

ORIGINAL ARTICLE

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Crown heights in the permanent teeth of 47,XXY males and 47,XXX females

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ABSTRACT

Objective: Earlier results based on dental casts and radiographs have shown that additional X and Y chromosomes influence permanent and deciduous tooth crown sizes, with 47,XXY males exhibiting greater crown heights than 46,XY males. We studied here the effect of both X and Y chromosomes on tooth crown heights.

Material and methods: The series consisted of 48 47,XXY males, 22 of their male relatives, and seven 47,XXX females with five female relatives. The population controls consisted of 27 males and 33 females. Measurements of all applicable teeth except for the third molars on both sides of the jaws were made on panoramic radiographs with a sliding digital calliper.

Results: Apart from a few teeth, the mean crown heights in the 47,XXY males were greater than those in the male population controls, the differences being statistically significant for one tooth in the maxilla and ten teeth in the mandible. With the exception of two teeth, the 47,XXX females had taller tooth crowns than the female population controls, the differences in the two teeth being statistically significant. The 47,XXY males had greater tooth crown heights than the 47,XXX females, except in one tooth, and the differences were significant in two teeth. The tooth crown heights of the male relatives of the 47,XXY males and the female relatives of the 47,XXX females were close to those in the general population.

Conclusions: The present results demonstrated the effect of additional X and Y chromosomes in increasing crown heights. The differences between the 47,XXY males and 47,XXX females indicated a stronger effect of a Y chromosome on tooth crown height than of an X chromosome.

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Introduction

Klinefelter syndrome is the most common sex chromosome variant, occurring in one out of every 660 newborn males [1]. The typical characteristics are tall stature, narrow shoulders, small testicles and absence of spermatogenesis [1]. Klinefelter syndrome is the most common genetic reason for male infertility (4%) [2] and is also characterised by varying degrees of cognitive, behavioural, and learning difficulties. The most common karyotype (80%) is 47,XXY (a male with one extra X chromosome) [3]. Height is normal during childhood until the age of approximately six years, at which point growth is significantly accelerated as compared with healthy boys, resulting in a final average height that is 1.2 cm greater than in 46,XY males [4], although the difference has also been reported to be as great as 5.6 cm [5]. The excess body height in 47,XXY males is mainly caused by increased leg length [5]. It is important to note that normal stature, or even parentally inherited short stature, does not exclude Klinefelter syndrome.

Trisomy X, or 47,XXX (a female with one additional X chromosome), is the most common female chromosomal variant [6], occurring in approximately 1 in 1000 female births [7]. The most frequent karyotype (90%) is 47,XXX [7], and the most common physical features include tall stature (above the 75th percentile for height) [8], epicanthal folds, hypotonia and clinodactyly [9]. These individuals exhibiting aneuploidy typically have long legs, with a short sitting height [10]. Children with trisomy X have higher rates of motor and speech delays, with an increased risk of cognitive deficits and learning disabilities [6], and they also have fertility problems, presumably as a consequence of premature ovarian failure.

Interactions, gradients and spatial field effects of multiple genetic, epigenetic and environmental factors influence the development of individual teeth and tooth type [11]. Each tooth passes through a series of well-defined developmental stages [12] in which the enamel knots regulate the morphology and determine the sites of the tooth cusps. At the bell stage the mesenchymal odontoblasts differentiate first to

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 Supplemental data for this article can be accessed [here](#).

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form dentine, followed by the epithelial ameloblasts, which form enamel. All the permanent tooth crowns apart from those of the third permanent molars will reach their final size and shape between the ages of 3.3 and 7.4 years [13] and acquire their roots in certain phases by 15 years [14]. The X and Y chromosomes affect the crown sizes, root lengths and morphology of the teeth [15–30] usually resulting in larger mesiodistal and labiolingual crown dimensions in the deciduous and permanent teeth of 47,XYY males and the permanent teeth of 47,XXY males than those of male population controls [31,32], while in 47,XXX females the maximum mesiodistal diameters of the tooth crowns of the permanent incisors, excluding canines, are likewise greater than those of population control females [33]. Individuals with one extra sex chromosome, such as 47,XYY and 47,XXY males, have been reported to have longer tooth roots than the male population [34,35] and 47,XXX females to have longer tooth roots than the female population [36]. Previous results have shown increased numbers of taurodont mandibular molars in 47,XXY males and 47,XXX females [23,24,27–29,37] and an increased frequency of two-rooted mandibular premolars in 45,X and 45,X/46,XX females [17,29,30].

Measurements performed on maxillary permanent incisors, canines and molars of females and males of differing chromosome combination (45,X, 45,X/46,XX, 46,XY and 47,XXX females, and 47,XYY and 47,XXY males) have demonstrated that the Y chromosome promotes the growth of enamel and dentine [33–36,38,39] and increases cell division at various stages in tooth development [33,35]. The results have further shown that the X chromosome affects enamel development but has little or no influence on the growth of crown dentine [33]. The enamel thickness of the maxillary incisors and canines in 47,XXX females has been observed to be greater than in female population controls [33], while the thickness of the dentine has proved to be slightly increased in the incisors of 47,XXX females as compared with 46,XX females, with this trend reversed in the canines. Alvesalo and colleagues have reported that the enamel thickness of the permanent maxillary central incisors in 47,XXY males is significantly greater than in male population controls [39], while the dentine thickness of the incisors and canines is significantly greater than in 46,XX females, but less than in 46,XY males.

