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Neurocranial morphology and growth in Williams syndrome

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SUMMARY Williams syndrome (WS) is a rare congenital neurodevelopmental disorder with distinctive facial features, cardiovascular abnormalities, short stature, mental retardation, and behaviour and cognitive characteristics.

The aim of this study was to describe the neurocranial morphology and growth in a group of 62 individuals with WS. The neurocranium was analysed on lateral cephalograms and comparisons were made with neurocranial standards from longitudinal data derived from the Oslo University Craniofacial Growth Archive.

The size and morphology of the neurocranium in WS subjects differed from controls. Females as a group showed greater differences than males. The posterior cranial base length was shorter in both WS males and females, and the anterior cranial base length was shorter in WS females whereas it was close to normal in the WS male group. The cranial base angle was, however, not different from the control groups. A flattening was seen in the superior aspect of the parietal bone in both WS males and females. In the posterior part of the neurocranium, the prominence of the occipital bone was larger than in the control groups, which was also reflected in a larger total length of the neurocranium. The thickness of the frontal and occipital bones was considerably greater than in the control group. The deviant size and morphology of the neurocranium in WS subjects was already established in the youngest age group and maintained throughout the observation period.

The growth pattern of the neurocranium in WS subjects seemed to be similar to that of the control groups, except in a few individuals.

Introduction

Williams syndrome (WS) is a rare genetic disorder caused by a hemizygous microdeletion of chromosome 7 (7q11.23) affecting multiple organ systems. The syndrome was first reported independently by Williams *et al.* (1961) and Beuren *et al.* (1962). They described children with characteristic cardiac anomalies (supravalvular aortic stenosis), mental retardation, distinctive facial features, and dental aberrations.

During the last few decades, the clinical manifestations of WS have been well defined, but it was not until 1993 that the genetic deletion was discovered using fluorescent *in situ* hybridization (FISH) analysis (Ewart *et al.*, 1993). The predominant microdeletion includes codes for an estimated 26 genes, and seven of these genes are highly expressed in the brain (*WBSCR17*, *WBSCR20C*, *FZD9*, *STXIA*, *LIMK1*, *CYLN2*, *WBSCR20B*) (Schultz *et al.*, 2001; Merla *et al.*, 2002). The *de novo* or rarely inherited microdeletion of the WS critical region on one of the two chromosomes 7 is detectable in 90 to 98 per cent of individuals with the clinical phenotype of WS (Nickerson *et al.*, 1995; Lowery *et al.*, 1995; Morris *et al.*, 1999; Peoples *et al.*, 2000).

WS was previously estimated to occur in approximately 1 per 20 000 live births (Morris *et al.*, 1988; Kaplan *et al.*, 2001), but a recent Norwegian epidemiological survey suggested a prevalence of 1 in 7 500 (Strømme *et al.*, 2002). WS is equally prevalent in both sexes and is present in all populations throughout the world (Morris *et al.*, 1988).

Children with WS have a characteristic pattern of dysmorphic facial features, connective tissue abnormalities affecting the cardiovascular organs, developmental delay, short stature, a unique cognitive profile with learning difficulties and a distinctive personality, and in some cases transient infantile hypercalcaemia (Beuren, 1972; Morris *et al.*, 1988; Udwin and Yule, 1991). WS has been characterized as a combination of impaired and intact mental capacities (Rossen *et al.*, 1996), where language, face processing, and social skills are viewed as the intact components, and number, problem-solving and visual–spatial cognition as the impaired components. Syndrome-specific cross-sectional growth curves for WS have shown that short stature and premature puberty with an early growth spurt are frequent symptoms in both sexes (Cherniske *et al.*, 1999; Partsch *et al.*, 1999).

As the course of WS from infancy to adulthood has been followed in an increasing number of cases, it has become evident that WS is a slowly progressive disorder affecting many organ systems and there is a wide range of variability in clinical features and cognitive abilities (Morris *et al.*, 1990).

Despite the presence of a number of physical features and medical problems that are of potential clinical significance in individuals with WS, central nervous system (CNS) dysfunction predominates as the most impeding for daily life. Subjects with WS usually function within the mild to moderate mentally retarded range (Bellugi *et al.*, 2000).

Neuroanatomical investigations, using high-resolution magnetic resonance imaging (MRI) and autopsy studies on adults with WS, have documented a decreased overall brain size and disproportionate dimensions of the brainstem compared with other brain dimensions. Changes with relative preservation of frontal, cerebellar and temporal volumes have been reported (Bellugi *et al.*, 1990; Reiss *et al.*, 2000). Analyses of the cerebellum have revealed that adult individuals with WS have, in absolute terms, a normal cerebellar vermis size, but after correction for the smaller total cranial size, a proportionately larger cerebellum (Jerningan and Bellugi, 1990; Schmitt *et al.*, 2001a).

A close interrelation exists between the development of brain tissue and the bones surrounding the brain: the neurocranium. Analysis of neurocranial morphology should, therefore, be included in the pre-orthodontic cephalometric analysis of individuals with neurodevelopmental disorders and craniofacial malformations (Kjær *et al.*, 1999). This scientific discipline linking osseous and neurological analyses has been termed neuro-osteology (Kjær, 1998).

As abnormalities in the CNS have been well documented in WS, an assessment of the morphological aspects of the neurocranium in WS was of interest.

The overall aim of this study was to describe neurocranial size and morphology in a sample of children, adolescents, and young adults with WS by means of cephalometric analyses compared with recently published standards for normal neurocranial development (Axelsson *et al.*, 2003). As craniofacial morphology is related to the neurocranium, this study could serve as a basis for describing and understanding craniofacial morphology in WS.

Subjects and methods

This study was carried out at the Dental Faculty, University of Oslo, as well as at the TAKO-Centre, a national interdisciplinary resource centre for oral health in rare medical conditions (conditions with a frequency of less than 1 per 10 000 inhabitants). Health workers from different disciplines refer patients to the centre for diagnostic purposes, dental treatment planning, and treatment of complex cases. Most of the subjects included in the study were recruited from the files at the TAKO-Centre and from the Department of Medical Genetics, University Hospital (Rikshospitalet), Oslo, but also from among members of the Norwegian Williams Syndrome Association.

All individuals with a known diagnosis of WS, made by experienced paediatricians and geneticists, as well as their families were invited to participate in the study. One hundred subjects with WS were contacted, and 69 responded positively. However, seven of these were too young to co-operate with the examination and the taking of radiographs. They were, therefore, excluded. Twelve subjects responded negatively to participation and no response was received from the rest. There were more males than females in the two latter groups. The reasons given for not participating were, e.g. aggressive and hyperactive behaviour, anxiety, and the long distance to travel to the clinic. Informed consent was obtained from all participants and also from their parents or guardians.

The study protocol was reviewed and recommended by the National Committee for Medical Research Ethics in Norway.

Study population

A majority of the participants (48/62; 77 per cent) had a positive cytogenetic diagnosis of WS (positive FISH analysis for deletion on 7q11.23); 6/62 (10 per cent) had a negative result from the cytogenetic test but a clear clinical (medical and psychological history) diagnosis of WS. For the remainder (8/62; 13 per cent), no cytogenetic tests were performed, but they had a clear clinical (medical and psychological history) diagnosis.

Lateral cephalograms from 62 individuals with WS were analysed. The sample comprised all available lateral cephalograms of WS individuals taken at the Dental Faculty, University of Oslo on either of two identical cephalostats. The material included 25 males and 37 females ranging in age from 4.7 to 44.4 years. The males and females were divided into six age groups: less than 8, 8–10, 11–13, 14–16, 17–19, and more than 20 years. The division into sex and age groups was made according to the results from a similar cephalometric analysis on the control sample (Axelsson *et al.*, 2003).

From the total of 107 radiographs, two were excluded due to poor quality. When more than one radiograph from the same individual existed within a particular age group, the additional radiographs, eight altogether, were excluded. Thus, the same individual could appear with radiographs in more than one age group, but not more than once within the same age group. Among the 62 subjects, 39 had a lateral cephalogram in one age group,

15 had lateral cephalograms in two age groups, five had lateral cephalograms in three age groups, two had lateral cephalograms in four age groups, and one had lateral cephalograms in five age groups. The final sample thus comprised 97 radiographs (39 males and 58 females). The distribution into sex and age groups is shown in Table 1.

For comparison, lateral cephalograms from the Oslo University Craniofacial Growth Archive were used. This longitudinal reference material has been described in detail (Axelsson *et al.*, 2003).

Cephalometric analyses

The reference points identified on each radiograph and the calculated variables are illustrated and listed in Figure 1. All reference points and reference lines used are situated in the midsagittal plane.

The reference points were digitized and processed using the Dentofacial Planner® computer program (Dentofacial Software Inc., Toronto, Ontario, Canada). The measurements were calculated to the nearest 0.1 mm or 0.1 degree. The magnification of the linear measurements was corrected by the computer software program.

To supplement the analyses, a curvature index was used for descriptive purposes. Measurements of the curvature of the frontal, parietal, and occipital bones were provided by the relationship between the greatest perpendicular distance to the arch surface (n–br to the frontal bone, br–l to the parietal bone, and l–ba to the occipital bone) and the length of the cords (Young, 1956). The higher the index the greater the curvature of the bone surface. The use of indices is, however, doubtful from a statistical viewpoint.

$$\text{Curvature index} = \frac{\text{perpendicular distance}}{\text{length of the cord}} \times 100$$

Assessing errors of the methods

From the total sample of 97 radiographs, 25 were chosen at random and were traced and digitized on two separate occasions at least 2 weeks apart by the same investigator (SA). Measurement errors were estimated according to Dahlberg (1940). The coefficient of reliability and the variance of the duplicate measurements were also calculated, as recommended by Houston (1983). The errors of duplicate measurements were generally small. The range for linear measurements was 0.1–0.5 mm and for angular measurements 0.1–0.5 degrees. The largest variation found for an angular measurement was the cranial base angle (s–n–ba), and for a linear variable the length of the neurocranium (n–opc).

