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Sex chromosome aberrations and stature: deduction of the principal factors involved in the determination of adult height

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Abstract. Although sex chromosome aberrations are frequently associated with statural changes, the underlying factors have not been clarified. To define the factors leading to the statural changes, we took the following three steps: (1) determination of the mean adult height in non-mosaic Caucasian patients with sex chromosome aberrations reported in the literature (assessment of genetic height potential); (2) assessment of the validity of factors that could influence stature; and (3) correlation of the mean adult height with the effects of specific growth-related factors. The results indicate that the adult height in patients with sex chromosome aberrations may primarily be defined by the dosage effect of pseudoautosomal and Y-specific growth genes, together with the degree of growth disadvantage caused by alteration of the quantity of euchromatic or non-inactivated region.

Introduction

Sex chromosome aberrations are frequently associated with statural changes. Monosomy for the X chromosome invariably results in severe short stature (Ranke et al. 1983), and the presence of an extra X or Y chromosome usually leads to moderate tall stature (Court Brown 1968; Ratcliffe et al. 1982; Linden et al. 1988). In addition to the numerical abnormalities, structural abnormalities of the X and the Y chromosomes are also often manifested by short stature (Simpson 1975; Buhler 1980; Therman and Susman 1990). However, the pertinent factors leading to the statural changes have not been determined.

The methods to clarify the factors responsible for the statural changes can be broken down into three steps. The first step is to determine the mean adult height in patients with sex chromosome aberrations. This will allow an assessment of genetic height potential in various sex chromosome aberrations. The second step is to assess the validity of factors that could influence statural growth in sex chromosome aberrations. The last step is to correlate the mean adult height with the effects of specific growth-related factors. If the distribution of the mean adult height is explained by the effects of specific growth-related factors, it can be said that such factors contribute to the statural changes in sex chromosome aberrations.

In this paper, we take each of the above steps and propose principal factors involved in determining adult height in patients with sex chromosome aberrations. In addition, several remarks inherent in this study are discussed.

Step I: Determination of the mean adult height

Selection of patients

All the height data of patients with sex chromosome aberrations were taken from the literature using the following selection criteria: (1) description of karyotype; (2) absence of demonstrable mosaicism; (3) height recorded between 20 and 50 years of age, or confirmation of growth cessation; (4) apparent Caucasian patients of various nationalities; (5) no selection for height in the ascertainment of patients; (6) no therapeutic intervention that may cause statural alteration; and (7) lack of other associated disorders that may affect stature. Although several patients have been reported in multiple publications, only a single height record was used for each patient.

Data analysis

The mean adult height was determined for karyotypes in which more than five patients were ascertained. When possible, the population-specific mean adult height was also obtained, to allow for intra-Caucasian height variation (reviewed in Prader et al. 1989). The results are ex-

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Table 1. The mean adult height in patients with sex chromosome aberrations

Karyotype		Phenotype	Adult height (cm)		Reference (Appendix)
[A]	47,XYY	Male	185.4 ± 8.5	(n = 40)	1–18
[B]	47,XXY	Male	178.3 ± 7.2	(n = 85)	1, 4, 13, 19–22
[C]	47,XXX	Female	167.9 ± 7.7	(n = 19)	1, 20, 23–29
[D]	45,X	Female	143.3 ± 6.4	(n = 130)	1, 30–49
[E]	46,X,del(X)(p22.32)	Female	154.1 ± 4.9	(n = 13)	50
[F]	46,X,del(X)(p11)	Female	147.3 ± 5.9	(n = 16)	30, 54, 56–65
[G]	46,X,del(X)(q13–21)	Female	153.5 ± 7.6	(n = 10)	66–72
[H]	46,X,del(X)(q26)	Female	164.7 ± 7.1	(n = 6)	80–82
[I]	46,X,i(Xq)	Female	140.2 ± 4.6	(n = 14)	1, 30, 32, 36, 89–93
[J]	46,X,t(X;autosome)[a]	Female	162.4 ± 7.8	(n = 21)	93–110
[K]	46,X,Xp+ = Y(+) XX male[b]	Male	166.2 ± 5.8	(n = 14)	111–114
[L]	46,X,del(Y)(distal q11.2)[c]	Male	173.6 ± 7.9	(n = 12)	131–137
	46,XY (the British standard)		174.7 ± 6.7		152
	46,XX (the British standard)		162.2 ± 6.0		152

