

## Human Sex Chromosomes in Oral and Craniofacial Growth

Lassi Alvesalo<sup>1,2</sup>

<sup>1</sup>Institute of Dentistry, University of Oulu, Oulu, Finland

<sup>2</sup>School of Dental Sciences, University of Liverpool, Liverpool, England

Corresponding Author: Lassi Alvesalo, University of Oulu, Institute of Dentistry, Aapistie 3,  
FIN-90220 Oulu, Finland

Tel. +358-8-537 5497, Fax +358-8-537 5503

E-mail: [lassi.alvesalo@saunalahti.fi](mailto:lassi.alvesalo@saunalahti.fi)

University of Liverpool, School of Dental Sciences, Edwards Building, Daulby Street,  
Liverpool L69 3GN, England

Tel. +44 151 706 5279, Fax +44 151 706 5809

E-mail: [alvesalo@liverpool.ac.uk](mailto:alvesalo@liverpool.ac.uk)

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## **Human sex chromosomes in oral and craniofacial growth**

### **Abstract**

Studies on tooth crown size and structure in families and in individuals with various sex chromosome anomalies have demonstrated differential direct effects of the human X and Y chromosome genes on growth. The Y chromosome promotes both tooth crown enamel and dentin growth, whereas the effect of the X chromosome on crown growth seems to be restricted to enamel formation. Enamel growth is decisively influenced by cell secretory function and dentin growth by cell proliferation. It is suggested that these differential effects of the X and Y chromosomes on growth explain the expression of sexual dimorphism in various somatic features. These include tooth crown and root size, crown shape and the number of the teeth, and under the assumption of genetic pleiotropy, torus mandibularis, statural growth, and sex ratio. It is of interest that molecular studies have shown that the gene loci for human amelogenin, the major protein component of the organic matrix in enamel are on both the X and Y chromosomes. Future questions include the role of the Y chromosome in the mineralization process, the concentric control of enamel and dentin growth, and gene expression.

## **Introduction**

The reason for sexual dimorphism in the growth of bony structures have commonly been attributed to differences in hormonal balance. The action of hormones during puberty in particular has been considered important for the expression of this difference, e.g. in average adult body height. On the other hand, it has been assumed since the 1960's, based mainly on observations of the heights of individuals with various sex chromosome anomalies, that human X and Y chromosomes contain genes (determinants) that influence final body height<sup>1,2</sup> and quite recent results suggest that deletions encompassing a novel homeobox gene within pseudoautosomal regions of the X and Y chromosomes cause growth failure in idiopathic short stature and Turner (45,X females, females with one X chromosome) syndrome<sup>3</sup>. Investigations of skeletal development in Klinefelter (47,XXY males, male with an extra X chromosome) and Turner syndrome patients have indicated that the Y chromosome may possess genes that cause a retardation of skeletal maturation<sup>4</sup>, and X linkage has been suggested for the rate and timing of ossification<sup>5</sup>. Interestingly enough, dermatoglyphic investigations have also indicated that sex chromosomes influence finger tip pattern size and the development of the palmar patterns of loops and triradii<sup>6,7</sup>, and it has been postulated that the Y chromosome regulates the rate and extent of growth of the primitive gonad<sup>8</sup>, pointing to a more general regulatory role for this chromosome. It has been proposed that differential ontogenesis of the sexes may depend entirely on a regulatory effect of the Y chromosome<sup>9</sup>.

## **Tooth crown size**

Human dental development begins with the formation of the deciduous incisors at about four weeks in utero, followed by that of the other deciduous and permanent teeth, each of which passes through a series of well-defined developmental stages. All the tooth crowns apart from those of the third permanent molars, have reached their final size and shape between the ages

of two months and eight years, and consequently sexual dimorphism in average crown size, males having larger teeth than females, is expressed at early and somewhat different stages of development. Based on correlative dental studies on normal relatives, X chromosome linkage was proposed for permanent tooth crown size and dental development<sup>5,10,11</sup>. It was also concluded that the Y chromosome apparently affects tooth crown growth, and that its effect differs from that of the X chromosome, so that the sexual dimorphism observed in average tooth crown size is connected with the influence of the Y chromosome<sup>11</sup>.