The sex chromosomes have been reported to have an effect on the cusp basal area rather than the cusp height, the cusp basal area being smallest in 45,X females, where the cusps are sharpest, larger in 46,XX females and 46,XY males, and even larger in 47,XYY males, who have the bluntest cusps [40]. The sex chromosomes influence cusp shape and size in all three dimensions, but may not influence the cusps and teeth equally, possibly due to the varying contributions of the enamel and dentine [40,41]. The permanent crown heights of all the teeth have been examined by Penttinen and colleagues are greater in 47,XYY males than in male population controls, while the mean relative differences in tooth crown heights (MRD%) between 47,XYY males and 46,XY males are 6.3% in the maxilla and 10.7% in the

mandible. The MRD% values for the separate tooth types are 10.4% for the molars, 4.8% for the premolars, 4.8% for the canines and 5.3% for the incisors in the maxilla and 12.3, 11.5, 11.6 and 7.9%, respectively, in the mandible.

Townsend and colleagues have observed increasingly fluctuating asymmetry in the tooth crown sizes as measured in the mesiodistal and labiolingual direction in 47,XXY males, reflecting a disruption in developmental stability [42]. That work has shown the general patterns of asymmetry are similar in 47,XYY males and 47,XXY males, with the more distal teeth in each tooth type tending to show greater asymmetry than the more mesial ones. Furthermore, both the permanent canines and the first permanent molars display relatively little asymmetry compared with the other teeth. Penttinen et al. [43] have observed that the tooth crown heights are greater on the right side than on the left in a few teeth in the upper jaws of 47,XYY males and in all the teeth in the lower jaws in both male and female population controls.

The aim of the present study was to look for a possible effect of the additional X or Y chromosome on permanent tooth crown heights in the 47,XXY and 47,XXX chromosome combinations, the expectations based on previous findings being that excess growth in tooth crown heights is greater in 47,XXY males than in 47,XXX females and that the additional growth is minor in the area of the maxillary canines and incisors and more prominent in the mandible than in the maxilla. Similarly, we hypothesised that the extra X chromosome would increase the asymmetry between the sides of the jaw in 47,XXY males and that the more distal teeth in each tooth type would show greater asymmetry than the more mesial ones in both the 47,XXY males and 47,XXX females.

Materials and methods

The patient series comprised part of Professor Lassi Alvesalo's KVANTTI material, compiled mainly in 1974–1987. The focus of this study was on individuals exhibiting aneuploidy or an additional X chromosome, and their first-degree relatives. The individuals were all of Finnish origin and came from various parts of the country. The protocol for the research was accepted by the Ethical Committee of the Faculty of Medicine at the University of Turku, Finland, in 1978, and the subjects were not at risk in any way during this research. The material consisted of 48 47,XXY males (males with an extra X chromosome) (Table 1), 22 male relatives of theirs (six brothers and 16 fathers), seven 47,XXX females (females with an extra X chromosome) and five female relatives (one sister and four mothers). The population control group consisted of 27 male and 33 female persons, who were relatives of groups other than the present aneuploid individuals in the KVANTTI material. All available tooth crowns except for the third molars were measured on the orthopantomograms (OPTGs). There was no evidence of extensive tooth wear on the dental casts or OPTGs in the present study, although it was possible to discern smaller amounts of wear in these records.

Table 1. Age distributions in the 47,XXY males, 47,XXX females and control groups.

Study groups	Mean age (years)	SD	Age range (years)	Median	n
47,XXY males	30.7	11.7	10.2–57.6	30.7	48
47,XXY males with a male relative	41.0	15.5	13.5–67.5	38.6	22
Male relatives of 47,XXY males	41.0	15.5	13.5–67.5	38.6	22
47,XXX females	16.5	5.7	9.0–26.1	17.5	7
Females relatives of 47,XXX females	37.0	11.9	24.7–55.6	36.2	5
Male population controls	22.8	11.7	11.6–44.9	15.3	27
Female population controls	26.6	10.1	13.3–51.8	26.0	33

Measurements

The measurements of tooth crown heights in the 47,XXY males, their male relatives, the 47,XXX females and their female relatives were made by RL, and the determinations of the teeth in the male and female population controls were performed by RL and RP. The measurement procedures were as detailed in previous work by Lähdesmäki [22] and by Pentinpuuro and colleagues [44]. The crown height was the perpendicular distance between two parallel lines, one of which was tangential to the outer edge of the cusp or incisor edge and the other situated between the mesial and distal cement-enamel junctions. The determinations were made to an accuracy of 0.01 mm on both sides of the jaws using a sliding digital calliper (Mitutoyo, digimatic 500–123 U, CD-15B, Andover, England).