[a] The mean adult height is 161.6 ± 7.6 cm in 17 females with 46,X,t(X;autosome) accompanied by non-random inactivation of the normal X chromosome [93–96, 98, 100–103, 105–110]

[b] The mean adult height in 33 XX males with no evidence for abnormal X;Y interchange is 166.4 ± 7.4 cm [1, 112, 115–130]

[c] The position of the breakpoints in the 12 patients has been based on normal fertility [131], cytogenetic findings [132–136], and molecular analysis [137]. Although an additional 9 patients have been reported to have non-fluorescent Yq deletions [137–144], the positions of the breakpoints are apparently at more proximal portions in 4 cases [137, 141, 142] and indistinct in 5 cases [138–140, 143, 144]; the height of the 9 patients ranged from 152 to 176 cm

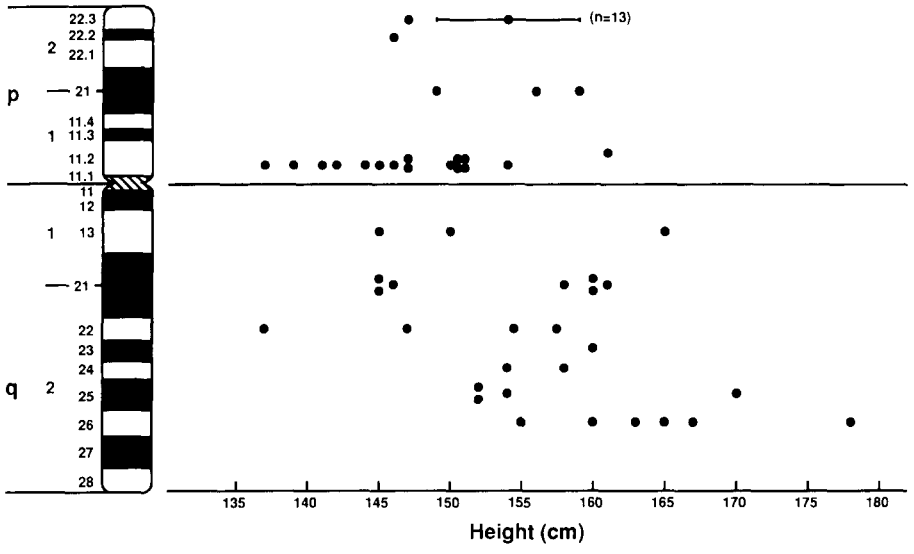

Fig. 1. A diagram showing the correlation between stature and breakpoint in Caucasian adult female patients with X chromosome terminal deletions (References, Appendix 30, 50–82). The *horizontal bar* represents the height range (mean ± SD) of 13 adult females with 46,X,del(X)(p22.32) [50]. Although it is uncertain whether all of the 13 adult female carriers meet the age criterion, they have been included in the present study as the sole exceptions. The patient reported to have 46,X,del(X)(q11) [83] has been excluded from the figure; this case may be an XY female, since an Xq deletion involving the inactivation centre at Xq13 (Brown et al. 1991) is believed to be incompatible with life. Besides the patients shown in the figure, 8 patients with breakpoints apparently in the proximal part of Xq have been reported [24, 76, 84–88], having heights between 142 and 165 cm (mean 152.8 cm)

Table 2. Statistical analysis. Height data are shown in Table 1. NS, not significant