Measurements of total tooth crown sizes in dental casts from individuals with various sex chromosome anomalies have shown that the permanent and deciduous teeth of 47,XYY males (male with an extra Y chromosome) and permanent teeth of 47,XXY males (male with an extra X chromosome) are generally larger than those of normal 46,XY males<sup>12,13,14,15,16</sup>, while permanent and deciduous teeth of 45,X females and permanent teeth of 45,X/46,XX females (female with one X and normal XX cell lines) and 46, Xi(Xq) females (female with one normal X and one isochromosome with the long arm duplicated) are smaller than those of normal 46,XX females<sup>17,18,19,20,21,22</sup>. Females with the complete form of testicular feminizing syndrome or 46,XY females, who are insensitive to androgens, have teeth of similar sizes to those of normal males<sup>23</sup>. These results have given proofs for growth promoting effects of the X and Y chromosome genes on tooth crown size, and that these chromosomes operate early and apparently in a continuous manner during dental development. The location of the growth promoting region within the X chromosome is probably in the short arm<sup>22</sup>, while that in the Y chromosome may be on the proximal, non-fluorescent portion of the long arm<sup>24</sup>. As regards the timing of dental development in these individuals, the present knowledge is limited to Turner females, in whom permanent tooth eruption and maturation<sup>17,25,26</sup> is definitely advanced compared to normal females.

### **Tooth crown structure**

The distance across the dentino-enamel junctions is determined at an early stage of tooth crown development, at the time when amelogenesis or enamel formation is beginning, and the mitotic activity of the cells of the inner enamel epithelium is the decisive factor in determining of this distance<sup>27</sup>. Enamel thickness provides a measure of the secretory activity of postmitotic, highly differentiated ameloblasts whereas dentin thickness reflects growth due to mitotic activity in the developing tooth germs. Measurements of enamel and dentin thickness on radiographs of maxillary permanent incisors, canines and molars in normal females and males and in 45,X, 45,X/46,XX and 47,XXX females (female with an extra X chromosome) and 47,XYY and 47,XXY males and in 46,XY females have demonstrated that the Y chromosome influences dental growth by promoting both amelogenesis or the growth of enamel and dentinogenesis or the growth of dentin<sup>28,29,30,31,32,33</sup>. It is conceivable that the mitotic potential is increased in the presence of the Y chromosome, which leads to an increase in cell division at various stages of development<sup>29,31</sup>. The results have further shown that the X chromosome exerts its influence on crown enamel deposition or it contains enamel gene, but it has little or no influence on the growth of crown dentin. It has become obvious that the enamel genes, conceivably structural by their function, in both the X chromosomes of normal females and in all three of those of 47,XXX females are active, possibly continuously so but without doubt intermittently. The effect of the X chromosome on metric enamel growth is of similar class of magnitude as that of the Y chromosome although there is a trend for the greater expression of the X chromosome influence. It has been known from pedigree studies that in addition to the various forms of autosomally inherited amelogenesis imperfecta or heritable defective development of tooth enamel, one hypoplasia type of this defect also

shows X-linked dominant inheritance. Therefore, the finding of the presence of the enamel gene on the X chromosome was not necessarily unexpected<sup>29</sup> (Figs. 1,2,3,4). Until lately, there have not been any pedigree e.g. in the form of Y-linked *amelogenesis imperfecta*, or other indications of the presence of specific enamel genes on the Y chromosome. This, among other things, has been considered suggestive of the regulative nature of the tooth growth genes of the Y chromosome at least with respect to enamel formation<sup>28</sup>. It is therefore of interest that molecular studies have shown that the gene loci for human amelogenin, which is the main protein component of the organic matrix in enamel, are on both the X and Y chromosomes<sup>34,35,36</sup>. The amino acid sequences of these X and Y amelogenin genes seem to differ to some extent, however, and the transcriptional products of the X and Y chromosomes are both quantitatively and qualitatively different. The Y chromosome locus encodes a functional protein even though its level of expression is only 10% of that of the locus on the X chromosome<sup>36</sup>. These genes are located on the distal short arm of the X chromosome, and possibly in the proximal long arm region of the Y chromosome<sup>34</sup>. The short arm of the Y chromosome has also been suggested as a possible location for the amelogenin gene<sup>35,36</sup>. As also against these molecular results, it is of ultimate interest that in the refereed X-linked *amelogenesis imperfecta* enamel in males' teeth is extremely thin and smooth whereas in females' teeth enamel is almost of normal thickness with defective vertical ridging.

