nasal spine; A, point A; B, point B; Snp, Posterior nasal spine; Pg, Pogonion; Gn, Gnathion; Me, Menton; Go, Gonion; Ar, Articulare; Cd, Condylion.*



University of Skopje, were selected as the control group. None of the patients had undergone previous orthodontic treatment. Those with TS were subdivided according to karyotype (monosomy X, mosaics, and isochromosomes) so that karyotypic phenotypic correlations could be studied. The karyotypes, age ranges, and mean ages of the study groups are presented in Table 1.

The craniofacial morphology was determined by cephalometric analysis of standardized lateral cephalometric radiographs with 15 angular and 19 linear parameters. The cephalometric points and measurements used in this study are shown in the Figure 1 and Table 2. Cephalometric analyses were handled manually twice by one investigator, who was blinded to the karyotypes of the participants.

Statistical analysis was performed by computer program (Minitab, 1991). [28] An analysis of variance (ANOVA) was used for simultaneous analysis of the differences between the means in two Turner subgroups and the control group. If the probability of significance was < 0.05, Tukey's multiple comparison test was used for range of means. The error of measurement was estimated by τ, calculated according to the formula $\tau = \Sigma d^2/2n$, where d is the difference between the double measurements and n is the sample size (Dahlberg, 1940). [29] In the statistical handling of linear measurements, the values were corrected for radiographic enlargement.

Table 3. *Comparison of calvarium and cranial base variables of TS and the control group*

	Variable	45,X (n=26)		Mosaics (M) and Isochromosomes (I) (n=14)		Controls (C) (n=40)		ANOVA		Tukey's test	
		Mean	SD	Mean	SD	Mean	SD	F	P	45,X/C	M+I/C
Calvarium	S-N-F	89.8	4.73	89.9	3.70	86.1	4.30	7.37	0.001	*	*
	S-Ba-Op	141	11.4	141	8.37	135	5.67	5.12	0.008	*	*
	Op-Ba	40.0	2.54	41.0	4.94	44.4	3.74	12.68	0.000	**	*
	Op-Br	164	6.34	163	6.65	170	4.71	12.22	0.000	**	**
	Ba-Br	143	6.31	141	7.32	148	5.57	11.53	0.000	*	**
Cranial base	NSBa	136	7.31	134	6.46	131	6.09	4.96	0.009	*	
	N-S	72.8	3.08	72.4	2.80	74.6	2.36	5.45	0.006	*	*
	S-Ba	39.7	4.53	37.2	6.09	43.9	4.53	12.27	0.000	**	**
	N-Ba	104	5.14	101	7.20	108	3.89	11.84	0.000	**	**

*P < 0.05; **P < 0.01. Standard deviation (SD)

RESULTS

A comparison of the means of the angular and linear craniofacial variables between patients with TS and the control group is presented in Tables 3-7. The results showed significant differences in the craniofacial size and morphology between the study groups.

Females with TS were characterized by reduced diameters of the head (Op - Br and Ba - Br), smaller foramen magnum (Op - Ba), and significantly increased prominence of the frontal bone (S - N - F) and the angle S - Ba - Op (Table 3). The cranial base angle (N - S - Ba) was increased and its total length (N - Ba) was reduced.

Table 4. Comparison of maxillary relation variables of TS and the control group

	Variable	45,X (n=26)		Mosaics (M) and Isochromosomes (I) (n=14)		Controls (C) (n=40)		ANOVA		Tukey's test	
		Mean	SD	Mean	SD	Mean	SD	F	P	45,X/C	M+I/C
Maxillary relations	S-N-A	76.5	3.75	77.5	5.66	82.3	3.25	20.01	0.000	**	**
	N-S/SpPl	13.1	4.95	12.0	2.82	7.12	3.25	21.72	0.000	**	**
	N-Sna	55.5	5.28	54.0	5.13	54.2	2.24	0.89	0.413		
	S-Snp	44.4	3.60	44.2	3.80	49.5	3.08	23.42	0.000	**	**
	Snp-A	49.7	4.07	49.7	4.56	53.2	2.24	10.48	0.000	**	*
	Sna-Snp	54.9	3.71	55.5	4.81	58.9	1.66	14.70	0.000	**	**

*P < 0.05; **P < 0.01. Standard deviation (SD)

The maxilla was smaller (Sna - Snp and Snp - A), retrognathic (SNA), and posteriorly inclined in relation to the anterior cranial base (N-S/SpPl) (Table 4). The upper anterior face height (N - Sna) was normal, while the upper posterior face height (S - Snp) was significantly reduced.