		46,XX	46,XY	[L]	[K]	[J]	[I]	[H]	[G]	[F]	[E]	[D]	[C]	[B]
[A]	47,XYY		$P<10^{-6}$	$P<10^{-3}$	$P<10^{-6}$								$P<10^{-6}$	$P<10^{-5}$
[B]	47,XXY		$P<10^{-4}$	$P<0.05$	$P<10^{-6}$								$P<10^{-6}$	
[C]	47,XXX	$P<10^{-2}$				$P<0.05$	$P<10^{-6}$	NS	$P<10^{-4}$	$P<10^{-6}$	$P<10^{-5}$	$P<10^{-6}$		
[D]	45,X	$P<10^{-6}$				$P<10^{-6}$	$P<0.05$	$P<10^{-6}$	$P<10^{-5}$	$P<0.05$	$P<10^{-6}$			
[E]	46,X,del(X)(p22.32)	$P<10^{-4}$				$P<10^{-2}$	$P<10^{-6}$	$P<10^{-2}$	NS	$P<10^{-2}$				
[F]	46,X,del(X)(p11)	$P<10^{-6}$				$P<10^{-6}$	$P<10^{-2}$	$P<10^{-4}$	$P<0.05$					
[G]	46,X,del(X)(q13–21)	$P<10^{-2}$				$P<10^{-2}$	$P<10^{-4}$	$P<0.05$						
[H]	46,X,del(X)(q26)	NS				NS	$P<10^{-6}$							
[I]	46,X,i(Xq)	$P<10^{-6}$				$P<10^{-6}$								
[J]	46,X,t(X;autosome)	NS												
[K]	46,X,Xp+ = Y(+) XX male	$P<0.05$	$P<10^{-3}$	$P<0.05$										
[L]	46,X,del(Y)(distal q11.2)		NS											

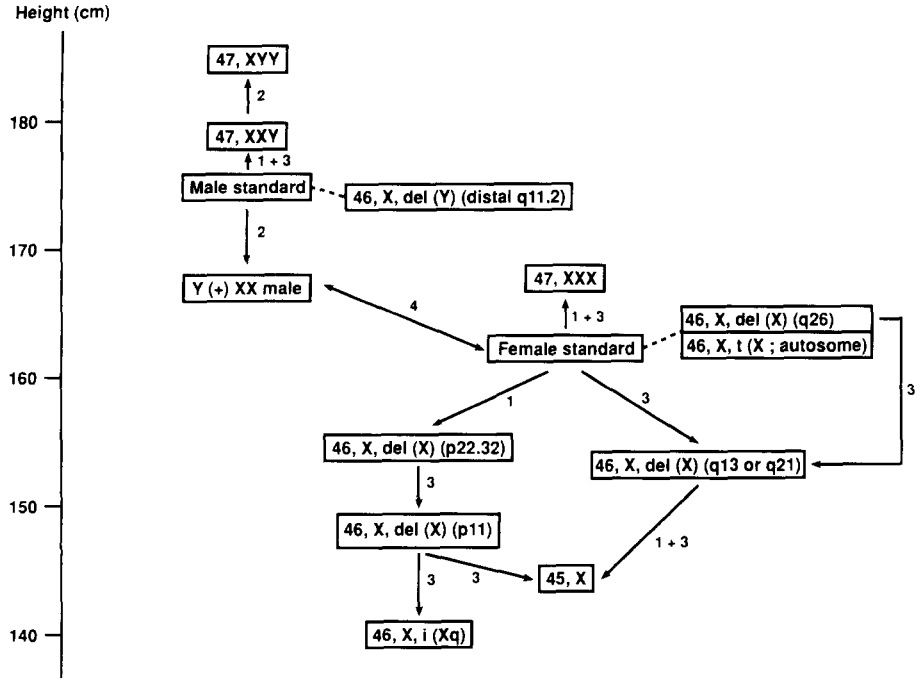

Fig. 2. The distribution of mean adult heights in Caucasian patients with various sex chromosome aberrations. The numbers 1–4 represent the major factors responsible for the adult height differences. Number 1 denotes the dosage effect of the pseudoautosomal growth gene(s), number 2 the dosage effect of the Y-specific growth gene(s), number 3 the growth disadvantage caused by alteration of the quantity of euchromatic or non-inactivated region, and number 4 the sex dimorphism in gonadal steroid. The British height standards are used as controls. The height differences designated by *arrwos* are statistically significant, whereas no significant difference is found for the height differences indicated by *dotted lines*

Table 3. Population-specific mean adult height in patients with sex chromosome aberrations