### **Tooth root size**

Permanent tooth root lengths, measured on radiographs, in 47,XYY and 47,XXY males were longer than in normal men and women, while the roots in the 45,X/46,XX females were shorter, respectively. Root lengths of the 46,XY females were similar to those for normal men. The root lengths of the canines, maxillary central incisors, and mandibular lateral incisors clearly differed between the normal men, women and 45,X/46,XX females, the men

having the longest roots, the mosaic females the shortest and the normal women lying between them. The root length in all the teeth measured differed between the mosaics, 45,X/46,XX females and the trisomies 47,XXY and 47,XYY males<sup>37,38,39,40,41</sup>. Permanent tooth root lengths in 45,X and 46,Xi (Xq) females have also been reported being shorter than in normal women<sup>17,42</sup>. It appeared that the X chromosome had a definite effect on root dentin growth which is in contrast to its effect on crown dentin growth.

The root lengths in the population control men were longer than those in the population control women<sup>37</sup>, as also observed previously on the measurements of natural teeth<sup>43</sup>. The mean difference between the sexes was five percent<sup>37</sup>, which is similar with the six percent reported by Garn *et al.* in mandibular canines, premolars and molars<sup>44</sup>. As an entire the refereed studies above by Lähdesmäki and Alvesalo indicate that the promoting effect of the Y chromosome on growth in root length is greater than that of the X chromosome, which may lead to the expression of sexual dimorphism in root size. It was suggested that the X and Y chromosome genes affecting crown growth are also expressed in the following root dentin growth.

### **Tooth crown shape**

The crown morphology in 47,XYY males is changed in that the degree of shovelling of the maxillary permanent lateral incisors is bigger and the palatal fossa is deeper than in their relatives, while the lateral incisors of 45,X females are less shovel-shaped than in normal women and the central incisors have a shallower fossa in addition to the tendency towards less cusps in the molars and simplified tooth crown shape<sup>45,46,47</sup>. Midtbø and Halse found an altered mamelon pattern in Turner women, especially in the incisal edge of the maxillary lateral incisors, together with atypical mesiobuccal cusps and nipped cusp tips of the

maxillary canines and premolars, whereas the Carabelli trait in the maxillary first molars was found far less often than in a normal Finnish population<sup>47,48,49</sup>. Sex chromosomes have an effect mainly on the cusp basal area rather than cusp height. The cusp basal area is smallest in 45,X females, with the sharpest cusps, becomes larger in normal women and men, and is even larger in 47,XYY males, who have the bluntest cusp form<sup>50</sup>.

It became clear that the sex chromosomes have a definite affect on cusp shape and size in all three dimensions but may not influence the developing cusps and teeth equally, possibly due to the varying contribution of enamel and dentin to the different measures<sup>50,51</sup>.

### **Cephalometric craniofacial pattern**

The results in 45,X females showed that they have marked changes in relatively few craniofacial areas. Most of the changes are located in the cranial base, so that the face is retrognathic. The mandible is short, whereas the maxilla is of normal length. These results support the view that the morphology of the cranial base is markedly affected in 45,X females, whereas most other craniofacial changes could be considered secondary to the cranial base abnormality. It is suggested that retarded cartilage growth may be a factor leading to the present findings<sup>52</sup>.

Also, the reduction of sex chromosome genetic material in 45,X/46,XX or mosaic Turner females results in the reduction of craniofacial dimensions, affecting dimensional ratios and especially plane angles of the cranial base<sup>53</sup>.

In 47,XXX females, or females with an extra X chromosome, lengths of the anterior and posterior cranial bases, the calvarium, mandibular ramus and posterior and upper anterior



face heights were found to be significantly shorter than in female controls. The angles between the foraminal and clival planes, the mandibular plane and cranial base, the maxillary and occlusal planes, the maxillary and mandibular planes and the foraminal and mandibular planes, and also the gonial angle, were significantly enlarged<sup>54</sup>.

Compared with female relatives, the 47,XXY males were larger in almost all craniofacial linear dimensions, but were similar in facial shape apart from greater mandibular prognathism. Mandibular dimensions in particular differed between the Klinefelter and unaffected males, the corpus length being larger, the ramus shorter and the gonial angle more obtuse in the 47,XXY group. Their craniofacial size with the majority of the mean values fell between those of males and females. The prominent facial profile, most marked in the mandible, was a dominant feature of the Klinefelter subjects who also displayed a more acute median cranial base angle than each control group. Generally, Klinefelter morphology was marked by greater variability or patterning of the craniofacial structures compared with relatives, possibly due to decreased developmental canalization. It is proposed that the 47,XXY complex may affect endochondral growth in the cranial base, as well as having a direct influence on jaw growth<sup>55</sup>.