Double determinations were performed on a total of 45 dental radiographs from the Kvantti research material in order to test the reliability of the measurements. The subjects in these cases were adult 45,X females and female and male relatives of the patients, with 15 persons in each group. The Intraclass correlation (ICC) in these measurements ranged from 0.657 to 0.899 (Mean 0.809, Standard deviation (SD) 0.074). The paired samples t-test was used to study the intra-examiner precision. Statistically significant differences between these two determinations were found in the four incisors in the mandible. Furthermore, the determinations were compared using the Bland-Altman method. The standard deviation between the double measurements was calculated and it was found that 95% of the differences were within the limits of +2 SD. The crown height measurements were considered acceptable for further calculations.

Statistical methods

The statistical analyses were carried out with the SPSS program, version 24.0 (SPSS, Inc., Chicago, IL) and with Microsoft Excel. Values of $p < 0.05$ were considered statistically significant. Characteristics of the age distributions were calculated for the various groups. Mean tooth crown heights were compared between the 47,XXY males and their male relatives and between the 47,XXX females and their female relatives by means of the paired samples t-test, and if the differences between the two groups were not normally distributed Wilcoxon's signed ranks test was used. The mean tooth crown heights of the 47,XXY males, 47,XXX females and population control males and females were compared using ANOVA. Tukey's HSD test was used as a post-hoc test and if equality of variance could not be assumed Tamhane's T2 test

was used. To find false positives across the analyses and to check whether the significant results could be explained by chance, we used the Benjamini-Hochberg method to calculate corrected p values. The relative difference in mean tooth crown heights between two groups was determined for each tooth using the formula: $RD\% = (CH1-CH2)/CH1 \times 100\%$ (where $RD\%$ = relative difference (percent) between the mean tooth crown heights in the two groups, $CH1$ = mean of the tooth crown heights in one group and $CH2$ = mean of the tooth crown heights in the other group). When $CH1$ is larger than $CH2$, the value of $RD\%$ is positive. The average relative difference was calculated from the $RD\%$ values of the teeth in the given tooth type. In order to look for directional asymmetry, the means of the differences (RLDs) in tooth crown heights between the right and left sides of the jaws in the 47,XXY males, 47,XXX females and population control males and females were calculated and compared using the paired samples t-test. Wilcoxon's signed ranks test was applied in order to look for directional asymmetry if the differences between the right and left side were not normally distributed. Mean fluctuating asymmetry (FA) in tooth crown heights between the right and left sides of the jaws was calculated in the 47,XXY males, 47,XXX females, population control males and population control females. A value for the fluctuating asymmetry (FA) was obtained by dividing the absolute difference between the sides by the absolute mean sizes of the left and right teeth, $FA = \text{abs} (R-L) / ((R + L)/2)$.

Results

Apart from three teeth in the maxilla, the mean tooth crown heights were greater in the 47,XXY males than in the male population controls, the differences being statistically significant in one tooth in the maxilla and ten teeth in the mandible, being highly significant ($p < 0.001$) in five of the latter (Table 2). The differences between the 47,XXY males and the population control females were statistically significant in all the teeth in the maxilla and mandible, except for two teeth in the maxilla, and highly significant in nineteen cases altogether. The crown heights of two teeth in the maxilla and four in the mandible were significantly greater in the 47,XXY males than in their male relatives (Supplementary Appendix Table 1). Apart from two teeth, the 47,XXX females had taller tooth crowns than the female population controls, the difference being statistically significant in one tooth (Table 2). As the groups of 47,XXX females and their relatives were small, however, we could calculate p values only for

Table 2. Mean tooth crown heights (Mean) (mm) in the 47,XXY males, 47,XXX females, population control males and population control females.

