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Turner syndrome isochromosome karyotype correlates with decreased dental crown width

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SUMMARY The aim of this project was to study possible influences of Turner syndrome (TS) karyotype and the number of X chromosomes with intact short arm (p-arm) on dental crown width. Primary and permanent mesio-distal crown width was measured on plaster casts from 112 TS females. The influence on crown width of four karyotypes: 1. monosomy (45,X), 2. mosaic (45,X/46,XX), 3. isochromosome, and 4. other, and the number of intact X chromosomal p-arms were investigated. In comparisons between karyotypes, statistically significant differences were found for isochromosome karyotype maxillary second premolars, canines, laterals, mandibular first premolars, and canines, indicating that this karyotype was the most divergent as shown by the most reduced crown width. When each karyotype group were compared versus controls, all teeth in the isochromosome group were significantly smaller than controls ($P < 0.01$–0.001). The 45,X/46,XX karyotype expressed fewer and smaller differences from controls, while 45,X individuals seemed to display an intermediate tooth width compared with 45,X/46,XX and isochromosomes. No significant difference in crown width was found comparing the groups with one or two intact X chromosomal p-arms. Both primary and permanent teeth proved to have a significantly smaller crown width in the entire group of TS females compared to healthy females. We conclude that the isochromosome group deviates most from other karyotypes and controls, exhibiting the smallest dental crown width, while individuals with 45,X/46,XX mosaicism seemed to have a less affected crown width. An influence of the number of intact p-arms on crown width could not be demonstrated in this study.

Introduction

Turner syndrome (TS) in females is caused by a complete or partial absence of the second X chromosome with or without cell line mosaicism and has a prevalence of 1/2000–1/3000 live born females (Nielsen and Wohlert, 1990; Gravholt *et al.*, 1996; Batch, 2002; Stochholm *et al.*, 2006). The principal features in this syndrome are short stature and ovarian dysgenesis, but several diseases and anatomical deformities occur as well, such as cardiac malformations, hypothyroidism, sensorineural hearing loss, and webbed neck (Barrenäs *et al.*, 1999; Saenger *et al.*, 2001; Batch, 2002; Gravholt *et al.*, 2006; Bondy, 2009). Skeletal malformations including cubitus valgus, scoliosis, and osteoporosis are also over-represented, as are affected craniofacial growth and malocclusions (Lippe, 1991; Midtbø and Halse, 1996; Landin-Wilhelmsen *et al.*, 1999; Kim *et al.*, 2001; Perkiömäki *et al.*, 2005; Dumancic *et al.*, 2010). A reduced size and an altered morphology of both dental crown and root in primary and permanent teeth have been reported as well (Townsend *et al.*, 1984; Midtbø and Halse, 1994a,b; Lopez *et al.*, 2002; Rizell *et al.*, 2010). Interestingly, there are studies that imply that an increased number of sex chromosomes enlarge the size of both the dental crown and root (Alvesalo *et al.*, 1987, 1991; Lähdesmäki and Alvesalo, 2004, 2007).

The smaller crown diameter in TS is primarily caused by a thinner layer of enamel (Alvesalo and Tammisalo, 1981; Zilberman *et al.*, 2000). The thickness of the enamel is determined during the secretory phase of the amelogenisis where the major protein amelogenin is secreted from the ameloblasts to form the enamel matrix (Simmer and Hu, 2001). The gene coding for amelogenin (AMELX) is located on the X chromosomal short arm (p-arm), and in the majority of TS women, the homologous gene is missing since one of the X-chromosomes is absent or exhibit aberrations (Sasaki and Shimokawa, 1995). However, some TS females possess with cell lines with two intact p-arms, for example, individuals with 45,X/46,XX constitution or deletions affecting genes on the long arm (q-arm) of the X chromosome. This illustrates the variation in chromosomal

constitution (i.e. karyotype) in TS and studies indicate that tooth width differs according to TS karyotype (for a summary, see Table 1). A main shortcoming in the literature is that due to the difficulties in collecting a sufficient number of TS cases, it has not always been possible to study differences according to karyotype. In addition, no previous studies have taken into consideration how the number of X chromosomes with unaffected p-arms influence dental crown width in TS females.

