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Mandibular morphology in monozygotic twins: a cephalometric study

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SUMMARY

Background. The understanding of relative effects of genetics and environmental factors on mandible growth would increase effectiveness of orthodontic therapy and treatment planning. The purpose of this study was to clarify whether the skeletal morphology of mandible is phenotypically alike in two individuals in a pair of young adult monozygotic (MZ) twins.

Methods. The 90 twin pairs were classified as MZ by 15 specific DNA markers and Amel fragment. Cephalometric analysis of mandible morphology using 27 parameters was done and Pearson's intra-pair correlation coefficient for each variable was calculated.

Results. The highest correlations of cephalometric variables between two individuals in the same MZ twins pair was in the total mandibular and corpus length (r=0.94). The lowest correlations was established for depth of antigonial notch (r=0.65) and articular angle (r=0.68) in female pairs. Statistically significant differences ($p \leq 0.05$) of intra-pair correlation coefficients between genders was found only for total mandibular length (distances Co-Gn and Ar-Gn).

Conclusions. Mandibular length has highest intra-pair correlation coefficient among similar linear cephalometric variables in MZ twins. The females demonstrated greater variability of mandible skeletal cephalometric measurements within the MZ twin pair than the men.

Key words: mandible, monozygotic twins, cephalometrics.

INTRODUCTION

The aetiology of malocclusion involves both major and minor genetic influences with variable interactions from environmental factors (1, 2). The separation of these factors in contribution to severity of malocclusion is significant for clinical orthodontics, because prognosis for orthodontic correction is determined by the extent to which a particular malocclusion can be influenced by therapeutic environmental intervention (3, 4). The use of growth-modifying appliances to alter anteroposterior, vertical and transversal discrepancies of the jaws and the facial skeleton has increased (5, 6). The correction of mandibular morphology and its growth rotations is the main target of the functional therapy and a particular interest of orthodontists.

The vast majority of research focused on estimation of relative genetic and environmental influences to craniofacial morphology is employing the twin model. Monozygotic (MZ) twins share the same genes, whereas dizygotic (DZ) twins on average share only half of their genes. Therefore, by assuming that both types of twins have been sampled from the same gene pool and that similar environmental factors act upon them, one can estimate the relative contributions of genetic and environmental influences to observed variation in facial and occlusal morphology (7). Monozygotic twins provide the most valuable data for ascertaining effects of the environment exerted on heredity (8).

Twin zygosity determinations can be performed with anthropologic, serologic, tissue type iden-

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tification and genetic markers (9). However, many of these methods are more than occasionally inefficient and sometimes inaccurate. Because of the misconception that MZ twins are necessarily identical in phenotype, many MZ twin pairs are mistakenly designated as dizygotic, if analysis is made without appropriate DNA testing (10). Until the last decade the heritability studies of craniofacial characteristics using twin model have used anthropologic, serologic or at the best case five genetic DNA markers. Such types of zygocity diagnostics might be questioned. The reliable zygocity recognition needs comprehensive DNA testing.

The occlusal and facial maturity develops at the late adolescence. The majority of the studies on heritability of craniofacial characteristics use the twins aged between 9 and 16 year, and the mean age varies from 10 to 13 years (11-13). Many of these twins at the time of examination even do not reached pre-pubertal growth spurt. The longitudinal cephalometric studies of developing craniofacial structures from 4 to 20 years, reported that heritability estimates of craniofacial variables increase with age (14). Therefore comparison of hereditary characteristics is more valid in the adulthood when the growth actually is completed.

The purpose of this study was to clarify whether the skeletal morphology of mandible is phenotypically alike in two individuals in a pair of young adult monozygotic twins with normal karyotype and the zygocity diagnosed by 15 specific DNA markers and *Amel* fragment.

