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Human sex chromosomes in oral and craniofacial growth☆

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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.

1. 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[1,2] 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.[3] 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,[4] and X linkage has been suggested for the rate and timing of ossification.[5] 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,[6,7] and it has been postulated that the Y chromosome regulates the rate and extent of growth of the

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primitive gonad,[8] 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.[9]

2. Tooth crown size

Human dental development begins with the formation of the deciduous incisors at about 4 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 2 months and 8 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.[5,10,11] 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.[11]

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,[12–16] 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.[17–22] 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.[23] 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,[22] while that in the Y chromosome may be on the proximal, non-fluorescent portion of the long arm.[24] 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[17,25,26] is definitely advanced compared to normal females.

3. 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.[27] 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.[28–33] 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.[29,31] 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[29] (Figs. 1–4). 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.[28] 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.[34–36] 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.[36] 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.[34] The short arm of the Y chromosome has also been suggested as a possible location for the amelogenin gene.[35,36] 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.

4. Tooth root size

Permanent tooth root lengths, measured on radiographs, in 47,XYY and 47,XXY males were longer than in normal men