The aim of this project was to study possible influences of TS karyotype and the presence of one or two X-chromosomes with intact p-arms on dental crown width.

Subjects

One hundred thirty-two girls and women with a diagnosis of TS living in the regions of Gothenburg, Uppsala and Umeå in Sweden gave their consent to take part in this study. These individuals are participating in a longitudinal and multidisciplinary ongoing study of girls and women with TS, where the overall aims are to investigate the influence of genetic factors on phenotype, health aspects related to risk factors, and the effects of growth promoting treatment. Fifteen individuals were excluded since their dental records were of poor quality or missing, four individuals were excluded because they had severe tooth loss or extensive dental restorations, and one girl since she was born with a total unilateral cleft. The age of the remaining 112 subjects ranged from 6 to 66 years, with a mean age of 18.6 years and a median age of 13.5 years. Genetic karyotyping was undertaken by routine chromosomal analysis of peripheral lymphocytes. The distribution of TS karyotype subgroups and number of intact p-arms is shown in Table 2.

Methods

Plaster casts were made from impressions of upper and lower dentition of each individual. If available, multiple plaster casts were used to enable measurements of both primary and permanent teeth. Measurement was made of mesio-distal tooth width in all primary and permanent teeth except from third molars, by one investigator (SR), using a modified digital calliper and was assessed according to Moorrees (Moorrees *et al.*, 1957). The investigator was blinded to the karyotype of the TS females during the measurements. Teeth that were partially erupted, restored approximally or damaged by trauma, caries or severe occlusal wear were excluded. To test the measurement error, the dental crown width registrations were repeated in ten randomly chosen plaster casts, four weeks apart. The error of measurement was calculated and did not exceed 0.10 mm (Dahlberg, 1940). Measures of mesio-distal tooth width from plaster casts of both primary and permanent teeth from healthy females with normal occlusion were used for control (Thilander, 2009). The TS females were grouped into four karyotype categories: 1. monosomy (45,X), 2. mosaic (45,X/46,XX), 3. isochromosome, and 4. other, as well as according to the presence of one or two unaffected X chromosomal p-arms (Table 2). The TS isochromosome karyotype has one normal X chromosome and one isochromosome displaying two identical arms due to duplication of the long arm (q-arm) and loss of the p-arm, i.e. altogether long arm trisomy and short arm monosomy.

The study was approved by the University of Gothenburg ethics committee.

Statistics

The difference in tooth width between right and left side was tested with *t*-test and was not statistically significant. In the statistical analysis, the mean of the measurements from the two contralaterals was used for calculation. In case one of the contralaterals was missing, data for the present tooth were used. Two-sample *t*-test was used to test data from the dental crown width measurement of the entire TS group against controls and to test each karyotype group one by one against controls. Analysis of variance was used to

Table 1 Studies published on the effect of TS karyotype on crown width measured on cast models.

References	Karyotypes	*n*	Karyotype correlation results
Varrela *et al.* (1988)	45,X/46,XX	15	45,X < 45,X/46,XX for mandibular M2($P < 0.05$)
	45,X	89	
Mayhall *et al.* (1991)	46,X,i(Xq)	6	46,X,i(Xq) < 45,X for maxillary I1, M1 ($P < 0.01$) and mandibular I1, P2 ($P < 0.05$)
	45,X	89	
Midtbø and Halse (1994b)	45,X	23	Ns (45,X versus remaining)
	45,X/46,XX	3	
	46,X,i(Xq)	3	
	45,X/46,X,i(Xq)	1	
	45,X/46,XY	1	
	45,X/46,r(Xq)	1	

I1, central; P2, 2nd premolar; M1, 1st molar; M2, 2nd molar.