MATERIAL AND METHOD

Study sample. The twins used in this study were selected from the register of Twin center at Lithuanian university of health sciences. This ongoing register already covers more than 800 twin pairs and multiple births voluntary registered, and willing par-

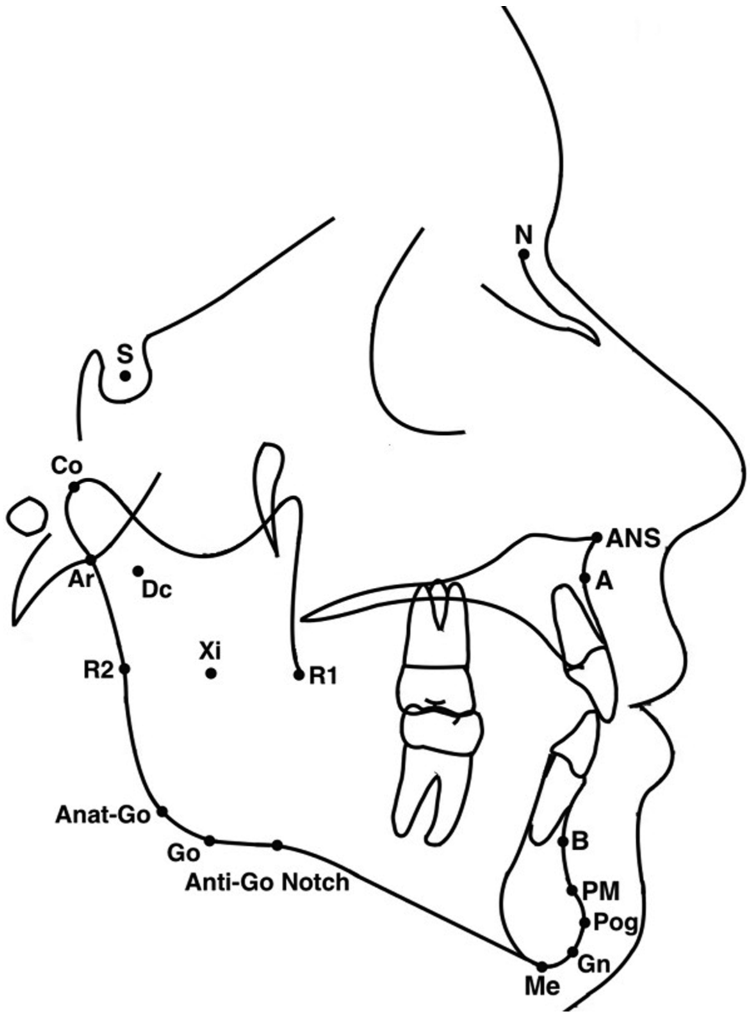

Fig. Cephalometric landmarks used in the study:

S – Sella: the midpoint of sella turcica.
N – Nasion: the extreme anterior point of the frontonasal suture.
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.
ANS – Point ANS: the tip of the anterior nasal spine.
Co – Condylion: the most posterior superior point of the condyle.
Ar – Articulare: the point at the junction of the posterior border of the ramus and the inferior border of the posterior cranial base.
Pog – Pogonion: the most anterior point of the chin.
Me – Menton: the most inferior point of the chin.
Go – Gonion: the most convex point along the inferior border of the ramus.
Anat-Go – Anatomical gonion: the midpoint of the mandibular angle between ramus and the mandibular corpus
Gn – Gnathion: the midpoint between Pogonion and Menton.
PM – Protuberance menti: the point at which the shape of symphysis mentalis changes from convex to concave.
Anti-Go notch – Anti-gonial notch: the highest point of the notch of the lower border of the ramus where it joins the body of the mandible.
R1 – Ramus point 1: the most concave point on the interior of the ramus.
R2 – Ramus point 2: the most convex point on the exterior border of the ramus along the vertical.
Xi – Xi point: the point located at the geometrical center of the ramus.
Dc – Dc point: the point representing the center of the neck of the condyle on the Basion-Nasion line.