Tooth	47,XXY males				47,XXX females				Population control males				Population control females			
	Mean (SD)	n	p ^a		Mean (SD)	n	p ^b		Mean (SD)	n	p ^c		Mean (SD)	n	p ^d	p ^e
Maxilla																
Right second molar	11.0 (1.0)	26	.880		10.7 (0.9)	6	.179		10.3 (0.7)	21	.880		10.0 (0.6)	32	.000***B	.463
First molar	11.1 (0.9)	23	.903		10.8 (0.6)	6	.133		10.5 (0.9)	20	.134		10.1 (0.8)	25	.001***B	.324
Second premolar	10.7 (0.7)	20	.630		9.6 (1.2)	4	.997		10.4 (0.5)	23	.358		9.9 (1.1)	28	.023*	.364
First premolar	11.1 (0.9)	28	.974		10.9 (0.9)	5	.645		11.2 (0.8)	19	.987		10.4 (1.0)	28	.024*	.021*
Canine	12.2 (1.5)	31	.268		11.5 (0.6)	6	.688		11.8 (1.2)	23	.857		11.0 (0.9)	32	.002***B	.044*
Lateral incisor	10.0 (0.9)	27	.748		9.7 (0.7)	7	.983		10.6 (1.0)	20	.085		9.8 (0.8)	32	.727	.005***B
Central incisor	11.5 (1.2)	32	.972		11.2 (0.8)	6	.787		11.3 (1.1)	24	.983		10.7 (0.6)	32	.014*	.166
Left central incisor	11.5 (1.1)	32	.380		10.9 (0.5)	6	.939		11.0 (0.9)	24	.173		10.7 (0.7)	32	.001***B	.421
Lateral incisor	10.0 (1.0)	28	.950		9.8 (0.6)	6	.994		10.2 (1.0)	24	.901		9.7 (0.7)	32	.518	.186
Canine	12.2 (1.2)	27	.371		11.4 (0.7)	6	.775		12.1 (1.2)	22	.980		10.9 (1.0)	31	.000***B	.002***B
First premolar	11.5 (1.0)	23	.748		11.0 (0.6)	5	.729		11.3 (0.9)	20	.883		10.5 (1.1)	30	.003***B	.045*
Second premolar	11.5 (1.0)	20	.323		10.6 (0.2)	5	.598		10.6 (1.1)	23	.023*		10.0 (1.0)	26	.000***B	.200
First molar	11.3 (0.7)	22	.797		11.7 (0.8)	5	.010 ^B		10.8 (0.8)	20	.231		10.3 (1.0)	26	.001***B	.297
Second molar	11.0 (0.9)	24	.240		10.2 (0.8)	5	.985		10.6 (0.8)	21	.299		10.1 (1.0)	25	.001***B	.216
Mandible																
Right second molar	11.4 (1.0)	19	.172		10.6 (0.9)	6	.622		10.3 (1.0)	20	.001***B		10.1 (0.7)	24	.000***B	.866
First molar	11.1 (0.7)	17	.032*		10.1 (1.1)	5	.742		9.8 (1.0)	19	.000***B		9.7 (0.6)	23	.000***B	.975
Second premolar	10.8 (1.5)	17	.209		9.7 (1.3)	5	.995		10.0 (1.2)	25	.123		9.5 (0.8)	23	.004***B	.455
First premolar	10.7 (1.2)	35	.973		10.5 (0.8)	6	.359		10.0 (1.1)	27	.064		9.7 (1.0)	31	.002***B	.701
Canine	11.6 (1.4)	41	.043*		10.1 (1.2)	6	.991		10.5 (1.1)	27	.005***B		10.0 (1.2)	33	.000***B	.325
Lateral incisor	9.7 (1.1)	42	.935		9.4 (0.6)	7	.276		8.8 (0.7)	26	.006***B		8.7 (1.0)	32	.000***B	.952
Central incisor	9.2 (1.2)	40	.763		8.8 (1.0)	6	.380		8.2 (0.9)	26	.002***B		8.0 (0.8)	31	.000***B	.907
Left central incisor	8.9 (1.0)	37	.655		8.4 (1.2)	6	.755		8.3 (1.2)	27	.066		8.0 (0.8)	32	.001***B	.601
Lateral incisor	9.4 (1.1)	39	.819		9.1 (1.4)	6	.430		8.8 (0.2)	27	.039*		8.4 (0.8)	32	.000***B	.450
Canine	11.3 (1.4)	40	.285		10.3 (0.9)	6	.844		10.1 (0.2)	27	.001***B		9.8 (1.2)	32	.000***B	.871
First premolar	10.8 (1.2)	36	.060		9.7 (1.1)	7	.571		9.7 (1.0)	26	.001***B		9.1 (0.8)	27	.000***B	.195
Second premolar	10.9 (1.2)	19	.232		9.8 (1.1)	4	.268		9.6 (0.8)	20	.001***B		8.9 (0.8)	24	.000***B	.099
First molar	10.6 (0.8)	18	.075		9.6 (0.8)	5	.949		9.8 (0.9)	21	.031*		9.4 (0.8)	21	.000***B	.220
Second molar	11.0 (0.9)	20	.144		10.0 (0.8)	6	.947		10.3 (0.9)	21	.083		9.8 (1.2)	25	.001***B	.342

Levels of statistical significance: * $p < .05$; ** $p < .01$; *** $p \leq .001$. Tukey's HSD test was used as a post-hoc test, and if equality of variances could not be assumed Tamhane's T2 test was used (p values marked in grey). If the p value was significant after Benjamini-Hochberg correction it was marked with "B" index. Benjamini-Hochberg corrected p values were compared p value 0.05.

^a47,XXY males vs 47,XXX females.

^b47,XXX females vs population control females.

^c47,XXY males vs population control males.

^d47,XXY males vs population control females.

^ePopulation control males vs population control females.

^BSignificant after Benjamini-Hochberg correction.

twelve teeth, where the differences were not statistically significant (Supplementary Appendix Table 2). All the tooth crowns but one were taller in the 47,XXY males than in the 47,XXX females, the differences being significant in two teeth (Table 2).

The teeth in the male population control group were also taller than those of the female controls, the differences being statistically significant for five teeth in the maxilla.