Statistical analyses

Data from all measurements were transferred to a statistical program (SPSS® Base 10.0, SPSS Inc., Chicago, Illinois, USA). The statistical differences between the arithmetic means of the measurements in the WS and control groups were compared using Student's *t*-test for independent data. The level of statistical significance chosen was $P < 0.05$.

Missing variables

It was not possible to identify the reference point bregma (br) on some of the radiographs, particularly in the older age groups, because the head was too large to fit the format of the radiographic cassette. In those cases, the reference point bregma was situated on the edge or just outside the radiograph. The following variables were affected by the missing reference point; s–n–f, ba–br, s–f, s–br, n–br, br–l, n–br to the frontal bone, br–l to the parietal bone, thickness of the frontal and parietal bones.

Table 1 The number of lateral cephalograms in each age group.

	Age groups	*n*	Mean age (years)	SD	Minimum	Maximum
Male	<8 years	6	6.8	1.3	4.7	7.9
	8–10 years	6	9.8	1.0	8.3	10.7
	11–13 years	10	12.6	0.7	11.4	13.6
	14–16 years	7	15.5	1.0	14.1	16.4
	17–19 years	6	18.4	0.7	17.5	19.1
	>20 years	4	22.9	2.2	21.2	26.0
Female	<8 years	11	7.0	0.7	5.9	7.9
	8–10 years	9	9.4	0.9	8.9	10.9
	11–13 years	15	12.3	0.9	11.0	13.9
	14–16 years	5	15.4	1.1	14.2	16.8
	17–19 years	6	18.9	0.9	17.4	19.8
	>20 years	12	26.6	7.7	20.9	44.4

SD, standard deviation.

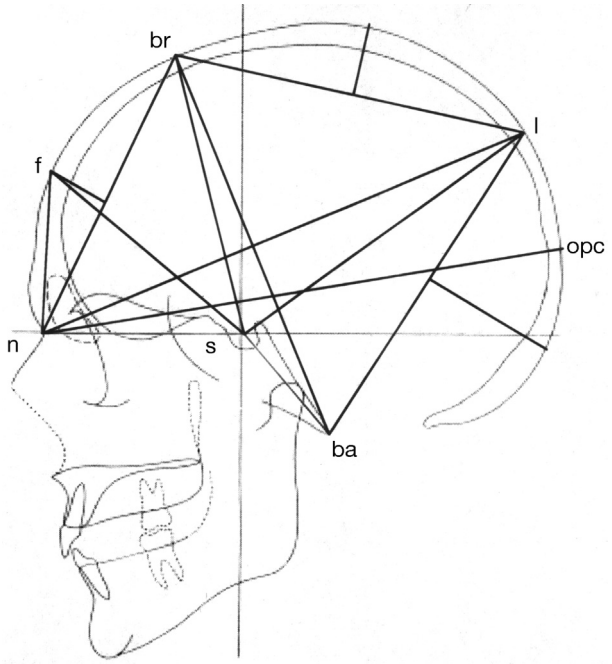

Figure 1 The following cephalometric reference points and variables were identified on each radiograph. Basion (ba): the most postero-inferior point on the clivus. Bregma (br): the intersection between the sagittal and coronal sutures on the surface of the cranial vault. Frontale (f): a point on the surface of the frontal bone determined by the perpendicular to the line joining nasion and bregma and passing through its midpoint. Lambda (l): the intersection between the lambdoid and sagittal sutures on the surface of the cranial vault. Nasion (n): the most anterior point on the fronto-nasal suture. Opisthocranion (opc): the most posterior point on the surface of the cranial vault defined as the point furthest from nasion (disregarding the external occipital protuberance). Sella turcica (s): the centre of sella turcica. The upper limit of sella turcica is defined as the line joining the tuberculum and dorsum sellae. Cephalometric variables: angular measurements (degrees): s–n–f, prominence of the frontal bone; n–s–ba, cranial base angle. Linear measurements (mm): s–n, anterior cranial base length; s–ba, posterior cranial base length; s–f, distance from sella to the frontal bone; n–br, distance from nasion to bregma; s–br, distance from sella to bregma; ba–br, distance from basion to bregma; br–l, distance from bregma to lambda; s–l, distance from sella to lambda; n–l, distance from nasion to lambda; n–opc, diameter of the neurocranium from nasion to opisthocranion; ba–l, distance from basion to lambda. The maximum distances from the cords nasion–bregma, bregma–lambda, and lambda–basion to the corresponding arch segments: n–br to the frontal bone; br–l to the parietal bone; l–ba to the occipital bone. The thicknesses of the frontal, parietal, and occipital bones were defined as the distances from the points where the perpendicular bisectors of the cords nasion–bregma, bregma–lambda, and lambda–basion intersected the inner and outer contours of the respective bones: thickness of the frontal bone; thickness of the parietal bone; thickness of the occipital bone. Definitions of the reference points according to Björk (1960) and Solow (1966) and of the variables according to Solow (1966) and Kisling (1966).

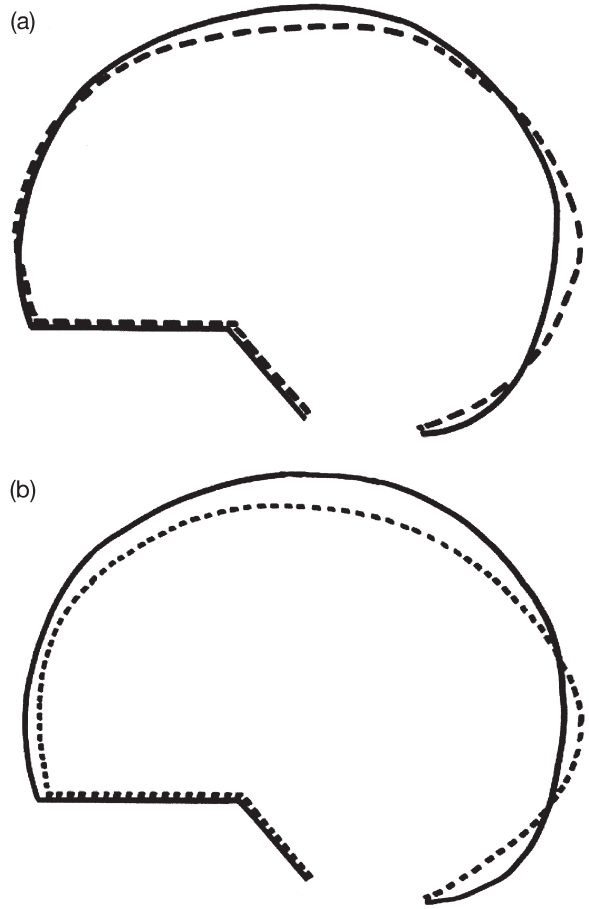

Figure 2 Mean drawings for (a) Williams syndrome (WS) males at 12 years of age (dotted line) and the control group (solid line), and (b) WS females at 12 years of age (dotted line) and the control group (solid line).

Mean tracings

Mean tracings for all 12-year-old males and females with WS superimposed on mean tracings for the 12-year-old male and female control groups are shown in Figure 2a and b. Superimposition was made on the nasion–sella line, registered at sella turcica (s).

Results

Data from the cephalometric measurements of the neurocranium for males and females, divided into six age groups, with arithmetic means, standard deviations, maximum and minimum values, number of individuals, and the level of statistical significance between the WS group and the control group were calculated (Tables 2–7). The different variables were also illustrated graphically, but only those variables with large differences between the WS groups and the controls are shown (Figures 3–9).

Cranial base

The values of the cranial base angle (n–s–ba) were similar for the WS and control groups. The length of the anterior cranial base (s–n) was similar for the male WS

Table 2a Cephalometric values for males at 6 years of age.

		WS, male (n = 6)					Control group, male (n = 35)					
		Mean	SD	Minimum	Maximum	n	Mean	SD	Minimum	Maximum	n	Significance
s–n–f	°	92.7	5.0	87.6	100.7	6	93.4	2.8	87.1	99.7	35	ns
s–n–ba	°	131.6	7.7	119.3	139.7	6	130.8	4.7	120.4	141.4	35	ns
s–n	mm	61.2	3.5	55.1	65.6	6	61.7	2.2	57.8	68.5	35	ns
s–ba	mm	30.3	2.6	25.9	32.6	6	37.4	2.4	32.7	41.5	35	***
s–f	mm	88.8	3.9	82.5	93.3	6	88.1	4.2	81.5	97.3	35	ns
n–br	mm	108.3	7.5	98.4	118.3	6	105.5	3.9	99.4	113.4	35	ns
s–br	mm	97.6	4.9	93.0	104.8	6	98.9	3.7	94.4	105.5	35	ns
ba–br	mm	123.9	6.7	118.6	133.0	6	132.0	4.2	123.5	139.7	35	***
br–l	mm	113.8	18.7	89.7	136.1	6	123.2	5.2	109.8	131.3	35	*
s–l	mm	113.0	6.5	105.9	124.5	6	113.9	5.3	102.7	122.4	35	ns
n–l	mm	164.1	8.0	155.8	178.5	6	169.4	5.2	159.9	181.2	35	*
n–opc	mm	178.2	6.8	170.4	190.4	6	170.9	5.2	161.7	182.1	35	**
ba–l	mm	112.1	8.4	98.3	121.5	6	113.2	4.9	100.1	124.3	35	ns
n–br to the frontal bone	mm	30.0	2.9	25.4	33.3	6	26.6	2.2	22.2	32.6	35	**
br–l to the parietal bone	mm	24.1	10.0	10.9	33.6	6	28.1	3.0	21.3	33.1	35	ns
l–ba to the occipital bone	mm	45.4	12.0	28.0	61.1	6	38.5	3.3	31.1	48.0	35	**
Thickness of the frontal bone	mm	5.6	1.8	3.9	8.1	6	4.2	0.8	2.7	6.3	35	**
Thickness of the parietal bone	mm	6.0	1.2	4.7	7.8	6	4.9	1.0	2.9	7.7	35	ns
Thickness of the occipital bone	mm	6.6	2.4	3.8	10.0	6	4.3	1.5	1.8	7.8	35	**
Curvature indices												
Frontal bone		27.7	1.6	25.8	30.1	6	25.2	1.8	21.8	29.8	35	
Parietal bone		20.5	6.2	11.7	25.7	6	22.7	1.9	17.6	25.8	35	
Occipital bone		40.2	9.6	28.5	54.2	6	34.0	2.7	28.5	38.6	35	

Table 2b Cephalometric values for females at 6 years of age.