The mandible was retrognathic, as shown by a significantly reduced SNB angle, posteriorly rotated (N - S/MPl) and reduced in antero - posterior length (Cd - Gn and Go - Me) in the TS group compared with the control individuals (Table 5).

Compared with the reference group, the TS females had reduced vertical facial dimensions except that of the upper anterior face height and total anterior face height (N - Me) (Table 6). A comparison of the means of ANB and B angle showed no significant differences between the two groups.

The dental relationships were normal except for the proclination of the maxillary incisors described by angle 11/N - A, only in 45,X patients (Table 7).

The investigation revealed no significant differences between the karyotypes.

DISCUSSION

In general, the patients with TS were characterized by smaller dimensions and an altered morphology of the craniofacial complex compared with the unaffected girls. The curvature of the frontal bone was significantly increased, while the diameter of the head was reduced. Both the maxilla and mandible were retrognathic and posteriorly rotated. The cranial base was shorter and flattened, making the face retrognathic. The short and retrognathic face characteristic of this syndrome is due largely to the increased cranial base angle, decreased posterior face height, and reduced maxillary and mandibular length. The similar craniofacial features in females with TS were reported in earlier studies by Jensen (1985), [18] Peltomaki et al. (1989), [21] Rongen - Westerlaken et al. (1992), [25] Midtbø et al. (1996), [22] Perkiömäki et al. (2005), [23] and Dumancic et al. (2010). [24]

Quantitative and qualitative changes in the X chromosomes in TS, due to different mechanisms, influence the processes of development and contribute to dysmorphology and changes in craniofacial morphology. Studying the complex mechanisms of craniofacial development, and the possible reasons for dysmorphology, Hall (1988) [30] stated that the development of the craniofacial morphology represents the culmination of a series of different situations that are superposed. All these events are associated with the three basic developmental processes - cell - term differentiation, morphogenesis, and growth-disorders in the development of any of which can cause irreversible effects on craniofacial morphology, as the result of their impact on pathogenesis in TS.

Individuals with structural and/or numerical aberrations on the X chromosome develop a specific model of craniofacial morphology with deviations in sagittal and vertical directions.

Midtbø et al. (1996), [22] suggested that deviations in craniofacial morphology originated from the period of the fetus when the primary cartilage formed the craniofacial complex, while Perkiömäki et al. (2005), [23] support the concept of the influence of the mother's genes on the growth of the characteristic cranial base and the size of mandibular retrognathism in children with this syndrome.

Exploring the pattern of mandibular growth, Babić et al. (1997) [31] established a significantly lower ratio between the anterior and posterior facial height in individuals with TS compared with those in the control group, which indicates the tendency toward changes in the backward and downward growth of the mandible as a result of the lack of one X chromosome.

According to Rongen-Westerlaken et al. (1992), [25] changes in the maxilla can be explained in various ways. They arise as a result of changes in the growth of the nasal cartilage and the cranial base, or due to disturbances in the intramembranous ossification of the maxilla. Jensen (1985) [18] noted that posterior inclination and retrognathism in both jaws can be connected with the changed form of the cranial base.

Table 5. *Comparison of mandibular relation variables of TS and the control group*

	Variable	45,X (n=26)		Mosaics (M) and Isochromosomes (I) (n=14)		Controls (C) (n=40)		ANOVA		Tukey's test	
		Mean	SD	Mean	SD	Mean	SD	F	P	45,X/C	M+I/C
Mandibular relations	S-N-B	73.9	4.72	74.6	5.20	78.8	2.92	13.35	0.000	**	*
	S-N-Pg	74.9	4.48	75.8	5.29	79.2	3.22	10.11	0.000	**	*
	N-S-Ar	128	6.94	125	6.50	126	5.39	1.55	0.218		
	Ar-Go-Me	130	6.24	128	6.92	128	2.85	1.99	0.143		
	N-S/MPl	39.1	4.03	36.7	8.00	33.9	3.44	9.76	0.000	**	
	Sna-Me	67.1	6.04	66.1	7.74	70.7	4.78	4.79	0.011	*	*
	Snp-Go	43.3	4.29	42.0	5.60	45.5	1.84	6.02	0.004	*	*
	Ar-Go	47.5	5.01	47.4	4.81	48.6	4.20	0.62	0.540		
	Go-Me	67.3	4.21	65.6	6.37	72.9	3.46	21.05	0.000	**	**
	Cd-Gn	110	6.42	106	8.17	116	4.61	19.20	0.000	**	**

*P < 0.05; **P < 0.01. Standard deviation (SD)

Table 6. *Comparison of maxillomandibular relation variables of TS and the control group*