The relative differences in tooth crown heights RD(%) between the 47,XXY males and population control males varied from -6.1 to 6.7 in the maxilla (mean 2.7) and from 2.5 to 9.9 in the mandible (mean 8.2) (Table 3). The differences in RD(%) between these two groups were smallest in the upper incisors (RD(%) 0.3) and highest in the mandibular canines (RD(%)10.0). The RD(%) between the 47,XXX females and female population controls ranged from -3.6 to 11.7 in the maxilla (mean 3.8) and from 1.4 to 9.7 in the mandible (mean 5.5), and those between the tooth types RD(%) ranged from 1.3 in the upper incisors to 7.6 in the lower incisors. The RD(%) values when comparing the 47,XXY males and 47,XXX females, varied between -3.5 and 10.7 in the maxilla (mean 4.4) and between 1.9 and 12.8 in the mandible (mean 6.7), while the RD(%) values for the tooth types varied

from 2.2 in the upper molars to 10.8 in the lower canines. In the comparison between the population control males and females the RD(%) values ranged from 3.1 to 9.4 in the maxilla (mean 5.5) and from 1.0 to 7.2 in the mandible (mean 3.9). The differences between the tooth types were lowest in the incisor region of the lower jaw (RD(%) 3.0) and highest between the canines in the upper jaw (RD(%) 8.2).

The means of the differences in tooth crown heights between the right and left sides of the jaws (RLD) were statistically significant in two premolars in the maxilla and in both incisors and the first molars in the mandible of the 47,XXY males (Table 4), whereas there were no statistically significant differences between the sides of the jaws in the 47,XXX females. The RLD values for one tooth in the maxilla and one in the mandible were significant in the population control males, while the population control females had four significant RLD values in the mandible but none in the maxilla. Tooth crowns tended to be taller in the left side than that in the right side in the upper jaws of the 47,XXY males and 47,XXX females, whereas the teeth on the right side were usually taller than those on the left side in the lower jaws. This trend was found in the population control males and population control females. The highest FA values were

Table 3. Relative differences in mean tooth heights (RD (%)) between the 47,XXY males, 47,XXX females, population control males and population control females.

Tooth	47,XXY males			47,XXX females			Population control males			Population control females		
	Mean (SD)	<i>n</i>	RD (%) ^a	Mean (SD)	<i>n</i>	RD (%) ^b	Mean (SD)	<i>N</i>	RD (%) ^c	Mean (SD)	<i>n</i>	RD (%) ^d
Maxilla												
Right second molar	11.0 (1.0)	26	3.3	10.7 (0.9)	6	6.6	10.3 (0.7)	21	3.1	10.0 (0.6)	32	2.4
First molar	11.1 (0.9)	23	1.3	10.8 (0.6)	6	6.9	10.5 (0.9)	20	4.2	10.1 (0.8)	25	2.4
Second premolar	10.7 (0.7)	20	1.2	9.6 (1.2)	4	-3.6	10.4 (0.5)	23	4.3	9.9 (1.1)	28	10.7
First premolar	11.1 (0.9)	28	-2.2	10.9 (0.9)	5	4.8	11.2 (0.8)	19	7.2	10.4 (1.0)	28	1.7
Canine	12.2 (1.5)	31	1.8	11.5 (0.6)	6	3.9	11.8 (1.2)	23	7.0	11.0 (0.9)	32	6.4
Lateral incisor	10.0 (0.9)	27	-6.1	9.7 (0.7)	7	-1.4	10.6 (1.0)	20	7.9	9.8 (0.8)	32	3.6
Central incisor	11.5 (1.2)	32	-0.5	11.2 (0.8)	6	4.3	11.3 (1.1)	24	5.1	10.7 (0.6)	32	2.8
Left central incisor	11.5 (1.1)	32	1.6	10.9 (0.5)	6	2.1	11.0 (0.9)	24	3.3	10.7 (0.7)	32	5.5
Lateral incisor	10.0 (1.0)	28	-3.6	9.8 (0.6)	6	1.0	10.2 (1.0)	24	4.7	9.7 (0.7)	32	2.1
Canine	12.2 (1.2)	27	0.0	11.4 (0.7)	6	4.1	12.1 (1.2)	22	9.4	10.9 (1.0)	31	6.5
First premolar	11.5 (1.0)	23	0.1	11.0 (0.6)	5	4.6	11.3 (0.9)	20	7.0	10.5 (1.1)	30	4.4
Second premolar	11.5 (1.0)	20	6.7	10.6 (0.2)	5	5.7	10.6 (1.1)	23	5.4	10.0 (1.0)	26	7.4
First molar	11.3 (0.7)	22	-0.1	11.7 (0.8)	5	11.7	10.8 (0.8)	20	4.3	10.3 (1.0)	26	-3.5
Second molar	11.0 (0.9)	24	2.3	10.2 (0.8)	5	1.5	10.6 (0.8)	21	4.9	10.1 (1.0)	25	7.6
Mandible												
Right second molar	11.4 (1.0)	20	5.8	10.6 (0.9)	6	4.7	10.3 (1.0)	20	2.0	10.1 (0.7)	24	7.5
First molar	11.1 (0.7)	18	5.9	10.1 (1.1)	5	3.6	9.8 (1.0)	19	1.0	9.7 (0.6)	23	9.2
Second premolar	10.8 (1.5)	19	4.4	9.7 (1.3)	5	1.4	10.0 (1.2)	25	4.9	9.5 (0.8)	23	10.5
First premolar	10.7 (1.2)	36	2.5	10.5 (0.8)	6	7.5	10.0 (1.1)	27	3.1	9.7 (1.0)	31	1.9
Canine	11.6 (1.4)	40	6.0	10.1 (1.2)	6	1.6	10.5 (1.1)	27	5.3	10.0 (1.2)	33	12.8
Lateral incisor	9.7 (1.1)	39	5.7	9.4 (0.6)	7	8.2	8.8 (0.7)	26	1.6	8.7 (1.0)	32	2.6
Central incisor	9.2 (1.2)	37	8.1	8.8 (1.0)	6	8.5	8.2 (0.9)	26	2.3	8.0 (0.8)	31	4.9
Left central incisor	8.9 (1.0)	40	5.0	8.4 (1.2)	6	5.0	8.3 (1.2)	27	3.7	8.0 (0.8)	32	5.4
Lateral incisor	9.4 (1.1)	42	4.3	9.1 (1.4)	6	7.5	8.8 (0.2)	27	4.5	8.4 (0.8)	32	4.1
Canine	11.3 (1.4)	41	6.5	10.3 (0.9)	6	4.5	10.1 (0.2)	27	2.5	9.8 (1.2)	32	8.8
First premolar	10.8 (1.2)	35	6.5	9.7 (1.1)	7	5.9	9.7 (1.0)	26	5.9	9.1 (0.8)	27	10.1
Second premolar	10.9 (1.2)	17	9.9	9.8 (1.1)	4	9.7	9.6 (0.8)	20	7.2	8.9 (0.8)	24	9.5
First molar	10.6 (0.8)	17	4.0	9.6 (0.8)	5	2.3	9.8 (0.9)	21	5.0	9.4 (0.8)	21	9.6
Second molar	11.0 (0.9)	19	3.5	10.0 (0.8)	6	2.5	10.3 (0.9)	21	4.8	9.8 (1.2)	25	9.2