Karyotype	Population	Adult height (cm)	Difference[a]	Reference (Appendix)
47,XYY	British	181.5 ± 5.7 (n = 20)	+ 6.8	1–10
	American	188.6 ± 7.6 (n = 14)	+12.1	11–13
47,XXY	British	177.7 ± 7.0 (n = 52)	+ 3.0	1, 4, 19, 20
	Dutch	182.3 ± 4.6 (n = 17)	+ 4.3	21
47,XXX	British	167.5 ± 8.6 (n = 14)	+ 5.3	1, 20, 23–26
45,X	British	140.1 ± 6.5 (n = 18)	−22.1	1, 30
	American	143.5 ± 6.1 (n = 54)	−20.1	31–38
	Swiss	143.3 ± 4.8 (n = 14)	−21.3	44
46,X,del(X)(p22.32)	American	154.1 ± 4.9 (n = 13)	− 9.5	50
46,X,del(X)(q13–21)	American	153.7 ± 8.5 (n = 6)	− 9.9	66–68
46,X,i(Xq)	American	140.4 ± 5.1 (n = 8)	−23.2	32, 36, 89, 90
46,X,t(X;autosome)	American	164.1 ± 7.9 (n = 7)	+ 0.5	94–99
46,X,Xp+ = Y(+) XX male	British	167.2 ± 5.8 (n = 11)	− 7.5	111, 112

[a] Difference from the following population-specific adult height standards (same sex): British, male 174.7 ± 6.7, female 162.2 ± 6.0 [Appendix 152]; American, male 176.5 ± 7.0, female 163.6 ± 7.0 [153]; Dutch, male 178.0 ± 6.4 [21]; and Swiss, female 164.6 ± 5.9 [156]

pressed as mean ± SD (cm). Statistical significance was determined by the two-tailed t-test.

Mean adult height

The mean adult height was determined for 12 abnormal karyotypes. The results are shown in Table 1, together with the British height standards, which occupy a roughly medium height position among Caucasian populations (reviewed in Prader et al. 1989). For X chromosome terminal deletions, the mean adult height was obtained for patients with small deletions (breakpoints at p22.32 and q26) and for those with large deletions (breakpoints at p11 and q13–21) (Fig. 1). The statistical data are summarized in Table 2. The distribution of the mean adult heights and the British height standards is shown in Fig. 2.

Population-specific mean adult height

In 9 of the 12 abnormal karyotypes given in Table 1, more than five patients were identified in the same country where the height standard is available. The results are

shown in Table 3, together with the height differences from the population standards. The statistical results obtained for the height differences between patients and normal individuals and between patients of different karyotypes in the same population were consistent with the data shown in Table 2, except for the lack of significant height difference between the American females with 45,X and those with 46,X,i(Xq) (however, the significance level differed in most cases, data not shown).

Step II: Assessment of the validity of factors that could influence stature

Pseudoautosomal growth gene(s)

The presence of a pseudoautosomal growth gene(s) [P-growth gene(s)] has been supported by the following findings: (1) karyotype-phenotype analysis in X chromosome rearrangements consistent with a growth gene(s) at the tip of Xp (Simpson 1975; Curry et al. 1984; Therman and Susman 1990); (2) similar analysis in Y chromosome rearrangements indicative of a growth gene(s) at the tip of Yp (Simpson 1975; Buhler 1980) distal to the sex determining Y gene *(SRY)*, which is located only 5 kb from the pseudoautosomal boundary (Sinclair et al. 1990); and (3) association between unequivocal short stature and terminal deletions within the pseudoautosomal region (PAR) (Ballabio et al. 1989; Henke et al. 1991; Ogata et al. 1992a). Furthermore, Ogata et al. (1992b) have localised the P-growth gene(s) to the region between *DXYS20* and *DXYS15* in the distal part of the PAR, on the basis of genotype-phenotype correlation in patients with partial monosomy of the PAR. Normal height in sex reversed girls with 46,X,Yp– (Rosenfeld et al. 1979; Magenis et al. 1984; Disteche et al. 1986) does not contradict the presence of the P-growth gene(s). Since the Yp– chromosomes are usually generated by abnormal X; Y interchange between sex-specific regions (Affara et al. 1987; Levilliers et al. 1989), the P-growth gene(s) is expected to be present in two copies in the 46,X,Yp– girls.