Table 2 Distribution of TS karyotypes, karyotype categories, and number of X chromosomes with an intact p-arm.

TS karyotype	Total *n* (%)	One intact p-arm, *n*	Two intact p-arms, *n*	Karyotype category
45,X	46 (41.1)	46	0	1
45,X/46,XX	12 (10.7)	0	12	2
Isochromosomes	26 (23.2)	26	0	3
Deleted X chromosomes	8 (7.1)	3	5	4
Translocated X chromosomes	2 (1.8)	1	1	4
Inverted X chromosomes	2 (1.8)	2	0	4
Marker chromosomes	6 (5.4)	0	6	4
Ring chromosomes	5 (4.5)	5	0	4
Y chromosomal material	3 (2.6)	3	0	4
45,X/47,XXX	2 (1.8)	0	2	4
Total	112 (100)	86	26	

Categorizing of TS karyotype: 1. monosomy (45,X); 2. mosaic (45,X/46,XX); 3. isochromosomes; and 4. other.

analyse possible differences in dental crown width between the karyotype groups and between the groups with one or two X chromosomes with intact p-arm, supplemented with Student–Newman–Keuls post hoc test indicating which karyotype groups were divergent. Because of the low numbers, the influence of karyotype or number of X chromosomes with intact p-arm on crown width was not tested for primary teeth. A P value less than 0.05 was considered as statistically significant. The level of significance is indicated with asterisks (*$P < 0.05$ **$P < 0.01$ ***$P < 0.001$).

Results

Comparisons of dental crown width between the karyotypes showed significant differences for maxillary 2nd premolars, canines, laterals, mandibular first premolars, and canines, indicating that the isochromosome karyotype was the most divergent group by demonstrating the most reduced dental crown width (Table 3). The mesio-distal tooth width for the four karyotype groups and for the groups with one or two X chromosomes with intact p-arm is shown in Table 4. The group by group versus controls comparison showed that all teeth in the isochromosome group were significantly smaller than controls ($P < 0.01$–0.001). Among females with 45,X/46,XX mosaicism, the differences from controls were fewer and smaller while individuals with 45,X monosomy seemed to display an intermediate tooth width compared to females with 45,X/46,XX and isochromosome. In testing presence of one or two X chromosomes with an intact p-arm, no statistically significant ($P > 0.05$) differences in crown width were found between the two groups. When the entire TS group was compared to healthy females, all permanent and primary teeth tested proved to have a statistically significantly smaller mesio-distal crown width (Tables 5 and 6).

Table 3 Comparison of mesio-distal crown width between the four karyotypes: 1. monosomy (45,X), 2. mosaic (45,X/46,XX), 3. isochromosome, and 4. other with analysis of variance (ANOVA).

	Permanent tooth	ANOVA	Student–Newman–Keuls
Maxilla	I2	$P = 0.02$	Isochromosomes versus 45,X/46,XX
	C	$P = 0.04$	Isochromosomes versus 45,X/46,XX
	P2	$P = 0.03$	Isochromosomes versus 45,X/46,XX
Mandible	C	$P = 0.01$	Isochromosomes versus remaining groups
	P1	$P < 0.01$	Isochromosomes versus other

Student–Newman–Keuls test indicating which karyotype groups were divergent. Remaining permanent teeth showed no significant differences between the karyotype groups. I2, lateral; C, canine; P1, 1st premolar; P2, 2nd premolar.

Discussion

The novel finding in the present study of genotype-phenotype correlations in TS was a smaller mesio-distal crown width in the isochromosome karyotype group, which was most obvious versus the 45,X/46,XX karyotype. To our knowledge, comparisons of tooth width (from cast models) in isochromosomes versus 45,X/46,XX karyotype is not previously described. However, there are indications of smaller crown width in isochromosomes compared with 45,X, which in turn tend to be smaller than 45,X/46,XX (Varrela *et al.*, 1988; Mayhall *et al.*, 1991). All TS karyotypes differed from controls, but the 45,X/46,XX karyotype group was the group most similar to the controls. An influence caused by the number of intact X chromosomal p-arms on crown width could not be verified in the present study, even though the presence of cell lines with two intact p-arms seemed to normalize the crown width (Table 4).