The relative difference between two groups was determined for each tooth using the formula: RD% = (CH1 - CH2) / CH1 x 100%.

^a47,XXY males and population control males.

^b47,XXX females and population control females.

^cpopulation control males and population control females and.

^d47,XXY males vs 47,XXX females.

Table 4. Means of differences (mm) (RLD) and fluctuating asymmetry (FA) in tooth crown heights between the right and left sides of the jaws in the 47,XXY males, 47,XXX females, population control males and population control females.

Difference	47,XXY males				47,XXX females				Population control males				Population control females			
	RLD (SD)	<i>n</i>	<i>p</i> ^a	FA (SD) ^a	RLD (SD)	<i>n</i>	<i>p</i> ^b	FA (SD) ^b	RLD (SD)	<i>n</i>	<i>p</i> ^c	FA (SD) ^c	RLD (SD)	<i>n</i>	<i>p</i> ^d	FA (SD) ^d
Maxilla^e																
Diff 17-27	-0.0 (0.7)	21	.947	0.0475 (0.03)	0.4 (0.5)	5	.154	0.0470 (0.03)	-0.2 (0.9)	20	.277	0.0660 (0.05)	-0.0 (0.8)	25	.940	0.0644 (0.05)
Diff 16-26	-0.4 (0.8)	18	.085	0.0560 (0.06)	-0.7 (0.9)	5	.138	0.0829 (0.05)	-0.3 (0.9)	20	.154	0.0730 (0.05)	-0.1 (0.8)	23	.440	0.0610 (0.05)
Diff 15-25	-0.8 (0.9)	13	.006**	0.0792 (0.06)	-0.8 (1.5)	3	.593	0.1139 (0.13)	-0.2 (0.9)	22	.436	0.0656 (0.05)	0.0 (0.9)	24	.879	0.0650 (0.06)
Diff 14-24	-0.6 (1.0)	20	.011*	0.0825 (0.07)	-0.4 (0.5)	4	.225	0.0462 (0.04)	-0.1 (0.8)	19	.562	0.0562 (0.05)	-0.1 (1.0)	26	.551	0.0838 (0.05)
Diff 13-23	-0.1 (0.9)	24	.603	0.0551 (0.05)	0.1 (1.1)	6	.876	0.0718 (0.05)	-0.1 (1.0)	22	.607	0.0566 (0.05)	0.1 (0.6)	30	.513	0.0469 (0.03)
Diff 12-22	-0.1 (0.9)	24	.604	0.0698 (0.06)	-0.1 (0.6)	6	.753	0.0538 (0.03)	0.4 (0.8)	20	.065	0.0610 (0.06)	0.1 (0.7)	32	.432	0.0536 (0.04)
Diff 11-21	0.1 (0.6)	30	.472	0.0431 (0.02)	0.3 (0.7)	6	.345	0.0508 (0.03)	0.2 (0.5)	24	.024*	0.0401 (0.02)	0.0 (0.4)	32	.754	0.0296 (0.02)
Mandible^f																
Diff 41-31	0.3 (0.6)	36	.004**	0.0593 (0.03)	0.4 (0.6)	6	.173	0.0684 (0.04)	0.1 (0.4)	26	.383	0.0391 (0.03)	0.1 (0.4)	31	.502	0.0374 (0.03)
Diff 42-32	0.3 (0.6)	35	.009**	0.0555 (0.04)	0.3 (1.0)	6	.467	0.0836 (0.09)	0.0 (0.7)	26	.858	0.0501 (0.05)	0.3 (0.7)	32	.015*	0.0662 (0.05)
Diff 43-33	0.1 (1.2)	34	.578	0.0773 (0.06)	-0.2 (0.8)	6	.753	0.0654 (0.04)	0.5 (0.9)	27	.026*	0.0685 (0.08)	0.2 (1.1)	32	.407	0.0918 (0.06)
Diff 44-34	-0.1 (1.1)	28	.700	0.0766 (0.06)	0.8 (1.3)	6	.116	0.1365 (0.05)	0.3 (1.1)	26	.381	0.0861 (0.07)	0.5 (0.7)	27	.002**	0.0734 (0.05)
Diff 45-35	0.0 (1.5)	11	.928	0.1000 (0.08)	0.4 (0.9)	4	1.000	0.0603 (0.09)	0.4 (1.1)	20	.093	0.0908 (0.07)	0.6 (0.4)	22	.000*** ^B	0.0734 (0.05)
Diff 46-36	0.4 (0.5)	15	.011*	0.0499 (0.03)	0.9 (0.5)	3	.109	0.0808 (0.04)	0.0 (0.8)	19	.809	0.0653 (0.04)	0.4 (0.5)	21	.002*** ^B	0.0510 (0.04)
Diff 47-37	0.3 (0.7)	18	.054	0.0504 (0.04)	0.4 (0.7)	5	.225	0.0597 (0.04)	0.0 (0.9)	20	.847	0.0691 (0.05)	0.2 (0.9)	23	.255	0.0639 (0.05)