X-specific growth gene(s)

An X-specific growth gene(s) [X-growth gene(s)] escaping X-inactivation could affect stature in individuals with X chromosome aberrations because of the dosage effect. In this context, although a growth gene(s) postulated at the tip of Xp appears to be localised to the PAR, the height differences between patients with small and large X terminal deletions could support the presence of an X-growth gene(s) escaping inactivation on both Xp and Xq (Table 1). However, height comparisons between patients with 45,X, 46,X,del(X)(p11), and 46,X,i(Xq) argue that an X-growth gene(s) escaping inactivation is absent from Xq (Table 1). This indicates that the height difference between small and large Xq terminal deletions may be caused by some factor(s) relevant to loss of gross chromosomal material rather than by the dosage effect of an X-growth gene(s), and it is possible that the same factor(s) may also contribute to the height difference between small and large Xp terminal deletions. However, there is no direct evidence that an X-growth gene(s) escaping inactivation is absent from Xp, so that such an X-growth gene(s) might be present on Xp.

Y-specific growth gene(s)

Karyotype-phenotype analysis in Y chromosome abnormalities has postulated a Y-specific growth gene(s) [Y-growth gene(s)] in the Yq11 region, proximal to the gene(s) for spermatogenesis (Buhler 1980). This assignment has been supported by recent molecular studies (Bardoni et al. 1991). Further evidence for a Y-growth gene(s) has come from adult height differences between patients with pure XX gonadal dysgenesis (XXGD) and XY gonadal dysgenesis (XYGD) and between patients with testicular feminization syndrome (TFS) and normal females (Table 4). The results suggest the presence of a Y-growth gene(s) that augments the adult height independently of the effects of gonadal sex steroids.

Euchromatic quantity

It has been proposed that chromosome imbalance may cause global developmental disruption, leading to growth failure. For example, Shapiro (1983) has argued that aneuploidy may decrease the buffering effect against genetic and environmental forces, resulting in a disruption of developmental homeostasis. A similar argument has also been stated by Gilbert and Opitz (1982). In addition, Mittwoch (1971) and Daniel (1979) have suggested that aneuploidy may impair cell proliferation, leading to growth and developmental retardation, although in vitro cell growth studies are still not conclusive (reviewed in Verp et al. 1988). These hypotheses may explain why several non-specific features such as "growth failure", maturational delay, mental retardation, and multiple anomalies are shared by most aneuploidies, irrespective of the origin of aneuploidy and of the type of alteration (monosomy or trisomy) (Smith 1982). [Characteristic features in each aneuploidy are believed to be due to the dosage effects of specific genes (Shapiro 1983).] Since the amount of heterochromatin often varies among normal individuals (Vogel and Motulsky 1986), it appears that alteration of euchromatic quantity is mainly, if not totally, responsible for the global developmental disruption.

One may argue that X chromosome abnormalities do not cause alteration of euchromatic quantity, since patients with X chromosome aberrations usually have a single normal active X chromosome, with the remaining X chromosome(s) being inactivated to form heterochromatin. However, the condensed X chromosome is not composed entirely of heterochromatin (Schempp and Meer 1983; Therman and Susman 1990), and several loci escaping inactivation have been isolated from various parts of the X chromosome (reviewed in Ballabio and Willard 1992). Quantitative alteration of the non-inactivated region would have deleterious effects similar to that of the euchromatic region.

Table 4. The mean adult height in Caucasian patients with pure XX and XY gonadal dysgenesis (XXGD and XYGD) and those with complete testicular feminization syndrome (TFS)

	Karyotype	Gonadal steroids	Adult height (cm)	Reference
XXGD[a]	46,XX	None	164.3 ± 7.7 (n = 22)	Ogata and Matsuo (1992)
XYGD[a]	46,XY	None	172.0 ± 7.0 (n = 24)	Ogata and Matsuo (1992)
TFS[b]	46,XY	Oestrogens	172.2 ± 6.5 (n = 23)	Appendix 1, 145–151
Normal male	46,XY	Androgens	173.8–178.0[c]	Appendix 152–156
Normale female	46,XX	Oestrogens	160.8–164.6[c]	Appendix 152–156

[a] Selection criteria for XXGD and XYGD patients include: (1) height recorded between 20 and 50 years of age, and (2) no description of steroid therapy before 20 years of age

[b] Selection criteria for TFS patients include: (1) height recorded between 20 and 50 years of age, or conformation of growth cessation, and (2) no gonadectomy before attaining the adult height

[c] The adult height of normal individuals represents the range of the mean adult heights in various Caucasian populations