The underlying causes of decreased tooth size in TS are presumably multiple. The smaller crown width in TS is mainly caused by a significantly thinner enamel layer, while the dentine is affected only to a minor degree (Alvesalo and Tammisalo, 1981; Zilberman *et al.*, 2000). A crucial factor for the final thickness of the enamel layer is the duration and timing of the secretory stage of amelogenesis (Berkovitz *et al.*, 2009) since this determines the length of the enamel crystals (Gibson *et al.*, 2001; Simmer and Hu, 2001). The major protein secreted from the ameloblasts is amelogenin, which constitutes 80–90 per cent of the total amount of the enamel matrix proteins (Simmer and Hu, 2001; Hu *et al.*, 2005). The amelogenin coding gene AMELX is located on the short arm of the X chromosome, Xp22.3-p22.1 (Chen *et al.*, 1981; Salido *et al.*, 1992; Sasaki and Shimokawa, 1995; Kurisu and Tabata, 1997; Simmer and Hu, 2001; Hu *et al.*, 2005). The majority of the genes on either the maternal or the paternal X chromosomes are silenced as a result of X chromosome inactivation, but more than 15 per cent of the genes escape silencing and another 10 per cent show a variable inactivation pattern (Carrel and Willard, 2005).

Table 4 Mean and SD of mesio-distal crown width (mm) in TS karyotype groups or TS with presence of one or two intact X chromosomal p-arms.

		45,X	45,X/46,XX	Isochromosome	Other	One intact p-arm	Two intact p-arms
	Permanent tooth	Mean ± SD (mm)	Mean ± SD (mm)	Mean ± SD (mm)	Mean ± SD (mm)	Mean ± SD (mm)	Mean ± SD (mm)
Maxilla	I1	8.0 ± 0.53***	8.3 ± 0.44	7.8 ± 0.55***	8.1 ± 0.42***	8.0 ± 0.53***	8.1 ± 0.44***
	I2	6.3 ± 0.64**	6.5 ± 0.46	5.9 ± 0.74***	6.3 ± 0.43*	6.2 ± 0.68***	6.4 ± 0.42*
	C	7.4 ± 0.37*	7.5 ± 0.46	7.2 ± 0.34***	7.4 ± 0.47	7.4 ± 0.39***	7.4 ± 0.50
	P1	6.5 ± 0.32***	6.5 ± 0.40***	6.3 ± 0.33***	6.5 ± 0.38***	6.4 ± 0.34***	6.5 ± 0.39***
	P2	6.1 ± 0.41***	6.3 ± 0.38**	5.9 ± 0.30***	6.1 ± 0.33***	6.1 ± 0.36***	6.1 ± 0.42***
	M1	9.4 ± 0.48***	9.6 ± 0.46***	9.2 ± 0.65***	9.4 ± 0.67***	9.3 ± 0.59***	9.5 ± 0.54***
	M2	8.9 ± 0.65***	9.0 ± 0.60*	8.8 ± 0.48***	8.8 ± 0.60***	8.8 ± 0.57***	8.9 ± 0.67*
Mandible	I1	4.9 ± 0.30***	5.0 ± 0.35***	4.8 ± 0.32***	5.0 ± 0.26***	4.9 ± 0.31***	5.0 ± 0.30***
	I2	5.5 ± 0.37***	5.6 ± 0.41**	5.3 ± 0.33***	5.5 ± 0.31***	5.5 ± 0.36***	5.5 ± 0.35***
	C	6.4 ± 0.36**	6.4 ± 0.42	6.1 ± 0.32***	6.4 ± 0.26***	6.3 ± 0.35***	6.4 ± 0.35**
	P1	6.7 ± 0.29***	6.7 ± 0.40*	6.5 ± 0.32***	6.9 ± 0.34	6.7 ± 0.34***	6.7 ± 0.36**
	P2	6.6 ± 0.35***	6.6 ± 0.45***	6.5 ± 0.36***	6.7 ± 0.36***	6.6 ± 0.36***	6.6 ± 0.40***
	M1	9.8 ± 0.50***	9.9 ± 0.45***	9.6 ± 0.59***	9.9 ± 0.69***	9.7 ± 0.55***	9.8 ± 0.66***
	M2	9.6 ± 0.52**	9.9 ± 0.72	9.3 ± 0.70**	9.4 ± 0.57***	9.5 ± 0.60***	9.6 ± 0.69