Levels of statistical significance. **p* < .05; ***p* < .01; ****p* < .001. Means of differences (RLDs) were compared using the paired samples t-test. Wilcoxon's signed ranks test was applied in order to look for directional asymmetry (*p* values marked in grey). The significant the *p* values after Benjamini-Hochberg correction were marked with ^{aB} index. A value for the fluctuating asymmetry (FA) was obtained by dividing the absolute difference between the sides by the absolute mean sizes of the left and right teeth, FA = abs (R-L)/((R+L)/2).

^aStatistical significance of RLD or the value of FA in the 47,XXY males.

^bStatistical significance of RLD or the value of FA in the 47,XXX females.

^cStatistical significance of RLD or the value of FA in the population control males.

^dStatistical significance of RLD or the value of FA in the population control females.

^eMean of the differences in tooth crown heights between the second molars (Diff 17-27) ... and central incisors (Diff 11-21) on the right and left sides of the maxilla.

^fMean of the differences in tooth crown heights between the central incisors (Diff 41-31) ... and second molars (Diff 47-37) on the right and left sides of the mandible.

^BSignificant after Benjamini-Hochberg correction.

detected in the premolar area and the lowest FA values were in the molars in the 47,XXY males and 47,XXX females. There were no major differences in FA values between the maxilla and mandible in the groups (Table 4) nor were there any statistically significant differences in the FA values when comparing the 47,XXY males, 47,XXX females, population control males and population control females (Supplementary Appendix Table 3).

Discussion

Previous results [38] have pointed to the presence of factors in the Y chromosome that control various growth processes. It has been suggested that the influence of the Y chromosome on amelogenesis is regulatory [38], and that the difference in tooth size between males and females can be explained by the differential growth-promoting effects of the Y and X chromosomes. Different effects of the sex chromosomes have previously been seen in the thickness of the enamel and dentine, tooth crown morphology and asymmetry between the sides of the jaw. Measurements of tooth crown sizes in mesiodistal and labiolingual directions performed on plaster casts have shown the presence of sexual dimorphism in the permanent and deciduous tooth crowns, such that 46,XY males have larger teeth than 46,XX females [45], and the present results regarding the relative differences (RD(%)s) in tooth crown heights between the population control males and females (5.5 in the maxilla and 3.9 in the mandible) were of the same magnitude as those reported for tooth root lengths (4% in all teeth) [22]. It has also been shown that the effect of excess X and Y chromosomes is different in the maxilla and mandible, as has been observed in tooth sizes measured in both the mesiodistal and labiolingual direction [46], tooth root lengths [22] and differences in crown heights between tooth types and between the jaws [43]. Root lengths in the mandible were greater in 47,XXY males than in 46,XY males, as has been also the case in the posterior regions of the maxilla [23]. Likewise, earlier results regarding tooth root lengths in 47,XXX females have shown longer roots than for 46,XX females in the mandible, but only in the posterior regions of the maxilla [24]. In the present research the teeth in both jaws of the 47,XXX females had greater crown heights than in the female population controls, and the teeth of the 47,XXY males were taller than in the male population controls. This is compatible with earlier results concerning tooth crown sizes and root lengths, in which both the X and Y chromosomes have increased tooth sizes and the Y chromosome has a greater effect than the X chromosome. We also observed that the increase in tooth crown heights in the 47,XXY males was most pronounced in the mandible and in the molar region of the maxilla, while in the 47,XXX females this concerned the incisor and premolar areas of the mandible, and the molars in the maxilla.