Heterochromatic quantity

Goldman et al. (1982) have suggested that stature could be positively correlated to the amount of facultative X-heterochromatin, on the basis of height analysis of patients with X chromosome deletions. However, the hypothesis does not explain why severe short stature is common to 45,X with no X-heterochromatin and 46,X,i(Xq) with a large amount of X-heterochromatin (Tables 1, 3). Furthermore, the possibility that quantitative alteration of the facultative X-heterochromatin may contribute to global developmental disruption is also unlikely because of the apparently normal phenotype of the XO mouse (Cattanach 1962). [The phenotypic difference between human and mouse XO females may lie in species difference in the completeness of X-inactivation. In the condensed mouse X chromosome, the non-inactivated region is apparently scanty (Lyon 1966) and genes escaping inactivation have not been identified, with the probable exception of *Sts* (reviewed in Ballabio and Willard 1992).]

For the constitutive Y-heterochromatin, Yamada et al. (1981) have reported a weak positive correlation (r = 0.17) between stature and Yq12 length in 142 normal Japanese males, with the regression equation being $Y = 0.00475X + 0.115$ (Y, Yq12 length; X, height). However, the regression equation gives a negative height value for short Yq12. In addition, normal stature in patients with 46,X,del(Y)(distal q11.2) argues against the notion (Table 1). Furthermore, the apparently normal phenotype in such patients (appendix 131–137), except for impaired spermatogenesis resulting from a deletion of a specific gene(s) (Ma et al.1992), is consistent with the notion that quantitative alteration of the Y-heterochromatin does not cause global developmental disruption.

Non-random X-inactivation

Gartler and Sparkes (1963) put forward the cell selection hypothesis to account for the association between growth failure and preferential inactivation of rearranged X chromosomes. According to this hypothesis, the normal and the abnormal X chromosomes are originally inactivated at random, and then less viable cells with a gross imbalance of genetic expression are gradually lost, resulting in apparent non-random inactivation. Such a selection may reduce the total number of viable cells in an individual, leading to growth failure. However, female patients with 46,X,t(X;autosome) were normal in height under non-random inactivation of the normal X chromosome (Table 1, footnote). This suggests that such a selection, if it occurs, does not affect stature.

Impaired endocrine status

Female patients with sex chromosome aberrations frequently have severe oestrogen deficiency (Grumbach and Conte 1985) and the resultant hyposecretion of growth hormone (Ross et al. 1985) and somatomedin-C (Cuttler et al. 1985). Consequently, the pubertal growth pattern of such patients is altered: they lack a pubertal growth spurt but continue to grow for a long time (Ranke et al. 1983). However, since the adult height is similar between XXGD patients and normal females and between XYGD patients and TFS patients (Table 4), it appears that these hormonal abnormalities do not exert a major influence on the adult height. In addition, although such patients are frequently treated with sex steroids, it has been reported that sex steroid therapy with a standard dose does not alter the adult height of Turner patients (Lev-Ran 1977; Sybert 1984).

Male patients with sex chromosome aberrations usually have slight or mild androgen deficiency (Grumbach and Conte 1985). In this context, the finding that XYGD and TFS patients are shorter than normal males (Table 4) suggests that severe androgen deficiency has a deleterious effect on stature. However, a longitudinal growth study of chromatin positive Klinefelter patients has shown that the mean height of such patients is around the 75th centile growth curve of normal males, before and after puberty (Schibler et al. 1974). Thus, in contrast to severe androgen deficiency, mild androgen deficiency is unlikely to exert an apparently deleterious effect on adult height.

Skeletal abnormality

It has been speculated that skeletal abnormality may play a role in the genesis of short stature in Turner syndrome (Rosenfeld 1989). However, the structure of the growth plate, which primarily defines the linear bone growth, has been reported to be normal in Turner syndrome (Lubin et al. 1989). In addition, the upper/lower body segment ratio has been shown to be comparable between Turner patients and height-matched normal females (Varrela et al. 1984). These findings argue that skeletal abnormality does not constitute a major etiological factor for short stature. Rather, skeletal abnormality may be the consequence of global developmental disruption, since it is frequently found in other types of chromosome imbalance as well (Smith 1982).

Summary

The above arguments indicate that the P- and the Y-growth genes may be relevant to the statural determination in sex chromosome aberrations, and that quantitative alteration of euchromatic or non-inactivated region could cause growth disadvantage through gobal developmental disruption. Although an X-growth gene(s) escaping inactivation might exist on Xp, the data in support of such an X-growth gene(s) could be explained by the growth disadvantage caused by loss of non-inactivated region. The remaining factors are unlikely to exert a major influence on adult height in patients with sex chromosome aberrations.