Asterisks indicate level of significance of TS versus female controls (Thilander, 2009). I1, central; I2, lateral; C, canine; P1, 1st premolar; P2, 2nd premolar; M1, 1st molar; M2, 2nd molar.

Table 5 Mesio-distal crown width of permanent teeth in TS.

	Permanent tooth	*n*	Mean ± SD (mm)	Range (mm)
Maxilla	I1	108	8.0 ± 0.51***	6.7–10.1
	I2	106	6.2 ± 0.63***	3.7–7.9
	C	93	7.4 ± 0.42***	6.4–8.6
	P1	87	6.4 ± 0.35***	5.5–7.1
	P2	87	6.1 ± 0.37***	5.2–6.8
	M1	102	9.4 ± 0.58***	7.5–10.6
	M2	71	8.9 ± 0.59***	7.6–10.4
Mandible	I1	109	4.9 ± 0.30***	4.2–5.7
	I2	110	5.5 ± 0.36***	4.7–6.6
	C	97	6.3 ± 0.35***	5.5–7.2
	P1	93	6.7 ± 0.34***	6.1–7.5
	P2	86	6.6 ± 0.36***	5.8–7.4
	M1	102	9.8 ± 0.57***	8.5–11.7
	M2	71	9.5 ± 0.62***	8.2–11.1

Asterisks indicate level of statistical significance of TS versus female controls (Thilander, 2009). I1, central; I2, lateral; C, canine; P1, 1st premolar; P2, 2nd premolar; M1, 1st molar; M2, 2nd molar.

Table 6 Mesio-distal crown width of primary teeth in TS.

	Primary tooth	*n*	Mean ± SD (mm)	Range (mm)
Maxilla	i1	2	5.7 ± 0.48 (nt)	5.4–6.1
	i2	3	4.8 ± 0.55 (nt)	4.5–5.5
	c	28	6.4 ± 0.43***	5.7–7.6
	m1	30	6.6 ± 0.40***	5.8–7.3
	m2	33	8.3 ± 0.64***	7.3–9.9
Mandible	i1	0		
	i2	1	4.3 (nt)	
	c	23	5.4 ± 0.35**	4.6–6.1
	m1	28	7.0 ± 0.45***	6.3–7.8
	m2	32	9.0 ± 0.55***	7.9–10.2

Asterisks indicate level of statistical significance of TS versus female controls (Thilander, 2009). Due to low numbers, no statistical analysis was made of primary incisors. i1, central; i2, lateral; c, canine; m1, 1st molar; m2, 2nd molar; nt, not tested.

Most of the escaping genes are located in the pseudoautosomal regions (PAR1 and PAR2) on the X chromosome, but there is also a lower proportion of escapees in the X-added region (XAR), where AMELX is located (Ross *et al.*, 2005). It is therefore feasible that the enamel volume is reduced as the loss of one AMELX gene will reduce the amount of its gene product amelogenin. However, the importance of AMELX for development of normal crown width could not be demonstrated in this study, with respect to the number of intact X chromosomal p-arms. This categorization may possibly be too unspecific since the p-arm can display an aberration but still express the amelogenin gene.