		WS, female (n = 11)					Control group, female (n = 37)					
		Mean	SD	Minimum	Maximum	n	Mean	SD	Minimum	Maximum	n	Significance
s–n–f	°	92.0	3.5	85.9	97.9	11	94.3	3.5	88.0	101.7	37	ns
s–n–ba	°	129.3	6.3	118.8	140.2	11	130.8	4.7	121.6	138.0	37	ns
s–n	mm	59.2	3.1	53.6	63.3	11	60.8	1.8	57.3	65.5	37	*
s–ba	mm	31.3	2.7	26.6	34.6	11	36.7	2.3	32.0	41.1	37	***
s–f	mm	83.9	2.9	79.6	89.1	11	87.2	3.3	82.2	96.4	37	**
n–br	mm	101.6	7.2	93.4	116.7	11	103.5	4.9	94.0	115.0	37	ns
s–br	mm	92.1	4.4	86.1	100.1	11	97.2	4.3	92.1	108.1	37	**
ba–br	mm	120.1	5.4	110.4	128.0	11	129.3	3.9	122.9	139.8	37	***
br–l	mm	107.4	15.4	78.5	123.5	11	119.6	6.2	109.6	136.4	37	***
s–l	mm	107.1	5.7	98.2	116.5	11	111.4	6.2	99.4	127.6	37	*
n–l	mm	159.3	8.8	145.0	173.6	11	165.7	6.5	152.6	180.4	37	*
n–opc	mm	170.1	5.7	161.5	178.9	11	167.3	7.2	152.3	183.1	37	ns
ba–l	mm	109.0	7.1	98.6	119.3	11	110.9	5.2	99.8	124.7	37	ns
n–br to the frontal bone	mm	27.5	2.4	24.1	31.1	11	27.0	2.3	23.7	32.6	37	ns
br–l to the parietal bone	mm	22.2	7.1	9.8	31.4	11	27.3	2.7	21.7	33.7	37	*
l–ba to the occipital bone	mm	43.1	7.0	36.6	56.9	11	37.3	3.4	30.1	44.8	37	***
Thickness of the frontal bone	mm	6.3	1.3	4.0	8.2	11	4.2	0.8	2.8	5.7	37	***
Thickness of the parietal bone	mm	5.4	1.0	4.5	7.5	11	5.1	0.7	3.9	6.4	37	ns
Thickness of the occipital bone	mm	5.8	2.4	2.3	8.7	11	3.7	1.4	2.1	7.6	37	***
Curvature indices												
Frontal bone		27.1	1.7	24.5	29.7	11	26.0	1.4	23.3	29.5	37	
Parietal bone		20.1	4.2	12.5	25.4	11	22.8	1.9	19.8	27.6	37	
Occipital bone		39.5	5.4	31.1	50.3	11	33.7	2.8	27.6	39.2	37	

WS, Williams syndrome; SD, standard deviation; ns, not significant.
Significant at *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Table 3a Cephalometric values for males 8–10 years of age.

		WS, male (n = 6)					Control group, male (n = 35)					
		Mean	SD	Minimum	Maximum	n	Mean	SD	Minimum	Maximum	n	Significance
s–n–f	°	90.0	3.5	85.0	93.3	5	91.1	2.6	85.5	95.3	32	ns
s–n–ba	°	129.3	4.5	121.1	134.7	6	130.1	4.5	118.6	138.9	35	ns
s–n	mm	63.6	3.5	58.5	67.1	6	64.5	2.6	60.6	72.5	35	ns
s–ba	mm	36.2	3.2	30.7	39.2	6	39.9	2.5	35.0	44.3	35	*
s–f	mm	89.9	9.2	82.5	101.2	5	88.6	3.8	81.5	98.7	32	ns
n–br	mm	110.1	9.2	102.7	123.3	4	107.6	4.1	100.1	115.5	32	(ns)
s–br	mm	97.7	8.8	92.1	110.7	4	99.3	3.8	94.2	109.3	32	(ns)
ba–br	mm	130.5	6.2	124.9	139.3	4	134.4	4.2	126.6	144.2	32	(ns)
br–l	mm	117.2	2.7	114.1	121.5	4	124.0	5.3	112.5	132.7	32	(ns)
s–l	mm	114.6	7.6	105.9	124.6	6	115.2	5.6	103.8	124.1	34	ns
n–l	mm	171.4	8.0	163.9	184.8	6	172.5	7.0	146.7	183.3	35	ns
n–opc	mm	181.7	8.0	173.3	195.1	6	175.1	5.3	165.1	186.9	35	*
ba–l	mm	110.4	7.9	99.4	119.8	6	114.7	5.4	101.1	125.2	35	ns
n–br to the frontal bone	mm	28.7	5.1	24.3	36.0	4	26.4	2.2	21.0	32.9	32	(ns)
br–l to the parietal bone	mm	26.4	0.5	26.1	27.1	4	28.2	2.9	20.9	33.2	31	(ns)
ba–l to the occipital bone	mm	41.0	2.8	36.3	41.9	6	38.8	3.3	31.9	45.8	34	ns
Thickness of the frontal bone	mm	5.9	1.0	4.9	7.3	4	4.5	0.7	3.1	6.3	32	(**)
Thickness of the parietal bone	mm	6.3	0.5	5.8	7.1	4	5.5	0.9	3.9	8.2	31	(ns)
Thickness of the occipital bone	mm	8.6	3.6	3.3	12.3	6	4.6	1.5	2.8	8.4	35	*
Curvature indices												
Frontal bone		26.1	2.5	23.1	29.2	4	24.5	1.7	20.8	29.4	32	
Parietal bone		22.5	1.6	21.3	24.7	4	22.7	1.8	17.2	26.0	31	
Occipital bone		37.1	3.9	30.3	40.7	6	33.8	2.7	28.3	39.2	34	

Table 3b Cephalometric values for females 8–10 years of age.

		WS, female (n = 9)					Control group, female (n = 37)					
		Mean	SD	Minimum	Maximum	n	Mean	SD	Minimum	Maximum	n	Significance
s–n–f	°	89.3	5.4	81.4	96.5	7	92.1	3.2	86.9	98.8	36	ns
s–n–ba	°	129.0	4.3	125.0	139.1	9	130.9	4.9	121.1	140.3	37	ns
s–n	mm	61.7	2.8	57.4	67.2	9	63.5	1.8	60.2	68.0	37	*
s–ba	mm	37.1	2.4	32.9	40.9	9	38.9	2.6	34.3	43.8	37	ns
s–f	mm	84.2	5.9	73.1	91.8	7	87.9	3.4	82.9	97.4	36	ns
n–br	mm	107.0	4.5	100.8	113.0	7	105.6	5.2	96.8	117.5	36	ns
s–br	mm	93.9	3.8	88.6	100.5	7	97.1	3.6	93.0	107.0	36	*
ba–br	mm	126.6	3.4	121.3	130.0	7	131.9	3.6	125.5	143.4	36	***
br–l	mm	115.0	10.6	94.6	127.9	7	120.3	5.2	110.2	135.0	35	ns
s–l	mm	112.1	2.7	108.5	116.7	9	112.7	6.3	101.2	129.1	35	ns
n–l	mm	168.7	4.2	162.8	176.0	9	169.5	6.7	156.4	184.0	35	ns
n–opc	mm	181.2	4.5	173.5	186.9	9	171.6	7.5	156.5	186.9	37	***
ba–l	mm	111.3	5.4	104.6	120.6	9	112.3	5.6	101.4	126.8	35	ns
n–br to the frontal bone	mm	28.8	2.3	25.2	31.3	7	26.8	2.5	23.3	33.5	36	ns
br–l to the parietal bone	mm	22.9	4.9	15.0	29.1	7	27.4	2.5	21.6	32.3	35	***
ba–l to the occipital bone	mm	41.9	7.0	34.8	54.5	9	37.6	3.7	32.5	46.3	35	*
Thickness of the frontal bone	mm	6.7	1.3	4.6	8.0	7	4.6	0.9	3.1	6.3	36	***
Thickness of the parietal bone	mm	5.8	1.2	3.8	7.8	7	5.6	0.7	4.3	7.5	35	ns
Thickness of the occipital bone	mm	7.9	3.5	3.6	13.6	9	4.1	1.1	2.3	8.0	35	***
Curvature indices												
Frontal bone		26.9	2.3	22.3	29.4	7	25.4	1.5	22.8	29.2	36	
Parietal bone		19.9	3.0	15.9	25.0	7	22.8	2.0	18.8	26.9	35	
Occipital bone		37.6	4.6	33.2	45.2	9	33.5	2.9	27.8	40.1	35	

WS, Williams syndrome; SD, standard deviation; ns, not significant.
Significant at *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. Parentheses indicate that the significance test is doubtful due to a low number of valid measurements in the study group.