The present results showed that the effect of the additional X chromosome in increasing tooth crown heights was stronger in the mandible than in the maxilla in 47,XXY males as compared with control males (Supplementary Appendix Table 4), and in many cases there were large differences in

mean tooth crown heights within the same tooth type. Previous studies of tooth crown heights in 47,YYY males have yielded similar results [43]. The largest mean RD% values in tooth groups were found in the molars, while the lowest values were in the incisor area in both the maxilla and the mandible of 47,YYY males and 47,XXY males. In addition, the largest increase in maxillary tooth crown heights in 47,XXX females was seen in the molars and the smallest in the incisors, whereas in the mandible the largest excess growth was in the incisors and the smallest in the canines and molars. Variability in tooth crown heights in the incisory and premolar areas was especially prominent in the mandible of 47,XXX females. The relative differences (RD(%)s) between the 47,XXY males and 47,XXX females were larger than the corresponding ones between the control females and control males in the case of all the tooth types in the mandible. The largest decrease in tooth crown heights in the 45,X females was found in the molars of both jaws and also in the premolars, while the RD% values were small in the areas of the incisors and canines in the maxilla and in the premolar area of the mandible (Supplementary Appendix Table 4).

It has been observed that additional or missing sex chromosome material can cause considerable changes in tooth crown sizes in all three dimensions. We observed the mean tooth crown sizes in the mesiodistal and labiolingual directions in groups of 46,XY males, 47,YYY males, 47,XXY males, 46,XX females and 45,X females, as seen in Supplementary Appendix Table 5, the material for which was gathered from previous studies concerning tooth crown sizes [31,32,34,46,47]. In the mesiodistal direction the increase in tooth crown sizes was greatest in the molar area and least in the canines or incisor area in both the maxilla and mandible of the 47,YYY males and 47,XXY males. When measured in the labiolingual direction the excess growth was greatest in the molars or premolars and least in the incisor area or in the canines of both the maxilla and mandible of the 47,YYY or 47,XXY males. The effect of an extra sex chromosome on tooth crown height in the maxilla and mandible was observed to be similar in the mesiodistal and labiolingual directions. It should be noted, however, that the eleven 47,XXY males had lost all their maxillary teeth, possibly due to the elevated incidence of dental caries observed earlier among 47,XXY males [48], while the groups of 47,XXX females and their female relatives were quite small, two facts which could have affected the present results. The partial or total absence of teeth was detected especially in the upper jaws or in the premolar and molar regions of the mandibles of the 17 47,XXY male patients, which may have caused increasing wear in the remaining teeth. When we considered the changed amount of wear due to missing teeth and slightly higher middle age in the 47,XXY males than in the other groups, the amount of wear in the 47,XXY males and 47,XXX females presumably did not significantly differ from population control males or population control females. However, this phenomenon may have affected the results. The statistically significant differences in tooth crown heights between the two sides were slightly increased in the 47,XXY

males relative to the male controls, whereas there was no significant increase in asymmetry in the 47,XXX subjects relative to the female controls. We observed that asymmetry between the right and left sides of the jaws was greater in the 47,XXY males than in the 47,XXX females. The present series included only a small number of 47,XXX females and a large number of missing teeth in the 47,XXY males, which may have affected the asymmetry results.

In a previous study Alvesalo and Tigerstedt [49] have observed that the highest heritability values for the mesio-distal dimension are recorded in the first incisors, canines and first premolars of the upper jaw and the second incisors, first premolars and molars of the lower jaw. Furthermore, the highest values for the labiolingual dimension are for the canines, first premolars and molars of the upper jaw and first premolars and molars of the lower jaw. It has been also shown that the relative phenotypic variability is higher in distal than in mesial members within the same tooth type, with the exception of the lower incisors [16], whereas Alvesalo and Tigerstedt [49] have shown that heritability is generally lower in distal members of a tooth type, with the exception of the lower incisors. It has been noted that differences in heritability between the teeth of the same type describe the variations in tooth phenotype better than does position in the dental arch [49]. It is possible that the present findings of altered asymmetry between jaw sides, differences between the upper and lower jaws and large variability in crown sizes within the same tooth type all represented a synergy of changed sex chromosome constitutions and variations in heritability between different teeth.

In conclusion, the present results confirmed the previous results of an increasing effect of additional sex chromosomes on tooth crown heights. All but one of the tooth crowns were taller in the 47,XXY males than in the 47,XXX females, although the additional crown height was minor in the maxillary incisors in both groups. The effect of an additional X chromosome on tooth crown heights in the mandible was stronger in the 47,XXY males than in the 47,XXX females, possibly on the account of the Y chromosome. A synergy of changed sex chromosome constitutions and variations in heritability between different teeth may have affected the results regarding asymmetry between the jaw sides and within the tooth groups. The differences in tooth crown heights in the mandible between the 47,XXY males and 47,XXX females were larger than corresponding ones between the control males and females in all the tooth types.

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Disclosure statement

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