Step III: Correlation of the mean adult height with the effects of specific growth-related factors

Karyotypes without gross chromosome imbalance

Among the karyotypes listed in Table 1, 46,X,del(X)(p22.32), 46,X,del(X)(q26), 46,X,t(X;autosome), 46,X,Xp+ (= Y(+) XX male), and 46,X,del(Y)(distal q11.2) are free from gross chromosome imbalance, and thus the growth disadvantage caused by quantitative alteration of euchromatic or non-inactivated region is expected to be small. Indeed, the non-specific features attributable to global developmental disruption are barely present in these karyotypes.

The mean adult height in this category may primarily be explained by the dosage effect of the P- and the Y-growth genes (Fig. 2). Short stature in 46,X,del(X)(p22.32) would be mostly due to the loss of the P-growth gene(s), although the loss of non-inactivated region at the tip of Xp will have a small deleterious effect, as suggested by the presence of subtle phenotypic abnormalities (Appendix 50). Normal stature in 46,X,del(X)(q26) and 46,X,t(X;autosome) is consistent with the P-growth gene(s) being present in two copies. The height difference between Y(+) XX males and normal males is explained by the loss of the Y-growth gene(s); the value is similar to the height differences between XXGD and XYGD patients and between TFS patients and normal females (Table 4). Since most Y(+) XX males are generated by the abnormal X;Y interchange between the X-specific region in the terminal Xp and the Y-specific region proximal to *SRY* (Page et al. 1987; Petit et al. 1987), the P-growth gene(s) is expected to be present in two doses after the abnormal interchange. In addition, the hight difference between Y(+) XX males and normal females would be due to the sex difference in gonadal steroid, since it appears that ovarian oestrogens play no major role in statural growth whereas testicular androgens have the potential to increase the adult height (Table 4). Normal stature in 46,X,del(Y)(distal q11.2) is accounted for by assuming that most of the euchromatic region including the Y-growth gene(s) is preserved.

Karyotypes with gross chromosome imbalance

Among the karyotypes listed in Table 1, aneuploidies, large X deletions, and Xq isochromosomes are associated with gross chromosome imbalance, and thus both the dosage effect of the growth genes and the growth disadvantage caused by quantitative alteration of euchromatic or non-inactivated region should be considered. Indeed, several features consistent with global developmental disruption, such as non-specific anomalies, maturational failure of various degrees, and mental retardation, are often observed in these karyotypes (Court Brown 1968; Ratcliffe et al. 1982; Smith 1982; Linden et al. 1988; Rosenfeld 1989; Therman and Susman 1990). [Characteristic features such as Turner or Klinefelter stigmata are thought to be due to dosage effects of specific genes (Patil et al. 1981; Richer et al. 1989; Ferguson-Smith 1991).]

The mean adult height in this category may be explained by assuming both the dosage effect of the growth genes and the disadvantageous effect caused by quantitative alteration of euchromatic or non-inactivated region (Fig. 2). The severe short stature in 46,X,del(X)(p11), 45,X, and 46,X,i(Xq) would be due to the total effects of the loss of the P-growth gene(s) and the growth disadvantage caused by alteration of the amount of non-inactivated region. Height comparisons between 46,X,del(X)(p22.32), 46,X,del(X)(p11), 45,X, and 46,X,i(Xq), in which the P-growth gene(s) is present in a single copy, suggest that the degree of growth disadvantage correlates with the degree of chromosome imbalance. The height decrease in 46,X,del(X)(q13–21) appears to be inexplicable without assuming the growth disadvantage caused by the loss of non-inactivated region, although no direct evidence for the presence of non-inactivated region has been found for the middle to distal parts of Xq. It might be possible that the P-growth gene(s) is subject to X-inactivation on Xq– chromosomes, as has often been claimed for the X-specific loci of *XG* (Polani et al. 1970) and *STS* (Ropers et al. 1981). However, the expression of the pseudoautosomal gene *MIC2* on Xq– chromosomes indicates that such an abnormal spreading of X-inactivation does not involve the pseudoautosomal loci (Goodfellow et al. 1984). In addition, normal height in 46,X,del(X)(q26) argues that the P-growth gene(s) is at least expressed on Xq– chromosomes of small deletions. The mild height increase in 47,XXY and 47,XXX would be due to the combined effects of the growth advantage of an extra copy of the P-growth gene(s) and the growth disadvantage of alteration of non-