The supernumerary Y chromosome in 47,XYY males results in larger craniofacial dimensions than in normal males, without substantial effects on dimensional ratios and plane angles. This general metric pattern is similar to that observed in relation to many adult body and head dimensions as well as dental arches and tooth crowns. The foramen magnum in 47,XYY males was found to be smaller in the sagittal plane than that in normal males and females<sup>56</sup>.

The findings of reduced linear measurements in 47,XXX females, together with the results of studies on the craniofacial complex of 47,XXY and 47,XYY males, suggest that dimensional variation between these groups results from the promoting effect of an extra Y chromosome and the retarding effect of an extra X chromosome on craniofacial growth<sup>53,54,55,56</sup>.

### **Occlusal morphology**

Turner patients or females with X chromosome anomalies such as 45,X; 45,X/46,XX and 46,Xi(Xq) females have an increase in class II malocclusions, lateral crossbites and anterior open bite<sup>57,58,59,60</sup>. Studies of occlusion in 47,XXY men showed that mesial molar occlusion was a relatively frequent anomaly, and that incisal open bite was also more common than in controls<sup>60</sup>. The 47,XYY men, like 47,XXY men, tended to have a mesial molar occlusion and a mandibular overjet more often than did other groups<sup>61</sup>, while 45,X women clearly had the highest frequency of distal occlusion and large overjet. The 47,XXY men has the highest frequency of most typical occlusal anomalies.

### **Palatal morphology**

There are a few reports of a high palate in Turner individuals, i.e. in women with one X chromosome (45,X women), but a normal palatal height but decreased width, with lateral palatine ridges commonly present, has also been reported<sup>62,63</sup>.

47,XXY males or men with one extra X chromosome show a tendency to have a shallower but longer palate than normal men. Their palate is also narrow. The mandible is clearly narrower but sagittally longer compared with the mandibles of normal men. The results indicate that the presence of one extra X chromosome in 47,XXY men is reflected in decreased growth of the maxilla transversely and vertically and of the mandible transversely.

Increased length of the alveolar arches might be partly a compensation for the decreased width of the alveolar arch. This change might be associated with larger tooth size in 47,XXY men<sup>62</sup>.

An extra Y chromosome in 47,XYY men caused an increase in palatal growth transversely and anteroposteriorly and in mandible arch length anteroposteriorly compared to normal men. Palatal height and mandibular width were smaller with this chromosome pattern. The findings in 47,XYY men are in accordance with the earlier observations that the palate becomes shallower with the addition of a sex chromosome. It is also apparent that the influence of X and Y chromosomes differs, at least regarding the magnitude of metric changes<sup>62</sup>. In general, increase in the number of sex chromosomes is associated with changes in palatal and mandibular arch dimensions.

### **Torus Mandibularis**

Ninety-three Finnish females with 45,X chromosome constitution were examined to determine the frequency and expression of torus mandibularis, a bony exostosis on the lingual surface of the mandibular corpus. The results indicate that among adults the frequency of the trait was significantly lower and the expression weaker in the 45,X females than in male control relatives. A similar trend was observed in comparison to normal female relatives. The findings suggest that the sex chromosomes may have an influence on the occurrence, expression, and timing of the development of mandibular torus. Sexual dimorphism in the manifestation of torus mandibularis as observed e.g. in Hailuoto population<sup>64</sup>, may result particularly from the effect of the Y chromosome on growth<sup>65</sup>. The early growth of tori in the 45,X females seems to be in pace with the advanced dental development rather than with the growth of facial or postcranial skeleton<sup>65,17,66,4</sup>.

### **The expression of sexual dimorphism**

Sex influenced inheritance or sex control in genetic texts traditionally refers to the more frequent expression of autosomal genes in one sex than in the other for some unknown reason although hormonal influence has been considered important in this respect. Missing and supernumerary teeth, which are mostly familial features, and which according to available knowledge also show dominant autosomal transmission, are dental examples of this phenomenon. Supernumerary permanent teeth are approximately twice as common in normal males as in normal females, while ordinary teeth are missing more frequently in females than in males.