ticipate in different medical and genetic studies. All twins or their parents were informed of the protocol of these studies. The protocol has been approved by the Kaunas Regional Ethical Committee. All twins present at the register were offered free zygosity determination and medical consultations including dental and orthodontic consultations. For some twins as a part of dental examination orthopantomograms or standardized lateral cephalographs were taken. All twins having lateral cephalographs and completed mandible growth were included in the study. The cervical vertebral maturation (CVM) method (15) was used to assess the completion of the mandibular growth. Only twins attained the CS6 stage (active growth completed) were included. Pairs of whom at least one member had orthodontic treatment, permanent teeth extractions or any facial trauma that could have resulted in bony fracture were excluded. A total of 90 pairs of twins were identified and allocated to MZ group by DNA method. The sample's age and gender characteristics are shown in Table 1.

Zygosity determination was carried out using a DNA test. The polymerase chain reaction set AmpFℓSTR® Identifiler® (Applied biosystems, USA) was used to amplify short tandem repeats and 15 specific DNA markers (D8S1179, D21S11, D7S820, CSF1PO, D3S1358, TH01, D13S317, D16S539, D2S1338, D19S433, vWA, TROX, D18S51, D5S818, FGA) and *Amel* fragment of amelogenin gene were used for comparison of genetic profiles. The zygosity determination using this molecular genetic technique reaches *99.9% accuracy.*

Cephalometric measurements. The cephalograms were taken in centric occlusion under standard conditions using digital x-ray equipment. For standardized positioning, a cephalostat was used to maintain the subject's head in constant relationship to the sensor (sensor-focus distance of 1.50 m, object-sensor distance 0.15 m). This in turn standardized the distance of the subject to the sensor, the x-ray exposure and magnification exposure. All subjects were asked to stand looking straight forward, with a lead apron on their chest. Ear rods were placed into the ear canals in a comfortable position and orbital pointer was accurately positioned. All radiographs were analized by the same investigator (M.S.) using commercially available software (Dolphin Imaging 11.7 Premium, Patterson Dental Supply, Chatsworth, USA). Cepahlometric landmarks used in the study presented in the Figure. 1. The twenty seven angular, linear and proportional measurements used in the study and their definitions presented in the Table 2. Anatomical structures farther to the x-ray source were chosen to reduce magnification effect (16), if bilateral structures were present . Landmark identification was carried out by manual dot tracing on the digital image using a mouse-driven cursor in a predetermined sequence. Cephalometric measurements were automatically calculated by using software.

Table 1. Descriptive statistics of the study sample age and gender

Groups studied	n	Mean age (years)	SD	Min	Max
MZ pairs	90	22.45	5.81	15.3	39.6
Male	29	22.1	4.82	15.8	36.4
Female	61	22.62	6.25	15.3	39.6

Statistical analysis. The following values of intra-pair differences for every cephalometric variable in MZ twins were calculated: mean, standard deviation (SD) and range. For the purpose of clarifying whether the mandible morphology of individuals within pair of MZ twins were phenotypically alike Pearson's intra-pair correlation coefficient was calculated. To compare gender difference on mandible morphology variables, probability of data being Gaussian was tested using Kolmogorov-Smirnov test and P value obtained with Mann-Whitney test.

Method error. Intra-observer method error was assessed using coefficient of reliability and a method suggested by Bland and Altman (17). The reliability of the method was tested by tracing and measuring 20 randomly selected lateral cephalograms twice. The estimated error between the measurements was calculated using the formula:

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

Where ±2 SD are the limits within which 95% of the differences between the repeated measurements are expected to lie; d1 = first measurement; d2 = second measurement; N = number of patients. The error of cephalometric measurements given in ±2SD of the differences between the repeated measurements we found insignificant on the reliability of our results.