Table 4a Cephalometric values for males 11–13 years of age.

		WS, male (n = 10)					Control group, male (n = 35)					
		Mean	SD	Minimum	Maximum	n	Mean	SD	Minimum	Maximum	n	Significance
s–n–f	°	88.0	2.0	85.9	91.0	8	89.2	3.0	82.2	95.6	27	ns
s–n–ba	°	131.8	2.7	126.8	134.8	10	129.5	4.3	120.3	137.7	35	ns
s–n	mm	65.8	1.9	61.9	68.3	10	66.1	3.0	60.6	74.5	35	ns
s–ba	mm	37.3	4.0	27.8	42.5	10	41.7	3.0	35.6	47.4	35	***
s–f	mm	87.2	2.0	84.7	91.2	8	88.7	4.0	81.3	98.5	27	ns
n–br	mm	106.1	4.0	99.9	112.1	8	108.8	4.1	102.7	116.7	27	ns
s–br	mm	94.4	3.5	90.5	101.8	8	99.0	3.5	94.4	106.8	27	**
ba–br	mm	126.4	6.4	119.6	138.7	8	135.4	4.0	126.5	143.3	27	***
br–l	mm	114.1	9.0	92.1	121.9	8	124.5	5.7	113.9	138.9	27	***
s–l	mm	112.3	3.2	106.7	116.3	10	115.9	5.4	104.9	125.9	35	ns
n–l	mm	170.9	3.8	165.5	175.5	10	176.2	5.3	165.1	185.7	35	*
n–opc	mm	180.9	7.2	166.1	191.3	10	178.3	5.3	167.5	190.6	35	ns
ba–l	mm	112.0	4.4	104.3	117.2	10	115.3	4.6	100.6	122.4	35	ns
n–br to the frontal bone	mm	26.8	2.4	24.7	30.6	8	26.0	2.4	20.9	32.2	27	ns
br–l to the parietal bone	mm	25.0	5.5	12.9	32.2	8	28.0	2.8	20.0	32.1	27	*
ba–l to the occipital bone	mm	44.4	8.4	33.7	62.7	10	39.3	3.1	34.3	45.5	35	*
Thickness of the frontal bone	mm	6.5	1.0	4.9	7.8	8	4.7	0.8	3.4	6.8	27	***
Thickness of the parietal bone	mm	6.5	1.7	3.9	9.0	8	6.0	1.2	3.6	8.9	23	ns
Thickness of the occipital bone	mm	7.8	1.7	5.2	10.1	10	5.0	1.7	2.5	9.8	35	***
Curvature indices												
Frontal bone		25.3	2.1	22.8	29.3	8	23.9	1.8	20.2	28.2	27	
Parietal bone		21.9	3.5	14.0	26.4	8	22.5	1.9	16.4	25.5	27	
Occipital bone		39.6	7.2	31.0	54.9	10	34.1	2.5	28.8	40.1	35	

Table 4b Cephalometric values for females 11–13 years of age.

		WS, female (n = 15)					Control group, female (n = 37)					
		Mean	SD	Minimum	Maximum	n	Mean	SD	Minimum	Maximum	n	Significance
s–n–f	°	88.4	4.9	77.2	98.4	11	89.6	3.1	85.2	95.8	29	ns
s–n–ba	°	129.9	4.6	123.6	140.7	15	130.2	4.9	121.4	141.9	37	ns
s–n	mm	62.1	2.6	57.3	66.6	15	65.5	2.2	61.4	70.8	37	***
s–ba	mm	35.5	2.9	30.2	39.6	15	41.0	2.6	65.1	46.0	37	***
s–f	mm	82.9	3.1	77.6	88.9	11	87.6	2.9	82.6	96.7	29	***
n–br	mm	102.0	3.6	96.8	106.3	11	107.2	5.9	98.5	127.9	29	*
s–br	mm	90.5	4.4	83.3	96.9	11	96.5	3.2	90.6	104.5	29	***
ba–br	mm	121.9	3.9	116.8	128.5	11	133.0	4.8	114.0	139.9	29	***
br–l	mm	110.0	7.1	92.5	117.6	11	120.9	5.3	109.5	133.8	29	***
s–l	mm	108.6	4.9	101.4	116.7	15	113.9	6.2	102.0	130.5	37	**
n–l	mm	164.4	5.7	158.0	175.7	15	173.0	6.7	159.2	186.6	37	***
n–opc	mm	176.9	7.0	165.1	189.9	15	175.7	7.1	160.1	189.7	37	ns
ba–l	mm	109.3	5.9	100.3	119.6	15	113.5	5.8	102.2	127.8	37	*
n–br to the frontal bone	mm	25.9	1.2	23.8	28.0	11	26.4	2.7	23.1	32.8	29	ns
br–l to the parietal bone	mm	21.2	3.6	13.0	25.9	11	27.5	3.0	20.8	32.3	28	***
ba–l to the occipital bone	mm	44.2	7.8	33.6	63.1	15	37.8	3.9	31.6	47.7	37	**
Thickness of the frontal bone	mm	7.0	2.0	4.4	9.5	11	5.2	1.0	3.2	7.7	29	*
Thickness of the parietal bone	mm	6.1	1.6	3.6	8.3	11	6.4	0.9	4.9	8.6	28	ns
Thickness of the occipital bone	mm	8.9	2.0	2.9	11.8	15	4.6	1.2	2.6	9.1	37	***
Curvature indices												
Frontal bone		25.4	1.7	22.4	27.9	11	24.6	1.6	22.0	28.8	29	
Parietal bone		19.3	2.5	14.1	22.5	11	22.7	2.1	19.0	27.5	28	
Occipital bone		40.4	5.5	32.9	52.8	15	33.3	2.9	27.4	39.3	37	

WS, Williams syndrome; SD, standard deviation; ns, not significant.
Significant at *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Table 5a Cephalometric values for males 14–16 years of age.

		WS, male (n = 7)					Control group, male (n = 35)					
		Mean	SD	Minimum	Maximum	n	Mean	SD	Minimum	Maximum	n	Significance
s–n–f	°	84.0	4.5	77.8	90.1	6	84.9	5.6	68.8	90.0	15	ns
s–n–ba	°	129.6	6.7	118.4	136.5	7	128.9	4.6	120.0	137.6	35	ns
s–n	mm	68.1	3.6	63.6	71.8	7	68.8	2.8	34.7	77.3	35	ns
s–ba	mm	38.2	5.2	30.4	46.1	7	43.7	2.8	38.1	49.0	35	*
s–f	mm	87.8	4.9	80.5	92.1	6	88.1	3.5	81.9	92.4	15	ns
n–br	mm	113.5	3.4	108.3	118.4	6	109.5	3.9	104.7	117.6	14	*
s–br	mm	97.4	2.0	95.4	100.8	6	96.7	3.2	89.8	101.9	14	ns
ba–br	mm	130.6	3.7	127.3	137.5	6	135.1	4.5	112.6	147.3	14	*
br–l	mm	110.9	9.4	92.6	118.1	6	123.1	8.0	109.4	139.0	14	**
s–l	mm	113.0	4.5	105.9	118.4	7	117.8	5.9	106.0	127.9	35	ns
n–l	mm	172.7	6.6	160.2	181.0	7	180.4	5.7	168.2	192.6	35	**
n–opc	mm	185.7	7.1	172.5	193.7	7	182.5	5.7	169.1	194.2	35	ns
ba–l	mm	114.4	7.8	105.2	125.7	7	117.9	5.6	104.4	130.1	35	ns
n–br to the frontal bone	mm	28.1	0.3	27.8	28.6	6	24.8	1.5	21.2	27.3	13	***
br–l to the parietal bone	mm	21.6	4.5	12.8	25.4	6	27.2	1.7	24.2	29.5	12	ns
ba–l to the occipital bone	mm	46.5	11.4	36.8	67.6	7	39.8	4.1	32.0	50.2	35	***
Thickness of the frontal bone	mm	7.0	2.3	4.3	10.8	6	5.1	0.9	3.9	6.8	15	ns
Thickness of the parietal bone	mm	6.0	1.6	3.1	8.2	6	7.1	1.1	5.5	9.5	19	ns
Thickness of the occipital bone	mm	10.5	3.5	6.0	16.0	7	5.8	2.0	2.4	10.1	35	***
Curvature indices												
Frontal bone		24.8	7.0	23.7	25.7	6	22.6	1.5	20.1	24.8	12	
Parietal bone		19.3	2.8	19.1	21.5	6	22.2	1.3	19.6	23.7	11	
Occipital bone		40.6	7.4	32.7	53.8	7	33.8	3.1	28.2	40.9	35	

Table 5b Cephalometric values for females 14–16 years of age.