It was suggested that these differences are explained by differential effects of the X and Y chromosomes on dental growth, particularly by the effect of the Y chromosome in increasing mitotic activity within the developing dental lamina, from which the teeth germinate<sup>28,67</sup>. These effects can also explain other sexual differences in human dentition. Among others, sexual dimorphism in average permanent tooth crown size, which is decisively due to dentin thickness<sup>29,68</sup> and tooth root dentin size<sup>37</sup>, in tooth crown morphology, where even the shape of the male tooth cusp seems to differ from that of females<sup>50</sup>, and in the developmental timing of the permanent teeth, where an increase in total tooth substance in males may relate to retardation of their dental development relative to females<sup>11,67</sup> (Fig. 5).

Assuming genetic pleiotropy, that the effects of the X and Y chromosomes on cell secretory function and proliferation are not limited to the teeth, sexual dimorphism in such matters as, torus mandibularis<sup>64,65</sup>, skeletal maturation<sup>11,33</sup> and statural growth are also explained by their differential action. The sex ratio (the ratio of the number of males to that of females) at birth as well as in the earlier stages of development may also relate to increased mitotic potential

due to the Y chromosome<sup>29,67</sup>, (Fig. 5). There is a significant change in the sex ratio with increasing duration of pregnancy. For example, in a Finnish study of 551 conceptuses from induced abortions, the embryonic sex ratio was as high as 164 and the foetal ratio 111, while the mean sex ratio at birth in Finland was 105<sup>69</sup>. It seems that the 46,XY chromosome complement makes for a better start than the 46,XX constitution<sup>67</sup>.

### **Prospect**

A number of questions arise regarding the manner and extent of the influence of the Y chromosome tooth growth gene(s). Among others, does the increase in mitotic potential due to the Y chromosome promote the penetrance of normal genes or inhibit that of defective genes involved in dental development, e.g. leading to sexual dimorphism in the number of the teeth? Does the Y chromosome wake up “sleeping” genes, and thereby in males leads to the greater expression of atavistic feature of our dentition in the form of supernumerary teeth? Is the Y chromosome involved in the mineralization process? Are enamel and dentin growth regulated by the same tooth growth gene within the Y chromosome? What is the role of the Y chromosome in uncontrolled growth? Answers to some of the questions may lie in the analyses of deciduous and permanent teeth that I have received from individuals with various sex chromosome anomalies and their first-degree female and male relatives.

