Comparison of adult height between patients with XX and XY gonadal dysgenesis: support for a Y specific growth gene(s)

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Abstract
Adult height was compared between published cases of patients with XX gonadal dysgenesis (XXGD) and those with XY gonadal dysgenesis (XYGD). The mean adult height of XYGD patients (171.0 cm (SD 7.8), n = 27) was significantly greater than that of XXGD patients (164.4 cm (7.7), n = 27) (p < 0.01). This finding supports the existence of a Y specific growth gene(s) which promotes stature growth independently of the effects of gonadal sex steroids.

Pure XX gonadal dysgenesis (XXGD) and XY gonadal dysgenesis (XYGD) are disorders of sexual development characterised by a rudimentary streak gonad and an apparently normal karyotype. Consequently, affected subjects of both sexes have gonadal steroid deficiency irrespective of sex chromosome complement. Thus, it is believed that phenotypic differences between XXGD and XYGD are directly caused by the difference in sex chromosome complement, independently of the effects of gonadal sex steroids. On the basis of this notion, we compared adult heights between patients with XXGD and those with XYGD.

Results
Twenty-seven patients were identified for both XXGD and XYGD. The mean adult height was 164.4 cm (SD 7.7) (range 148 to 180 cm) for the patients with XXGD and 171.0 cm (SD 7.8) (range 150 to 183 cm) for those with XYGD. This adult height difference of 6.6 cm was statistically significant (p < 0.01). Between the two groups, the distribution of ages was comparable (XXGD, mean 25.9 years, range 20 to 37; XYGD, mean 26.2 years, range 20 to 38) as was that of publication years (XXGD, mean 1968, range 1961 to 1982; XYGD, mean 1973, range 1964 to 1984).

Twenty-two patients with XXGD and 24 patients with XYGD appeared to be Caucasians of various nationalities; the remaining patients were two American blacks, five South Americans, and one African. The mean adult height of the 22 XXGD patients was 164.3 cm (SD 7.7) (range 148 to 175 cm) and that of the 24 XYGD patients was 172.0 cm (SD 7.0) (range 156 to 183 cm). This height difference of 7.7 cm was also significant (p < 0.01). Between the two subgroups, the distribution of ages was comparable (XXGD, mean 26.5 years, range 20 to 37; XYGD, mean 26.4, range 20 to 38) but that of publication years was statistically different (XXGD, mean 1967, range 1961 to 1971; XYGD, mean 1972, range 1964 to 1984) (p < 0.05), implying a small influence of secular height change (about 0.5 to 1.0 cm) on the adult height difference.

Discussion
The present study showed a significant difference in the mean adult height between XXGD and XYGD patients. This adult height difference is considered to be a direct consequence of a growth promoting effect of the Y chromosome. This notion is supported by the fact that patients with 47,XXY are taller than normal 46,XY males. In contrast, the possibility that the X chromosome has a growth suppressing effect is excluded by the fact that patients with 45,X are invariably short* and those with 47,XXX tend to be tall. If the Y chromosome is responsible for the adult height difference between XXGD and XYGD patients, it is expected that a growth gene(s) unrelated to gonadal sex steroids exists in the Y specific region. In this context, non-mosaic adult patients with 46,XY,del(Yq) are informative: in spite of a similar male sex development, those with apparently large Yq

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deletions had short stature\(^{-39-42}\) and those with apparently small Yq deletions did not have short stature\(^{-41-45}\). This finding is compatible with the presence of a Y specific growth gene(s) which promotes statural growth independently of the effects of gonadal sex steroids, although other mechanisms may also contribute to the growth failure associated with large chromosomal deletions. In agreement with this view, recent molecular analysis in patients with Y chromosome aberrations has also argued for the presence of the growth gene(s) in the proximal part of Yq\(^{-46}\). Although another growth gene(s) has been suggested on the tip of Yp\(^{-47}\) distal to the testis determining gene,\(^{-48}\) genotype-phenotype correlations in patients with sex chromosome abnormalities have indicated that the growth gene(s) on the tip of Yp is not Y specific but pseudoautosomal\(^{-49}\).

Our results suggest that the putative Y specific growth gene(s) may exert an influence of about 7 cm on adult height. This value is in close agreement with the adult height difference between normal males (174.7 cm (SD 6.7)) and SRY positive XX males (166.1 cm (SD 3.3), \(n = 8, 20\) to 50 years of age)\(^{-51}\) in the United Kingdom. Since the SRY positive XX males had normal external genitalia indicative of sufficient testosterone secretion\(^{-51}\) and are expected to have two copies of the pseudoautosomal growth gene(s), the height decrease of the XX males can be simply explained as a loss of the Y specific growth gene(s). In addition, it is known that patients with testicular feminisation syndrome (TFS) are 5 to 10 cm taller than normal females, despite having similar sex steroid hormone status.\(^{-52-54}\) This height increase of TFS patients is also explicable by the effect of the Y specific growth gene(s).

The adult height difference between XXGD and XYGD patients was smaller than that between normal males and females (about 13 cm).\(^{-55}\) This indicates that sex dimorphism in gonadal steroids also contributes to the sex difference in the mean adult height of normal subjects. Since the mean adult height of XXGD patients is similar to the adult female standards and that of XYGD patients is shorter than the adult male standards,\(^{-55,56}\) it appears that ovarian oestrogens play a relatively minor role in statural growth, whereas testicular androgens have the potential to increase the adult height. In favour of this notion, it has been reported that androgens have a more beneficial effect on the production of somatomedin-C (a potent stimulus for linear growth) than oestrogens.\(^{-56}\) Furthermore, this notion can explain the adult height differences between XX males and normal females and between TFS patients and normal males.

It should be pointed out, however, that possible variations in several factors influencing the adult height, such as secular trend, racial group, parental height, and socioeconomic status,\(^{-14-18,51-54}\) are not eliminated between the XXGD and XYGD patients analysed. The distributions of ages and publication years imply a possible small secular height change between the two groups of patients. In addition, although the exclusion of non-Caucasian patients allowed the height comparison in a more homogeneous population, intra-Caucasian height variation still exists.\(^{-50,55}\) Furthermore, no parental height was available in the published reports, nor was there any indication of socioeconomic status. Thus, it is uncertain at this time whether the adult height difference between XXGD and XYGD patients (about 7 cm) is totally attributable to the Y specific growth gene(s). Further accumulation of patients will be required for the more precise estimation of the quantitative effect of the Y specific growth gene(s).

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