		WS, female (n = 5)					Control group, female (n = 37)					
		Mean	SD	Minimum	Maximum	n	Mean	SD	Minimum	Maximum	n	Significance
s–n–f	°	85.7	1.9	83.9	87.6	3	88.0	2.8	82.9	92.9	22	ns
s–n–ba	°	129.4	7.3	122.7	140.8	5	130.1	4.7	122.0	140.1	37	ns
s–n	mm	65.2	1.6	63.1	67.1	5	67.1	2.1	62.8	72.2	37	ns
s–ba	mm	35.0	2.9	32.3	39.2	5	41.8	2.9	37.1	47.4	37	***
s–f	mm	86.9	5.4	86.4	87.4	3	87.9	2.1	84.2	93.5	22	(ns)
n–br	mm	107.4	2.0	105.4	109.3	3	107.3	3.5	100.8	113.9	22	(ns)
s–br	mm	92.8	2.8	90.0	95.6	3	95.9	3.8	83.8	102.0	22	(ns)
ba–br	mm	118.9	11.3	107.6	130.3	3	133.8	3.4	127.4	139.2	22	(ns)
br–l	mm	113.0	2.0	111.0	115.1	3	120.1	4.3	111.5	129.1	22	(**)
s–l	mm	110.7	5.5	104.0	118.2	5	113.9	5.8	100.4	125.0	37	ns
n–l	mm	167.2	14.6	141.8	177.7	5	174.8	5.9	160.9	187.0	37	ns
n–opc	mm	187.2	5.6	181.6	193.5	5	177.5	7.2	160.4	190.8	37	**
ba–l	mm	110.9	8.1	102.6	121.2	5	115.1	6.3	104.7	139.1	37	ns
n–br to the frontal bone	mm	26.8	3.0	23.8	29.8	3	25.8	1.5	23.1	28.3	22	(ns)
br–l to the parietal bone	mm	23.3	0.7	22.6	24.0	3	27.2	2.1	24.3	30.9	19	(**)
ba–l to the occipital bone	mm	42.5	7.2	34.1	51.3	5	38.0	3.7	31.7	46.5	37	ns
Thickness of the frontal bone	mm	9.9	0.7	9.2	10.5	3	5.6	1.2	3.6	8.7	22	(***)
Thickness of the parietal bone	mm	7.5	1.7	6.0	9.4	3	6.9	1.4	4.0	9.5	19	(ns)
Thickness of the occipital bone	mm	8.0	2.2	5.1	11.0	5	5.1	1.6	2.8	10.5	37	***
Curvature indices												
Frontal bone		25.0	3.3	21.8	28.3	3	24.0	1.0	21.8	25.7	22	
Parietal bone		20.6	1.0	19.6	21.6	3	22.6	1.6	19.9	26.8	19	
Occipital bone		38.3	5.6	29.8	42.3	5	33.0	2.9	26.5	38.8	37	

WS, Williams syndrome; SD, standard deviation; ns, not significant.
Significant at *$P < 0.005$; **$P < 0.01$; ***$P < 0.001$. Parentheses indicate that the significance test is doubtful due to a low number of valid measurements in the study group.

Table 6a Cephalometric values for males 17–19 years of age.

		WS, male (n = 6)					Control group, male (n = 35)					
		Mean	SD	Minimum	Maximum	n	Mean	SD	Minimum	Maximum	n	Significance
s–n–f	°	85.3	5.8	79.2	90.9	4	85.5	3.5	80.3	91.2	6	(ns)
s–n–ba	°	130.7	3.7	125.9	136.1	6	128.3	4.7	119.2	137.7	35	ns
s–n	mm	70.9	3.0	66.3	75.4	6	70.3	3.0	64.9	79.2	35	ns
s–ba	mm	39.8	2.4	35.6	41.9	6	44.4	2.5	39.6	49.6	35	***
s–f	mm	93.1	4.2	90.8	99.4	4	87.8	3.5	83.3	92.7	5	(ns)
n–br	mm	118.8	7.1	108.3	123.4	4	110.6	2.7	106.7	113.5	5	(*)
s–br	mm	104.1	3.3	99.7	107.2	4	97.7	3.0	93.5	100.6	5	(*)
ba–br	mm	139.1	2.2	137.5	142.2	4	135.0	4.9	130.0	410.2	5	(ns)
br–l	mm	102.3	10.2	88.4	111.2	4	124.6	10.3	114.3	138.5	5	(*)
s–l	mm	122.3	5.9	113.3	128.3	6	118.4	5.9	107.3	128.1	35	ns
n–l	mm	178.6	8.6	164.6	189.1	6	182.7	5.7	171.0	193.7	35	ns
n–opc	mm	191.7	4.7	187.1	196.3	4	184.7	5.7	174.5	197.0	35	(*)
ba–l	mm	120.0	6.3	107.2	122.9	6	118.7	5.7	104.1	129.6	35	ns
n–br to the frontal bone	mm	27.6	3.9	25.5	33.4	4	24.4	1.9	21.1	25.5	5	(ns)
br–l to the parietal bone	mm	18.8	3.3	14.1	21.7	4	25.5	0.6	24.9	26.3	4	(**)
ba–l to the occipital bone	mm	52.1	11.2	37.0	64.4	6	40.4	3.9	34.2	51.1	35	***
Thickness of the frontal bone	mm	8.3	2.8	4.2	10.6	4	5.1	0.9	4.3	6.3	5	(*)
Thickness of the parietal bone	mm	6.4	2.3	3.5	8.7	4	7.9	1.1	7.0	9.1	3	(ns)
Thickness of the occipital bone	mm	11.0	2.1	8.0	13.7	5	6.4	2.0	2.9	11.2	35	***
Curvature indices												
Frontal bone		23.2	3.3	20.7	27.7	4	22.0	1.3	19.8	23.2	5	
Parietal bone		18.4	2.9	13.6	20.0	4	20.9	1.9	18.1	22.2	4	
Occipital bone		41.8	8.2	32.2	52.7	6	34.0	2.7	28.7	40.7	35	

Table 6b Cephalometric values for females 17–19 years of age.

		WS, female (n = 6)					Control group, male (n = 35)					
		Mean	SD	Minimum	Maximum	n	Mean	SD	Minimum	Maximum	n	Significance
s–n–f	°	88.0	4.1	83.3	95.1	6	88.3	3.8	83.3	99.1	17	ns
s–n–ba	°	130.9	4.8	126.5	139.0	6	130.1	4.8	122.3	140.4	37	ns
s–n	mm	63.8	2.7	59.4	66.7	6	67.4	2.1	63.0	72.8	37	***
s–ba	mm	36.3	3.8	30.4	40.5	6	41.6	2.6	35.5	45.8	37	***
s–f	mm	85.5	4.5	80.6	91.1	6	87.7	2.5	84.4	93.6	17	ns
n–br	mm	106.1	6.5	99.0	117.0	6	107.5	3.9	100.8	114.0	17	ns
s–br	mm	93.2	4.1	89.0	99.9	6	96.0	3.4	91.6	102.3	17	ns
ba–br	mm	123.7	4.9	116.3	129.1	6	133.2	4.5	123.6	139.2	17	***
br–l	mm	106.6	9.0	92.5	117.4	6	121.2	7.0	108.1	136.2	17	***
s–l	mm	108.1	3.9	102.8	113.0	6	114.9	5.9	102.8	131.3	37	*
n–l	mm	164.5	5.5	159.2	172.7	6	175.8	6.3	161.8	188.9	37	***
n–opc	mm	176.1	6.2	169.6	183.6	6	178.4	7.0	162.4	192.1	37	ns
ba–l	mm	108.6	8.4	101.2	124.4	6	115.2	6.1	104.9	134.4	37	*
n–br to the frontal bone	mm	27.7	2.5	25.4	32.4	6	25.6	1.9	23.0	29.2	17	ns
br–l to the parietal bone	mm	18.3	5.0	11.1	22.7	6	27.1	2.6	23.7	31.6	15	**
ba–l to the occipital bone	mm	45.9	9.4	36.9	64.0	6	37.8	3.8	31.2	46.6	37	***
Thickness of the frontal bone	mm	8.6	1.0	7.1	10.3	6	6.0	1.3	4.1	8.9	17	***
Thickness of the parietal bone	mm	7.7	1.2	6.2	9.6	6	7.5	1.4	5.3	10.0	15	ns
Thickness of the occipital bone	mm	10.2	0.8	8.7	10.9	6	5.3	1.6	2.8	8.8	37	***
Curvature indices												
Frontal bone		26.1	1.3	24.2	27.7	6	23.8	1.2	21.7	26.1	17	
Parietal bone		17.2	3.5	12.0	21.4	6	22.3	2.3	19.0	26.6	15	
Occipital bone		42.3	7.4	32.9	51.4	6	32.9	3.0	27.0	39.2	37	

WS, Williams syndrome; SD, standard deviation; ns, not significant.
Significant at *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. Parentheses indicate that the significance test is doubtful due to a low number of valid measurements in the study group.

Table 7a Cephalometric values for males greater than 20 years of age.