RESULTS

Descriptive analysis, gender differences and Pearson's intra-pair correlation coefficients of cephalometric variables within the MZ twin pair shown in Table 3. The highest correlations of cephalometric variables between two individuals in the same MZ twins pair was found in three parameters: total mandibular length from condylion (r=0.93 for variable Co-Gn) and from articulare (r=0.94 for variable Ar-Gn) also for mandibular corpus length (r= 0.94 for variable Xi-Pm). The lowest correlations between male pairs was observed in Witts appraisal (r=0.65), articular (r=0.73 for S-Ar-Go) and mandibular arc (r=0.72 for Dc-Xi to Pm-Xi) angles. The lowest correlations between female pairs was established for depth of antigonial notch (r=0.65) and articular angle (r=0.68 for variable S-Ar-Go). Statistically significant differences of intra-pair correlation coefficients between genders was found only for mandibular length-distances Co-Gn and Ar-Gn with p value 0.02 and 0.05 respectively.

DISCUSSION

The focus on variability of craniofacial morphology within MZ twins has captured the interest of dentists and biologists over the several last decades. These type of studies provide an opportunity to estimate impact of genetic, environmental and epigenetic factors on phenotype expression.

Townsend *et al.* (18) studied the variation in the prevalence of agenesis and supernumerary permanent teeth in Australian MZ twin pairs. They studied 278 pairs of MZ twins and found that at least one upper lateral incisor or second premolar was missed in 24 pairs and 9 pairs had mesiodens. Twenty one pair of these 24 MZ pairs demonstrated discordant expression for missing teeth and eight from 9 MZ pairs displayed being discordant for mesiodens. The authors postulated, that minor variations in local epigenetic events in tooth-forming regions, possibly related to spatial arrangements of cells or temporal events during odontogenesis, may account for such extremely distinctive differences in MZ twins despite their identical genotypes.

MZ twins also provide valuable material for craniofacial development studies. Christensen and

Table 2. Cepahlometric measurements and definitions used in the study

Measurements	Variables	Definitions
Angular	SNA	Angle determined by points S, N and A.
	SNB	Angle determined by points S, N and B.
	S-N-Pog	Angle determined by points S, N and Pog.
	S-Ar-Go	Angle determined by points S, Ar and Go.
	N-S-Gn	Angle determined by points N, S and Gn.
	N-Gn-Anatomical Go	Angle determined by points N, Gn and anatomical Go.
	MP-SN	Angle formed by Go-Me plane and SN plane.
	Co-Go-Me	Angle determined by points Co, Go and Me.
	Ar-Go-Me	Angle determined by points Ar, Go and Me.
	Dc-Xi to PM-Xi	Angle formed by plane Dc-Xi and PM-Xi plane.
Linear	Wits appraisal	Distance between perpendiculars from points A and B onto the occlusal plane in mm.
	Co-Go	Distance between points Co and Go in mm.
	Co-Gn	Distance between points Co and Gn in mm.
	Co-Pog	Distance between points Co and Pog in mm.
	Co-B	Distance between points Co and B in mm.
	Ar-Go	Distance between points Ar and Go in mm.
	Ar-Gn	Distance between points Ar and Gn in mm.
	Ar-B	Distance between points Ar and B in mm.
	Pog-NB	Perpendicular distance from the point Pog to NB line in mm.
	Go-Gn	Distance between points Go and Gn in mm.
	Xi-PM	Distance between points Xi and PM in mm.
	Ramal width at Xi	Distance between points R1 and R2 in mm.
	Antigonial notch	Perpendicular distance from the line between points Go and Me to the point Anti-Go notch in mm
	N-Me	Anterior facial height, distance between points N and Me in mm.
	N-ANS	Upper facial height, distance between points N and ANS in mm.
	ANS-Me	Lower facial height, distance between points ANS and Me in mm.
Proportional	N-ANS/ANS-Me	Upper to lower facial height percentage