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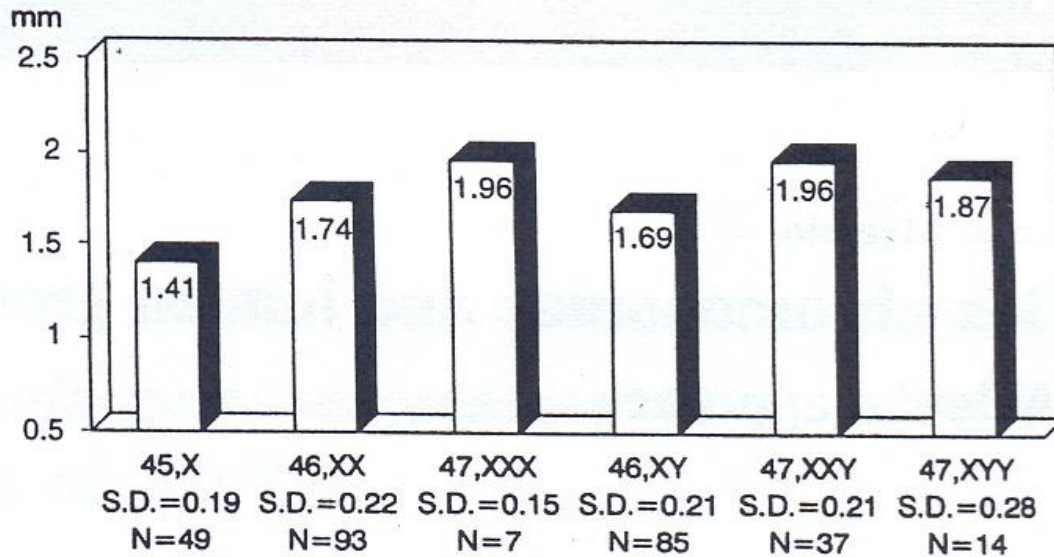
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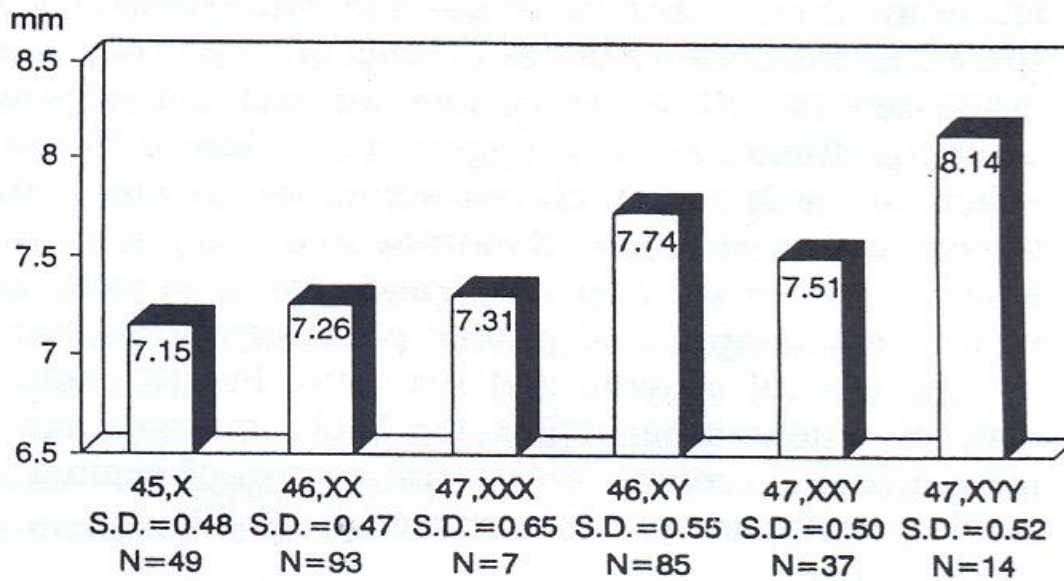
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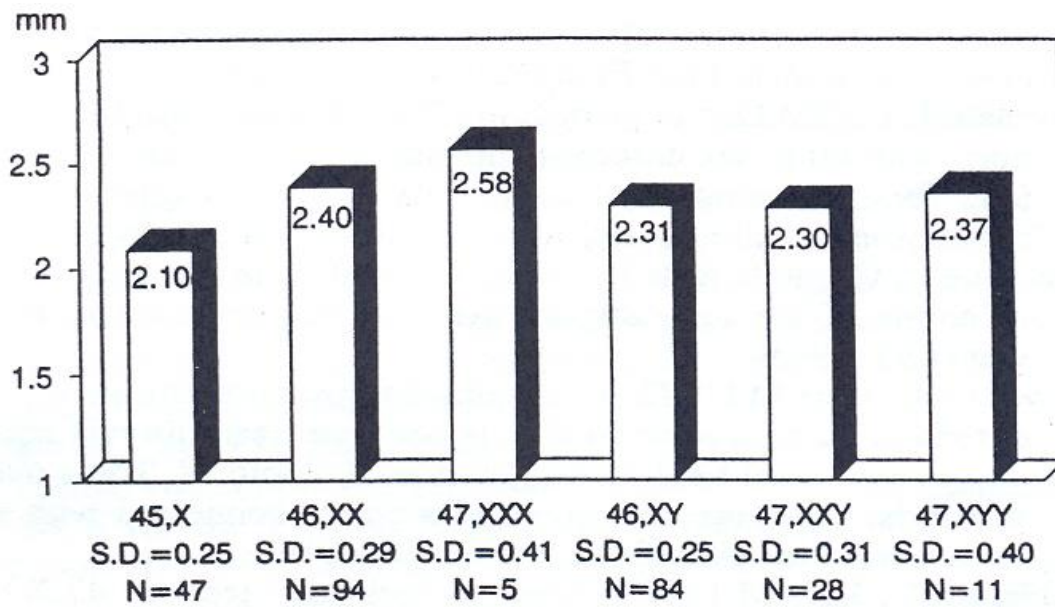
**FIGURES and LEGENDS**