		WS, male (n = 4)					Control group, male (n = 19)					
		Mean	SD	Minimum	Maximum	n	Mean	SD	Minimum	Maximum	n	Significance
s–n–f	°	88.9	7.5	80.6	97.2	4	87.9	–	85.7	90.3	3	–
s–n–ba	°	130.2	3.8	127.1	135.1	4	127.6	5.0	118.6	136.1	19	(ns)
s–n	mm	68.0	1.6	66.6	69.9	4	70.5	3.4	66.4	80.0	19	(ns)
s–ba	mm	41.4	2.5	39.0	45.0	4	45.0	1.8	42.0	48.9	19	(**)
s–f	mm	90.1	7.7	83.1	101.0	4	92.5	–	92.3	92.7	2	–
n–br	mm	109.5	10.6	97.4	122.3	4	113.8	–	113.6	114.0	2	–
s–br	mm	98.2	10.4	88.5	112.9	4	99.8	–	98.7	100.9	2	–
ba–br	mm	135.4	11.8	125.8	152.6	4	140.3	–	139.3	141.3	2	–
br–l	mm	111.0	15.7	94.0	128.8	4	121.8	–	119.9	123.6	2	–
s–l	mm	113.8	5.6	109.3	122.0	4	117.5	6.0	105.9	127.3	19	(ns)
n–l	mm	172.7	3.5	168.0	176.0	4	182.4	6.1	169.4	191.3	19	(**)
n–opc	mm	187.5	6.8	179.1	195.1	4	184.8	6.1	174.1	196.4	19	(ns)
ba–l	mm	118.5	11.0	109.6	134.0	4	118.4	6.6	103.8	130.1	19	(ns)
n–br to the frontal bone	mm	27.6	6.2	21.3	35.4	4	28.7	–	26.6	30.7	2	–
br–l to the parietal bone	mm	19.6	6.1	11.9	25.6	4	27.6	–	26.9	28.3	2	–
ba–l to the occipital bone	mm	52.0	9.4	43.9	65.5	4	39.1	3.2	33.1	45.0	19	(ns)
Thickness of the frontal bone	mm	11.3	3.4	8.2	15.9	4	6.1	–	5.6	6.6	2	–
Thickness of the parietal bone	mm	9.4	3.3	6.7	13.9	4	7.0	–	6.2	7.8	2	–
Thickness of the occipital bone	mm	10.4	3.2	6.0	12.9	4	6.3	2.4	2.8	12.4	19	(***)
Curvature indices												
Frontal bone		25.2	3.3	21.9	28.9	4	25.2	2.5	23.4	26.9	2	
Parietal bone		17.7	3.3	12.7	19.9	4	22.7	0.3	22.4	22.9	2	
Occipital bone		43.8	7.6	28.9	54.7	4	33.1	3.0	28.9	40.8	19	

Table 7b Cephalometric values for females greater than 20 years of age.

		WS, female (n = 12)					Control group, female (n = 15)					
		Mean	SD	Minimum	Maximum	n	Mean	SD	Minimum	Maximum	n	Significance
s–n–f	°	86.7	4.4	80.1	94.6	11	85.1	–	82.9	87.3	2	–
s–n–ba	°	129.4	4.5	122.0	135.5	12	133.2	5.6	123.0	141.0	15	ns
s–n	mm	63.6	2.6	58.5	66.6	12	67.5	1.7	64.6	71.7	15	***
s–ba	mm	36.4	5.0	27.1	43.3	12	41.7	2.4	38.8	45.9	15	**
s–f	mm	86.5	4.3	81.1	93.6	11	87.4	–	86.4	88.3	2	–
n–br	mm	111.8	6.6	103.3	125.6	11	111.4	–	110.1	113.0	2	–
s–br	mm	95.6	4.7	89.6	100.7	11	97.1	–	94.5	99.6	2	–
ba–br	mm	126.4	5.8	119.1	136.2	11	133.2	–	130.5	135.8	2	–
br–l	mm	103.7	11.9	78.2	118.9	11	115.6	–	113.5	117.6	2	–
s–l	mm	109.9	4.3	103.9	119.0	12	114.4	5.3	101.9	123.0	15	*
n–l	mm	166.8	5.4	155.3	173.4	12	175.5	5.9	161.8	185.0	15	***
n–opc	mm	181.7	6.1	174.5	192.8	12	177.9	6.4	162.6	187.9	15	ns
ba–l	mm	111.8	8.5	100.5	129.5	12	113.8	4.7	103.0	120.4	15	ns
n–br to the frontal bone	mm	29.6	2.7	24.1	34.0	11	26.6	–	25.4	27.7	2	–
br–l to the parietal bone	mm	19.6	4.7	11.6	28.2	11	24.2	–	22.6	25.8	2	–
ba–l to the occipital bone	mm	47.7	10.0	37.6	67.8	12	36.5	3.8	31.2	42.9	15	**
Thickness of the frontal bone	mm	9.7	1.7	7.8	12.3	11	6.4	–	6.2	6.6	2	–
Thickness of the parietal bone	mm	8.0	1.8	5.4	10.8	11	8.5	–	7.6	9.4	2	–
Thickness of the occipital bone	mm	12.2	3.9	4.7	17.8	12	4.8	1.2	3.1	6.8	15	***
Curvature indices												
Frontal bone		26.5	1.5	22.9	29.2	11	23.8	1.0	23.1	24.5	2.0	
Parietal bone		18.9	4.7	11.9	29.8	11	20.9	1.4	19.9	21.9	2.0	
Occipital bone		42.7	5.6	36.4	53.3	12	32.1	2.9	27.5	37.1	15.0	

WS, Williams syndrome; SD, standard deviation; ns, not significant.
Significant at $*P < 0.005$; $**P < 0.01$; $***P < 0.001$. Parentheses indicate that the significance test is doubtful due to a low number of valid measurements in the study group.

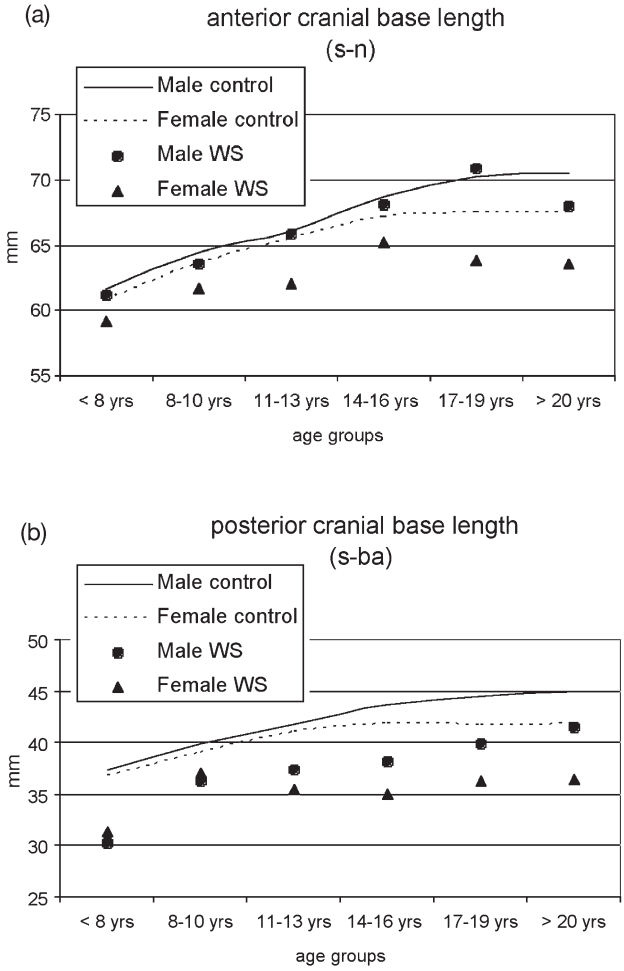

Figure 3 Graphic illustration of (a) anterior (s–n) and (b) posterior (s–ba) cranial base lengths for males and females in the Williams syndrome (WS) and control groups.

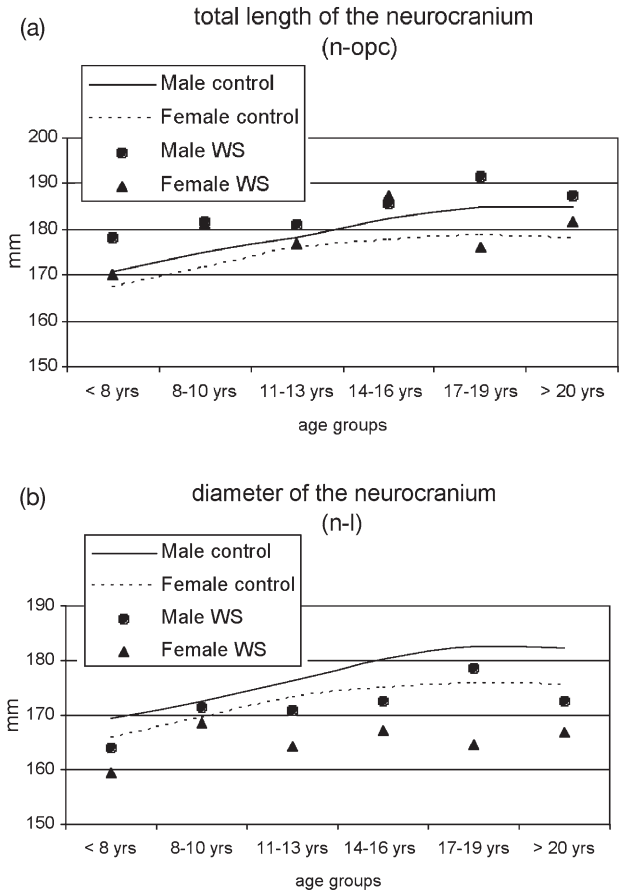

Figure 4 Graphic illustration of (a) the total length (n–opc) and (b) the diameter (n–l) of the neurocranium for males and females in the Williams syndrome (WS) and control groups.

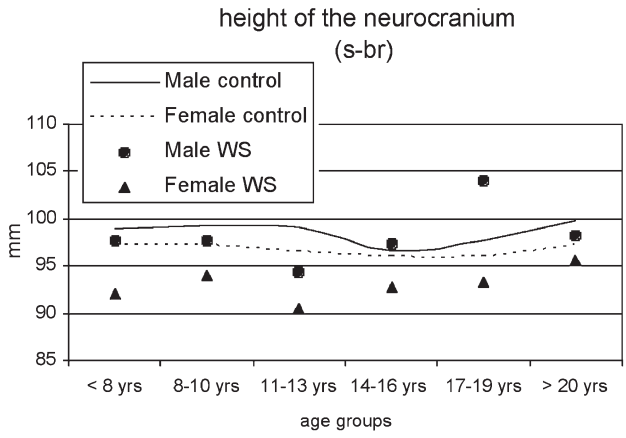

Figure 5 Graphic illustration of the height of the neurocranium (s–br) for males and females in the Williams syndrome (WS) and control groups.