Fogh-Andersen (19) studied the prevalence of cleft lip, cleft palate and combined cleft lip/ palate in MZ twins. Eight of the 14 MZ twin pairs had no similarity, while six of the 14 monozygotic pairs had identical cleft types. These results may explain some heritability paths of the oro-facial clefts. The studies of the most stabile structure of the cranium, sella turcica in MZ twins, showed that it size varies in the individuals within the twin pairs (20). The 2D radiological examination of frontal sinuses (21) and 3D computer tomography based genetic study on the paranasal sinuses anatomic variations in MZ twins (22) concluded, that sinus development and morphology is not determined solely by genotype, but other factors as well, e.g. environment and epigenetics events in its broad sense are involved. The studies of MZ twins is valuable instrument to estimate genetic and non-genetic influence on dentofacial morphology. This type of estimation is usually a first step in genetic studies, because it provides idea of how much phenotypic variation is attributable to genetic effects.

We found that the total mandibular length and mandible corpus length have the highest correlations between two individuals in the same MZ twin pair. This is in agreement with results of Dudas and

Table 3. Descriptive analysis, intra-pair correlation coefficient (r) and gender differences (P) of cephalometric variables

Cephalometric variables	MZ twins n=90				Male n=29				Female =61				P value
	Mean	SD	Range	r	Mean	SD	Range	r	Mean	SD	Range	r	
SNA (°)	2.17	1.79	0.1-8.7	0.79	2.64	2.07	0.1-8.7	0.83	1.95	1.62	0.1-6.6	0.73	N.S.
SNB (°)	1.93	1.76	0-9.8	0.82	2.10	1.83	0.1-8.0	0.86	1.86	1.73	0-9.8	0.77	N.S.
S-N-Pog (°)	2.09	1.79	0-9.9	0.81	2.21	1.90	0.3-8.1	0.85	2.03	1.75	0-9.9	0.76	N.S.
S-Ar-Go (°)	4.37	3.27	0-16.7	0.68	4.43	2.62	0 - 10.5	0.73	4.34	3.56	0.1-16.7	0.68	N.S.
N-S-Gn (°)	2.06	1.85	0.1-9.1	0.80	2.46	2.05	0.2-9.1	0.79	1.88	1.73	0.1-8.4	0.80	N.S.
N-Gn-Go (°)	2.32	1.97	0-10.2	0.79	1.85	1.87	0.2-10.2	0.84	2.54	1.99	0-9.9	0.78	N.S.
MP-SN (°)	4.02	3.47	0-15.1	0.77	3.94	3.73	0-13.5	0.78	4.06	3.37	0-15.3	0.76	N.S.
Co-Go-Me (°)	3.54	2.72	0-12.6	0.74	3.28	2.53	0.1-10.7	0.79	3.66	2.82	0-12.6	0.71	N.S.
Ar-Go-Me (°)	3.30	2.91	0.1-15.7	0.82	3.12	3.16	0.2-15.7	0.82	3.39	2.81	0.1-13.0	0.82	N.S.
Dc-Xi to PM-Xi (°)	3.22	2.69	0.1-12.7	0.73	3.26	2.63	0.2-11.7	0.72	3.20	2.74	0.1-12.7	0.74	N.S.
Wits appraisal (mm)	2.11	1.71	0-9.6	0.67	2.24	2.01	0 - 9.6	0.65	2.05	1.56	0.1-6.2	0.69	N.S.
Co-Go (mm)	2.99	2.73	0.1-13	0.82	3.42	2.92	0.4-13.0	0.76	2.79	2.64	0.1-10.0	0.76	N.S.
Co-Gn (mm)	2.95	2.45	0.1-11.7	0.93	2.20	2.27	0.1-11.7	0.94	3.30	2.47	0.1-10.3	0.91	0,02
Co-Pog (mm)	3.00	2.49	0-11.5	0.92	2.42	2.29	0.1-11.0	0.93	3.28	2.55	0 - 11.5	0.89	N.S.
CO-B (mm)	2.68	2.49	0-11.3	0.91	2.11	2.33	0 - 10.3	0.92	2.96	2.53	0-11.3	0.90	N.S.
Ar-Go (mm)	3.09	2.60	0.1-11.8	0.79	3.28	2.86	0.1-11.8	0.78	3.00	2.48	0.1-11.2	0.71	N.S.
Ar-Gn (mm)	2.43	2.22	0-11.8	0.94	1.88	2.02	0-8.8	0.95	2.70	2.27	0-11.8	0.92	0.05
Ar-B (mm)	2.29	2.13	0-12.9	0.93	1.71	1.58	0.1-7.1	0.95	2.57	2.30	0-12.9	0.91	N.S.
Pog-NB (mm)	0.69	0.61	0-3.8	0.87	0.83	0.80	0 - 3.8	0.86	0.62	0.48	0-2.3	0.85	N.S.
Go-Gn(mm)	2.55	2.07	0-9.8	0.91	2.62	1.97	0.1-9.8	0.91	2.52	2.13	0-8.4	0.91	N.S.
Xi-PM (mm)	1.80	1.36	0-5.6	0.94	1.82	1.37	0.1-5.6	0.92	1.80	1.37	0-5.1	0.93	N.S.
Ramal width at Xi (mm)	1.79	1.37	0-5.7	0.78	1.50	1.03	0.2-3.8	0.87	1.93	1.49	0-5.7	0.74	N.S.
Antigonial notch (mm)	0.66	0.57	0-2.8	0.68	0.59	0.46	0 - 1.7	0,73	0.70	0.61	0-2.8	0.65	N.S.
Na-Me) (mm), AFH	2.77	2.49	0-11.7	0.93	3.20	2.64	0.1-10.1	0.87	2.56	2.41	0-11.7	0.94	N.S.
N-ANS (mm), UFH	1.93	1.73	0-7.7	0.83	2.26	2.04	0.1-7.7	0.72	1.78	1.56	0-6.8	0.84	N.S.
ANS-Me (mm), LAFH	2.37	1.91	0-9.3	0.91	2.11	1.42	0.1-6.1	0.93	2.50	2.10	0-9.3	0.90	N.S.
UAFH/LAFH ratio (%)	4.47	3.26	0.1-14.9	0.74	4.20	2.86	0.8-10.9	0.82	4.60	3.45	0.1-14.9	0.70	N.S.