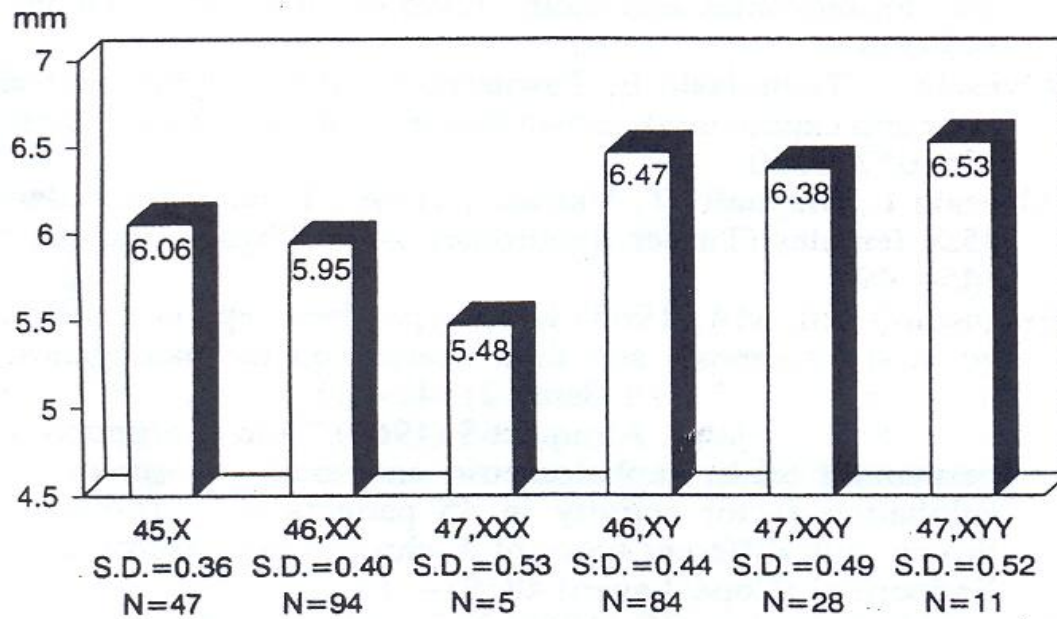
**Fig. 1.** Mean enamel thickness (mesial enamel layer plus distal enamel layer) of the maxillary permanent central incisors of normal 46,XX females<sup>29</sup>, normal 46,XY males<sup>29</sup> and individuals with various sex chromosome anomalies, including 45,X<sup>29</sup> and 47,XXX<sup>31</sup> females and 47,XXY<sup>33</sup> and 47,XYY<sup>32</sup> males. Enamel thicknesses were determined from standardized intra-oral radiographs. P-value <0.000 1 in one-way analysis of variance. 45,X female; female with one X chromosome, 47,XXX female; female with an extra X chromosome, 47,XXY male; male with an extra X chromosome, 47,XYY male; male with an extra Y chromosome.



**Fig. 2.** Mean dentin thickness (maximum mesio-distal dimension of tooth crown minus enamel layers) of the maxillary permanent central incisors of normal 46,XX females<sup>29</sup>, normal 46,XY males<sup>29</sup> and individuals with various sex chromosome anomalies, including 45,X<sup>29</sup> and 47,XXX<sup>31</sup> females and 47,XXY<sup>33</sup> and 47,XYY<sup>32</sup> males. Determinations were made from standardized intra-oral radiographs. P-value <0.000 1 in one-way analysis of variance. 45,X female; female with one X chromosome, 47,XXX female; female with an extra X chromosome, 47,XXY male; male with an extra X chromosome, 47,XYY male; male with an extra Y chromosome.