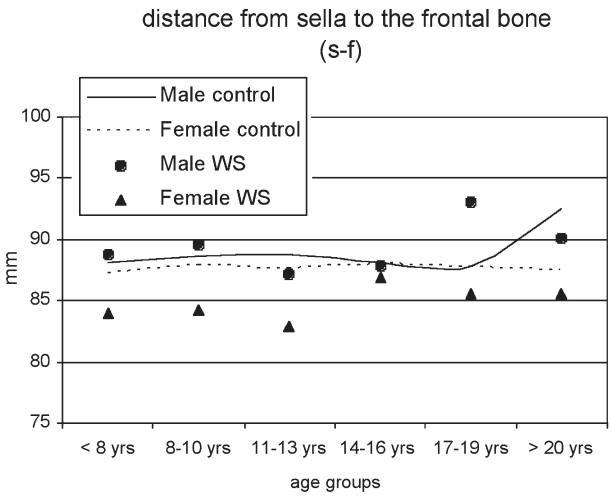

Figure 6 Graphic illustration of the distance from sella to lambda (s–l) for males and females in the Williams syndrome (WS) and control groups.

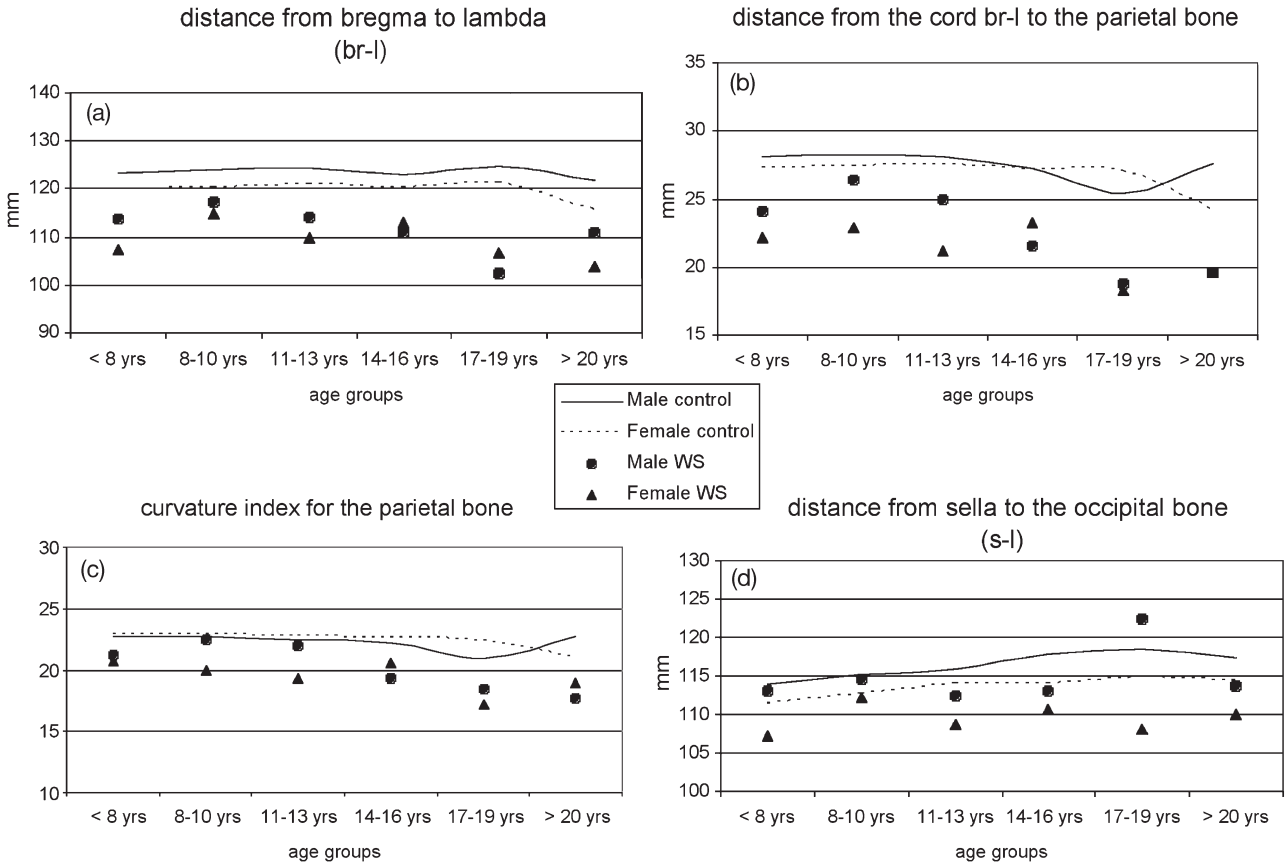

Figure 7 Graphic illustration of (a) the length of the parietal bone (br–l), (b) the perpendicular distance from the cord br–l to the outer surface of the parietal bone, (c) the curvature index for the parietal bone, and (d) the distance from sella to lambda for males and females in the Williams syndrome (WS) and control groups.

group compared with the male control group, but the female WS group showed a statistically significantly shorter anterior cranial base length (Figure 3a). In both the male and female WS groups, the posterior cranial base length (s–ba) was statistically significantly shorter compared with the controls (Figure 3b).

Length of the neurocranium

The length of the neurocranium (n–opc) was, in general, larger in the male WS group compared with the controls. The female WS group showed more variable results, with a tendency towards similar values to the control group (Figure 4a). The diameter of the neurocranium (n–l) showed smaller values for both the male and female WS groups compared with the control groups (Figure 4b).

Height of the neurocranium

The height of the neurocranium (s–br) was almost identical for the male WS group compared with the male controls (Figure 5). In the female WS group, the height of the neurocranium (s–br) was reduced, but the differences were statistically significant only for the three lower age groups. The reduced height of the neurocranium measured from basion to bregma (ba–br) in the WS group was strongly influenced by the shorter posterior cranial base length (s–ba) compared with the controls.

Anterior part of the neurocranium (frontal region)

Most measurements in the anterior part of the neurocranium (s–n–f; s–f; n–br, cord n–br to the frontal bone, and curvature index of the frontal bone) were similar for the WS groups compared with the controls, indicating a normal size and shape of the forehead. However, the female WS group showed smaller values for the variable sella to frontale (s–f), especially in the three lower age groups (Figure 6).

Middle part of the neurocranium (parietal region)

The results from the analyses of the variables of the middle part of the neurocranium indicated a more deviant morphology in WS subjects. The cord bregma to lambda (br–l) was statistically significantly smaller in both males

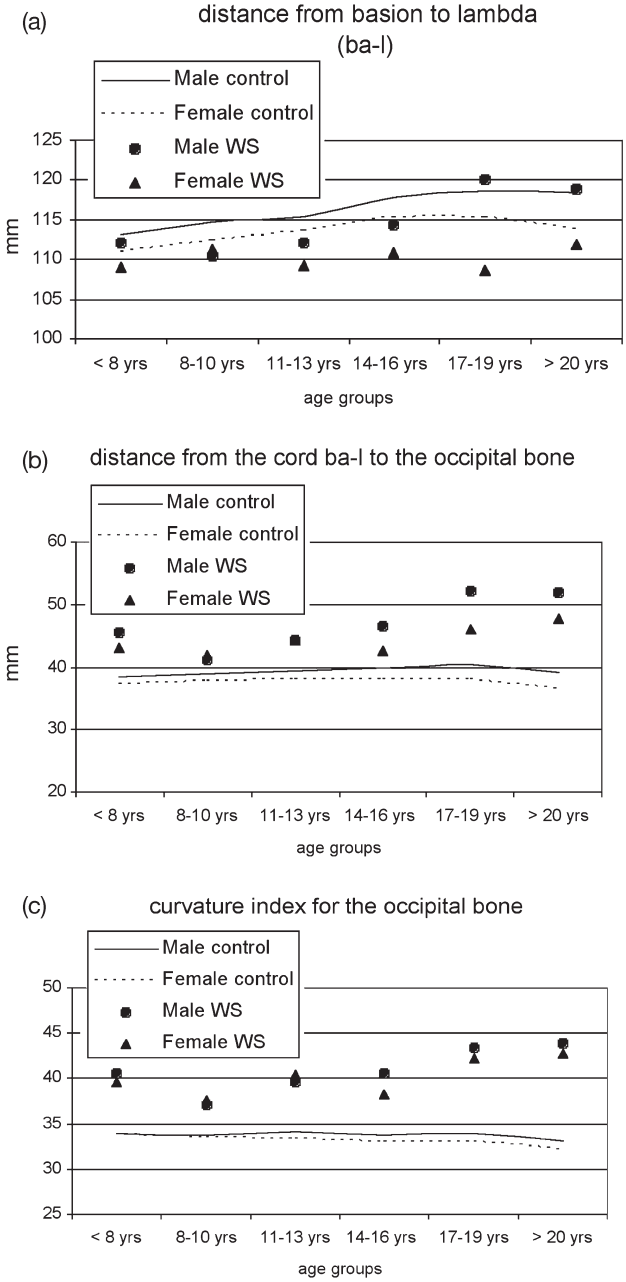

Figure 8 Graphic illustration of (a) the distance from basion to lambda (ba–l), (b) the perpendicular distance from the cord ba–l to the occipital bone, and (c) the curvature index of the occipital bone for males and females in the Williams syndrome (WS) and control groups.