inactivated region (apparently milder growth disadvantage in 47,XXX and 47,XXY as compared with that in 45,X is compatible with the notion that deletions usually cause more severe effects than corresponding duplications (Daniel 1979)). Finally, the height difference between 47,XYY and 47,XXY may be accounted for by the dosage effect of the Y-growth gene(s), and that between 47,XXY and 47,XXX may be explained by both the dosage effect of the Y-growth gene(s) and the difference in gonadal sex steroid. Since chromosome balance is believed to be comparable between the normal 46,XX and 46,XY chromosome complements, the condensed X and the normal Y chromosomes appear to have a similar effect on chromosome balance. This implies that the degree of chromosome imbalance and the resultant growth disadvantage are similar between 47,XYY, 47,XXY, and 47,XXX.

For growth disadvantage caused by X chromosome deletions, the following findings may be noteworthy: (1) the height decrease caused by loss of most of Xq between 46,XX and 46,X,del(X)(q13–21) is larger than that caused by loss of the whole Xq between 46,X,del(X)(p11) and 45,X; and (2) the height decrease caused by loss of most of Xp between 46,X,del(X)(p22.32) and 46,X,del(X)(p11) appears to be larger than that caused by loss of the same Xp segment between 46,X,del(X)(q13–21) and 45,X [(the height decrease between 46,X,del(X)(q13–21) and 45,X would be mostly due to the loss of the P-growth gene(s)] (Fig. 2). The findings may imply that considerable loss of non-inactivated region between the normal state and large X deletions causes a severe growth disadvantage, whereas further loss of non-inactivated region between large X deletions and monosomy X causes a relatively minor growth disadvantage.

In this category, however, it should be pointed out that although the height distribution is plausibly explained by the dosage effect of the P- and the Y-growth genes and the growth disadvantage caused by alteration of euchromatic or non-inactivated region, this does not exclude the possibility that an X-growth gene(s) escaping inactivation might be present on Xp. If such an X-growth gene(s) indeed exists on Xp, it could also contribute to the statural changes of most karyotypes in this category.

Remarks and conclusion

Several remarks should be considered in the present study. First, the possibility of latent mosaicism cannot be excluded. In particular, a cryptic 45,X cell line is possible in cases of rearranged sex chromosomes. Secondly, except for a few cases studied by molecular analysis (Appendix 50, 51, 137, 143, 144), most structural abnormalities have been determined only by cytogenetic studies, which are not necessarily reliable (Goldman et al. 1982; Ferguson-Smith 1991). In particular, it might be possible that several Xp terminal deletions are virtually interstitial deletions preserving the P-growth gene(s), and that several Yq– chromosomes are actually i(Yp) chromosomes having two copies of the P-growth gene(s). Thirdly, although patients with sex steroid deficiency almost attain the final height at about 20 years of age, they still continue to grow afterwards with an extremely small height velocity (Schibler et al. 1974; Ranke et al. 1983). Thus, the adult height in such patients may be underestimated slightly. Fourthly, it was impossible to allow for an influence of intra-Caucasian height variation in several karyotypes. Fifthly, it was also impossible to allow for several influences on stature such as parental height (Mueller 1985), socioeconomic status (Eveleth 1985), and secular height change (van Wieringen 1985). Finally, there may be other growth-related factors not discussed here.

In spite of the above caveats, the present study offers a useful clue to the elucidation of the principal factors defining adult height in patients with sex chromosome aberrations. In conclusion, we propose that the adult height in such patients may primarily be defined by the dosage effect of the P- and the Y-growth genes, together with the degree of growth disadvantage caused by quantitative alteration of euchromatic or non-inactivated region.

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Note added in proof. With the same selection criteria, 8 male patients with a 47,XY,i(Xq) karyotype have been identified in the literature, with the mean adult height being 170.9 ± 10.9 cm (reviewed in Zelante et al., Am J Med Genet 41:267–268, 1991). The mild height decrease is also explained as a consequence of growth disadvantage caused by quantitative alteration of the non-inactivated region.