Still, an absence or inactivation of genes on the p-arm cannot fully explain why the greatest reduction in tooth size was found in the isochromosome and not the monosomy group, the latter being by far the larger group. The reduced thickness of the enamel layer might instead be caused by the triplication of the long q-arm that is present in the isochromosome karyotype. An increased amount of cellular genetic material *per se* or triplication of some specific gene can slow down the cell cycle (Paton *et al.*, 1974; Simpson and Lebeau, 1981). According to the cell cycle delay hypothesis, the growth retardation in TS is partly due to a reduction in cell number as a result of incapacity to up-regulate the cell cycle velocity maximally during the

short developmental time window available for organs and structures in the head and neck region (Barrenäs *et al.*, 2000). This hypothesis also implies developmental problems caused by changes in timing, for example that a delayed signalling from certain growth factors important to amelogenesis may be ineffective because the cellular environment is no longer favourable.

Another possible explanation used to describe the more severe phenotype in the isochromosome group (here expressed as the smallest crown width) is that of genomic imprinting as the parental origin of the X chromosome is believed to influence the phenotype as concerns several features and conditions (Chu *et al.*, 1994; Skuse *et al.*, 1997; Hamelin *et al.*, 2006; Sagi *et al.*, 2007). Among TS cases with an isochromosome karyotype, the intact X chromosome is more often of paternal origin than among the monosomic group (Hamelin *et al.*, 2006; Sagi *et al.*, 2007) and isochromosomes exhibit a deviant TS phenotype concerning several health aspects, such as smaller birth size, growth hormone (GH) deficiency, bone age delay, hypothyreosis, and sensorineural hearing loss (Zinman *et al.*, 1984; Schmitt *et al.*, 1997; Hultcrantz, 2003; Hagman *et al.*, 2010). At present, we do not have data on the origin of the intact X chromosome being maternal or paternal. This would be an interesting issue for a future study.

Endocrine factors may also be important for tooth development, especially GH and the insulin-like growth factors I and II (IGF-I and IGF-II). Studies have shown that production of amelogenin can be induced *in vitro* by IGF-I and IGF-II (Takahashi *et al.*, 1998). It has also been found that GH status influence crown width, root length, dentin thickness, and enamel mineralization (Symons and Seymour, 2000; Smid *et al.*, 2007). Circulating GH appear in 22 kDa and non-22-kDa isoforms, and an increased proportion of non-22-kDa GH isoform is found in TS (Blethen *et al.*, 1994; Boguszewski *et al.*, 1997). The non-22-kDa GH isoform stimulates the GH receptor less effectively than the 22-kDa molecule, which might partly explain the enamel deficiency found in TS. Interestingly, GH deficiency occurs more commonly among TS cases with an isochromosome genotype than among the monosomic 45,X group (Schmitt *et al.*, 1997). The present results with a more normalized crown width in 45,X/46,XX karyotype supports both the importance of AMELX, the delayed cell cycle theory and the influence of GH and IGFs since the presence of 46,XX cell lines appears to mitigate the effect of the chromosomal aberration.

The TS prevalence of 1/2000 born females limits the possibilities to study genotype–phenotype correlations, particularly in karyotypes with low prevalence (Gravholt, 2004). In the present study, a relatively large material was obtained by including three TS centres, which increased the significance of our findings. Additionally, consideration was taken to an influence of the number of intact X chromosomal p-arms on crown width, even if no impact on crown width was found in this study.

Conclusions

This study has shown that TS karyotype has an impact on tooth width, the isochromosome group exhibiting the smallest dental crown width. In the 45,X/46,XX mosaic karyotype, with a normal 46,XX cell line present, the crown width tended to be less affected, while 45,X monosomy seemed to express an intermediate tooth width as compared to females with 45,X/46,XX and isochromosome. However, the number of intact X chromosomal p-arms was not shown to affect crown width. Additionally, mesio-distal crown width in TS was statistically significantly smaller in both primary and permanent teeth.

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