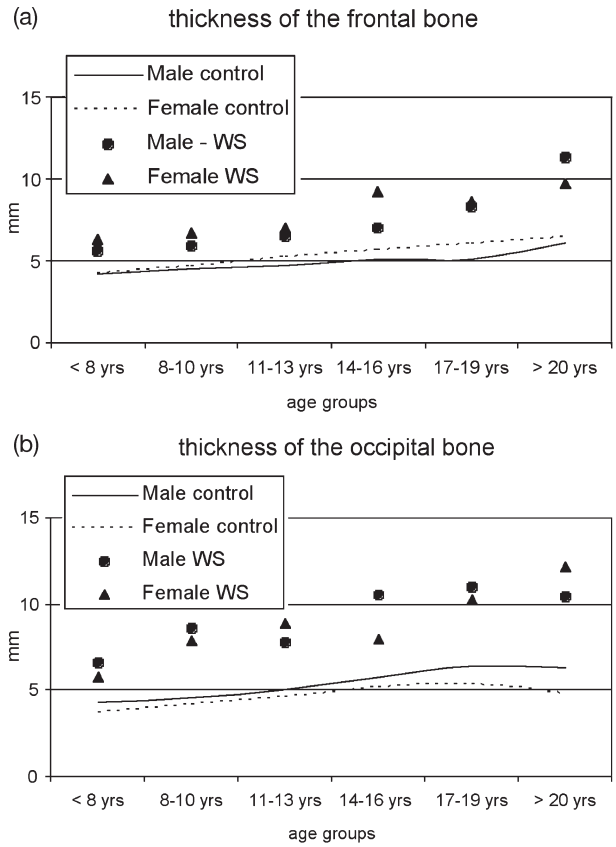

Figure 9 Graphic illustration of the thickness of (a) the frontal and (b) the occipital bones for males and females in the Williams syndrome (WS) and control groups.

and females compared with the controls (Figure 7a). The distance from the cord (br–l) to the outer surface of the parietal bone was also smaller for the WS groups, with a high level of statistical significance for the WS females (Figure 7b). This was also reflected in the smaller values of the curvature index for the parietal bone, indicating a slightly less curved parietal bone in WS subjects (Figure 7c). The shorter length of the parietal bone was also reflected in the measurements of the distance sella–lambda (s–l), especially in WS females (Figure 7d).

Posterior part of the neurocranium (occipital region)

The posterior part of the neurocranium in the WS subjects had a different shape compared with the control groups. This was evident in the shorter distance of the cord, basion–lambda (ba–l) (Figure 8a), and the larger distance from the cord to the outer surface of the occipital bone for both the male and female WS groups, but the differences were larger for males (Figure 8b). This was also reflected in the higher values of the curvature index for the occipital bone, indicating a larger curvature of the occipital bone (Figure 8c).

Thickness of the calvarian bones

The thickness of the cranial vault bones was measured at three locations: in the middle section of the frontal, parietal, and occipital bones. The differences between the WS groups and controls were obvious; the frontal and occipital bones being thicker than the parietal bone, in contrast to the controls where the frontal and parietal

bones had similar thicknesses, and the occipital bone was the thickest (Figure 9a, b).

Mean tracings

When the mean values of the various variables were constructed into composite tracings for the 12-year-old WS males and females and superimposed on their respective 12-year-old controls, as visualized in Figure 2a and b, the shape of the neurocranium showed differences in all regions in WS females and in the middle and posterior regions in WS males. The slope of the forehead was reduced in WS females, but in males was similar to that of the controls. The size of the forehead was also smaller in the WS female group. There was a more pronounced curvature of the occipital bone in both the WS male and female groups.

Growth

The growth changes in the various measurements of the neurocranium differed during the observation period within the WS group as well as within the control group. The growth changes in the various parameters in WS subjects seemed to be similar to those of the controls.

Generally, WS females demonstrated more deviant neurocranial morphology than WS males compared with the control groups, as shown by a greater number of statistically significant differences (Tables 2–7, Figure 2a, b). WS males, as well as the male control group, showed larger values for most variables in the neurocranium compared with their female counterparts. However, the variability was greater in WS subjects than in the controls, as indicated by generally higher standard deviations. The differences in the size of the neurocranium in WS subjects, compared with the controls, was already established in the youngest age group (less than 8 years) and maintained throughout the observation period. Neurocranial morphology in the WS male and female groups showed small differences in the frontal region, but larger differences in the parietal and occipital regions.

Discussion

This research is part of a systematic investigation of subjects with WS concerning dental, oral, and craniofacial characteristics.

Cephalometric studies of individuals or groups of individuals with WS in the literature are scarce. Some case reports have been published, but in those the cephalometric analyses were primarily concentrated in the dentofacial region. Jones and Smith (1975) reported from a clinical evaluation of 19 individuals with WS that the anterior cranial base was short. In a more comprehensive cephalometric study, Mass and Belostoky (1993) analysed lateral cephalograms of eight young children with WS. The cranial base angle was found to be normal, but the anterior cranial base was short.

The findings of the present study show that the lengths of both the anterior and posterior cranial base are shorter than normal. The shorter anterior cranial base contributes to the retrusion in the midnasal area, often described as a ‘depressed nasal bridge’. The smaller dimension in the posterior cranial base appears to be due to a shorter length of the clivus.

This cephalometric study has shown that the neurocranium in WS subjects has an aberrant size and shape compared with normal controls. The differences were evident in the youngest children and remained throughout adolescence and adulthood. Females with WS demonstrated more deviant neurocranial morphology than males compared with controls. This is shown by a greater number of statistically significant differences.

The mean calvarial shape in the WS groups was different from the normal controls (Figure 2a, b). The forehead was not so prominent in the WS females compared with the controls, whereas the WS males were more similar to the control group. In the middle part of the neurocranium, the length of the parietal bone was shorter than in the controls and the height of the neurocranium significantly smaller in the WS female group. The smaller length of the parietal bone and the reduced height of the neurocranium were also reflected in less curvature of the parietal bone. In the posterior part, the occipital squama was more prominent, leading to a significant lengthening of the neurocranium. These findings could, in part, be correlated to the results from neuroimaging studies.

Studies investigating the adult WS brain using high-resolution MRI have revealed some significant neuroanatomical aberrations. The most obvious morphological finding was a significant reduction in total volume compared with normal controls (Jernigan and Bellugi, 1990; Jernigan *et al.*, 1993; Reiss *et al.*, 2000; Schultz *et al.*, 2001). However, the brain volume reduction appears to be unevenly distributed, as the frontal and temporal lobes, as well as the cerebellar region, were less affected, whereas the parietal lobes were severely reduced (Jernigan *et al.*, 1993; Wang and Bellugi, 1993; Bellugi *et al.*, 1999; Reiss *et al.*, 2000; Schmitt *et al.*, 2001b). This is in agreement with the cephalometric findings in this study, where the height of the neurocranium and the lengths of the cranial base were the most reduced parameters.

In agreement with previous reports, the height of the neurocranium was decreased compared with normal controls. Autopsy observations of adult WS brains have shown reductions in the parieto-occipital cortices and in the height of the brain (Galaburda and Bellugi, 2000; Schmitt *et al.*, 2001b). The observed flattening or reduced curvature of the parietal bone and the smaller diameter of the neurocranium in the present study could

be explained by the reduced height of the brain in the parietal region.

The total length of the neurocranium in the midsagittal plane in the WS groups was increased compared with the controls in this study. This finding is in agreement with Trauner *et al.* (1989), and was also confirmed by Bellugi *et al.* (1990) in a preliminary MRI investigation which showed that subjects with WS had an elongated posterior to anterior length compared with normal controls.

The thickness of the calvarian bones, especially the frontal and occipital bones, was significantly larger than in the controls. The reason might be reduced bone resorption on the internal surface due to reduced intracranial growth. During the growth period there is bony deposition on both the outer and the inner surfaces of the calvaria. This growth increases the thickness of the calvarial bones. The process of remodelling also adjusts for the changes in the curvature of the calvarial bones during their outward displacement as the brain increases in size (Enlow and Hans, 1996).

The present findings show greater differences in neurocranial size and shape in females than males with WS compared with their controls, but this might be an effect of more females than males participating in the study. Several other factors, such as physical growth and maturation, which could contribute to this difference, were not investigated.

The present sample was relatively large and represents approximately two-thirds of all known individuals with WS in Norway, but it may reflect a skewed subset of individuals in the WS population. It could be argued that willingness to participate in a study of mapping the oral, dental, and craniofacial characteristics in WS is higher if the person (or parent/guardian) is aware of a dental and/or craniofacial aberration already present, which may introduce bias. Despite the fact that there are no sex differences in the incidence of WS, the female group in this study was almost 1.5 times larger than the male group. The explanation for this is that more males did not want to participate in the study.

In the present research, approximately 200 significance tests were performed, with a significance level of 5 per cent. Thus, it is likely that the analysis would present about 10 false-positive results, even if there were no differences between WS subjects and the controls. However, the analysis showed approximately 100 significant results, and for about 40 of these the *P*-value was below 0.001. Thus, it is highly unlikely that more than a small fraction of the significant results were false positive.

Conclusions

The results of this study indicate that the size and morphology of the neurocranium in WS subjects differ from normal controls.

The largest differences were seen in the middle and posterior parts of the neurocranium, primarily as a reduced height of the neurocranium, a flattening of the parietal bone, and a greater prominence of the occipital bone. The frontal and occipital bones were considerably thicker compared with controls. The differences in various parameters were established in the youngest age group and were maintained throughout the observation period. The growth pattern of the neurocranium in WS subjects was similar to that of the normal controls.

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