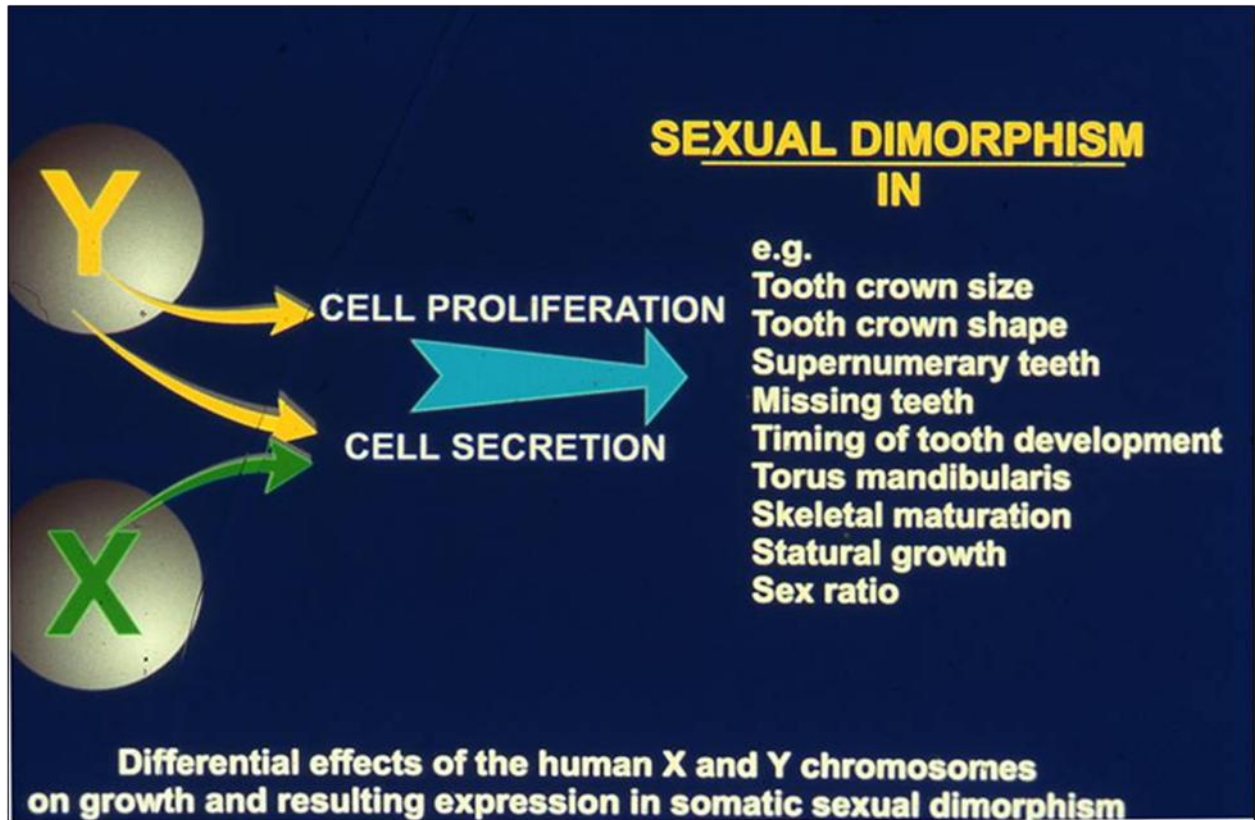
**Fig. 3.** Mean enamel thickness (mesial enamel layer plus distal enamel layer) of the maxillary permanent canines of normal 46,XX females<sup>29</sup>, normal 46,XY males<sup>29</sup> and individuals with various sex chromosome anomalies, including 45,X<sup>29</sup> and 47,XXX<sup>31</sup> females and 47,XXY<sup>33</sup> and 47,XYY<sup>32</sup> males. Enamel thicknesses were determined from standardized intra-oral radiographs. P-value <0.000 1 in one-way analysis of variance. 45,X female; female with one X chromosome, 47,XXX female; female with an extra X chromosome, 47,XXY male; male with an extra X chromosome, 47,XYY male; male with an extra Y chromosome.



**Fig. 4.** Mean dentin thickness (maximum mesio-distal dimension of tooth crown minus enamel layers) of the maxillary permanent canines of normal 46,XX females<sup>29</sup>, normal 46,XY males<sup>29</sup> and individuals with various sex chromosome anomalies, including 45,X<sup>29</sup> and 47,XXX<sup>31</sup> females and 47,XXY<sup>33</sup> and 47,XYY<sup>32</sup> males. Determinations were made from standardized intra-oral radiographs. P-value <0.000 1 in one-way analysis of variance.

45,X female; female with one X chromosome, 47,XXX female; female with an extra X chromosome, 47,XXY male; male with an extra X chromosome, 47,XYY male; male with an extra Y chromosome.





**Fig. 5.** A schematic model describing differential effects of the human X and Y chromosomes on tooth crown growth and resulting expression in somatic sexual dimorphism. An assumption of genetic pleiotropy of these effects is made as regards torus mandibularis, statural growth, skeletal maturation and sex ratio.

Figures 1 – 5 published in Hum Genet 1997, 101(1): 1-5