$P \leq 0.05$; N.S. – not significant.

Sassouni longitudinal twin study. They reported high genetic determination for mandibular length (23). Carels *et al.* also suggested, that mandibular length seems to be determined by dominant genes (12). Monozygotic twins are genetically identical, so it could be presumed that the phenotypic differences in mandible morphology is mainly expression of different activity of environmental and epigenetic factors. But this assumption must have strong background of evidence based data. The design of our study, unfortunately, did not allowed assess genetic dominance with high precision. As Neale and Cardon (24) stated, it is difficult to investigate the influence of genetic dominance in studies of twins raised together unless the sample size is very large.

In the current study, linear measurements had slightly higher intra-pair correlations than angular variables. This may be due to the fact that linear measurements have greater genetic determination than angular measurements (25). We also found statistically significant differences for mandibular length variability within MZ twin pair, between males and females. The females demonstrated higher variability within the MZ twin pair for distances Co-Gn ($p=0.02$) and Ar-Gn ($p=0.05$). This interesting fact may indicate a role of hormonal influence on mandible growth and possible greater stress of the twinning process in girls as it is a case with dental crown development and eruption (26). Therefore, full understanding of the interplay between environmental and genetic patterns involved in the mandible development and growth required more detailed studies.

CONCLUSION

Total mandibular and corpus lengths has highest intra-pair correlation coefficient among similar linear cephalometric variables in MZ twins. The females demonstrated greater variability of mandible skeletal cephalometric measurements within the MZ twin pair than the men.

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