	Variable	45,X (n=26)		Mosaics (M) and Isochromosomes (I) (n=14)		Controls (C) (n=40)		ANOVA		Tukey's test	
		Mean	SD	Mean	SD	Mean	SD	F	P	45,X/C	M+I/C
Maxillo-mandibular relations	A-N-B	2.9	1.67	2.8	3.64	3.6	1.40	1.19	0.310		
	B	26.7	6.68	25.6	7.44	26.9	4.49	0.26	0.770		
	N-Me	121	7.76	117	11.6	122	6.27	2.09	0.130		
	S-Go	75.7	6.31	74.2	7.08	79.8	5.09	6.35	0.003	*	*

*P < 0.05; **P < 0.01. Standard deviation (SD)

Significantly, the reduced upper posterior face height reflects posterior rotation of the maxilla, and the reduction in the dimension of the lower anterior face height indicates a considerable reduction of the lower facial height in patients with TS, reflected in the aesthetics of the lower facial third and thus the individual's overall aesthetics.

Among the different karoytypes, no statistically significant differences were determined in the dimensions of the craniofacial complex in individuals with TS, which is in accordance with the findings of Midtbø et al. (1996) [22] and Rongen - Westerlaken et al. (1992), [25] but is contrary to the findings of Rizell et al. (2013), [27] who found that karyotypes had an impact on craniofacial growth, where isochromosomes had more significant differences compared with the reference group, 45,X/46,XX, but fewer than 45,X.

A SHOX gene (short stature homeobox - containing) plays a vital role in the determination of height and bone development of humans. Loss of this X chromosome gene seems to play a key role in causing the short stature of girls with TS. Most of the participants in this study had been treated with growth hormone, and for that fact, at the beginning there was a concern and doubt about the reliability of the results. However, previous studies have shown that although statural height was increased in TS children treated with this hormone, the growth hormone has little or no impact on the growth of the jaws and craniofacial morphology. [25,32,33] According to Hass et al. (1992), [33] the growth hormone therapy in Turner syndrome does not correct the craniofacial growth deficiencies that produce the characteristic facies of the syndrome.

Growth and its regulatory mechanisms are under the influence of genes on the X chromosome, and because of this, these genes have an impact on the size of the maxilla and teeth, as a result of the interaction between mesenchyme and epithelium. [34] Numerical aberrations of the X chromosome influence the quantitative and qualitative excretion of amelogenin, which causes a reduction in the dimensions of the dental crown and enamel hypoplasia. [35]

The study of craniofacial morphology in individuals with different chromosomal aberrations has shown the influence and different effects of the sex chromosomes on the growth of the craniofacial complex. Babić et al. (1993), [26] analyzing the influence of sex chromosomes on growth, shape, and position of the craniofacial structure in patients with Turner syndrome and Klinefelter syndrome, have determined reduced cranial growth in both syndromes.

The extra X chromosome causes deviations in sagittal jaw relationships, while its absence affects mandibular form. [26] Relative to the impact of the X and Y chromosomes on craniofacial morphology, Grön (1999) [36] found that the reduction in chromosomal genetic material in individuals with karyotype 45,X/46,XX results in smaller craniofacial dimensions, with significant effects on the cranial base angle, and the presence of one extra Y chromosome results in larger craniofacial dimensions, without significant effects on the cranial base angle.

The genes on the human X chromosome are critical for the harmonious growth and development of the craniofacial complex. The reduction of X chromosomal genetic material in females with Turner syndrome results in the reduction of craniofacial dimensions. Our findings indicate that the karyotype has no effect on craniofacial morphology and confirm the hypothesis that a specific model of craniofacial morphology in individuals with Turner syndrome is present in early childhood.

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Table 7. *Comparison of dental relation variables of TS and the control group*

	Variable	45,X (n=26)		Mosaics (M) and Isochromosomes (I) (n=14)		Controls (C) (n=40)		ANOVA		Tukey's test	
		Mean	SD	Mean	SD	Mean	SD	F	P	45,X/C	M+I/C
Dental relations	11/N-A	24.4	6.15	20.2	9.04	20.0	3.36	5.22	0.007	*	
	41/N-B	24.0	4.76	23.1	6.74	26.4	3.80	3.47	0.036		
	11/41	131	8.99	131.8	8.65	133	5.99	0.57	0.568		
	11→N-A	3.7	2.35	3.4	2.30	3.6	2.02	0.08	0.917		
	41→N-B	3.2	1.28	3.4	2.12	3.5	0.99	0.39	0.674		

*P < 0.05; **P < 0.01.

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