Abnormal Sex Chromosome Constitution and Longitudinal Growth: Serum Levels of Insulin-Like Growth Factor (IGF)-I, IGF Binding Protein-3, Luteinizing Hormone, and Testosterone in 109 Males with 47,XXY, 47,XYY, or Sex-Determining Region of the Y Chromosome (SRY)-Positive 46,XX Karyotypes

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Context: Growth is a highly complex process regulated by the interaction between sex steroids and the GH IGF-axis. However, other factors such as sex chromosome-related genes play independent roles.

Aim: The aim of the study was to evaluate the role of abnormal chromosome constitution for longitudinal growth in relation to reproductive hormones, IGF-I, and IGF binding protein (IGFBP)-3.

Setting: The study was conducted at an outpatient clinic, Copenhagen University Hospital.

Participants: Participants included 86 47,XXY males, 14 46,XX-males, and nine 47,XYY.

Main Outcome Measures: Standing and sitting height, serum levels of reproductive hormones, IGF-I, and IGFBP-3 were measured.

Results: In boys with 47,XXY and 47,XYY karyotypes, growth was accelerated already in childhood, compared with healthy boys. 46,XX-males were significantly shorter than healthy boys but matched the stature of healthy girls. In 47,XXY sitting height to height ratios were lower than expected, whereas body proportions in 46,XX-males and 47,XYY were normal. In all subjects serum levels of IGF-I and IGFBP-3 were within normal limits. The boys with 46,XX and 47,XXY karyotypes presented with low normal testosterone and elevated LH levels after puberty, whereas the sex hormone secretion of the 47,XYY boys remained normal.

Conclusion: We found accelerated growth in early childhood in boys with 47,XXY and 47,XYY karyotypes, whereas 46,XX-males were shorter than controls. These abnormal growth patterns were not reflected in circulating levels of IGF-I and IGFBP-3. The boys with 46,XX and 47,XXY karyotypes developed hypogonadism in puberty, but androgen secretion in 47,XYY boys remained normal. The abnormal stature of these patients may be a result of abnormal gene expression due to the underlying chromosome aberration resulting in excessive expression of growth-related genes. **(*J Clin Endocrinol Metab* 93: 169–176, 2008)**

Human growth is a highly complicated process influenced by genetic, hormonal, environmental, dietary, metabolic, and socioeconomic factors. It is well established that the interaction between sex steroids and the GH-IGF axis is of major importance in regulating linear bone growth. Although the interaction between sex steroids and the GH-IGF axis is of major

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Abbreviations: CV, Coefficient of variation; GA, gestational age; IGFBP, IGF binding protein; SDS, SD score; SHOX, short stature homeobox-containing gene; SRY, sex-determining region of the Y chromosome; T, testosterone.

importance in regulating growth, multiple genetic factors, especially located on the sex chromosomes, also play a role. Thus, it is commonly acknowledged that boys with 47,XXY karyotype tend to have eunuchoid body proportions due to increased childhood growth and end up with a final height above their predictions based on parental heights. However, these assumptions are based on a longitudinal study on height carried out more than 3 decades ago (1–5). A few recent studies evaluated maturation of the pituitary-gonadal axis in 47,XXY children (2, 6–8), but to our knowledge, the GH-IGF axis has been evaluated in only five patients with 47,XXY karyotype so far (2).

To describe the influence of supernumerary sex chromosomes on growth, we report longitudinal growth charts and serum levels of reproductive hormones, IGF-I and IGF binding protein (IGFBP)-3 in boys and adolescents with 47,XXY karyotype (n = 86), sex-determining region of the Y chromosome (SRY)-positive 46,XX-male syndrome (n = 14) and 47,XYY karyotype (n = 9) from birth to adulthood and discuss the possible underlying mechanisms.

Subjects and Methods

Subjects

Eighty-six boys and adults with nonmosaic Klinefelter syndrome (47,XXY), 14 boys with SRY-positive 46,XX karyotype, and nine boys with 47,XYY karyotype referred to our endocrine clinic were studied. The youngest boys and adolescents [47,XXY (n = 54), 46,XX-male (n = 9), and 47,XYY (n = 9)] were studied in a longitudinal follow-up. These boys were followed up with biochemical and clinical evaluation, including anthropometric measurements, every 6–12 months from referral. At the last follow-up, the median age of 47,XXY boys was 12.8 yr (range 1.06–19.8 yr); 46,XX-males, 15.3 (range 4.3–20.0 yr); and 47,XYY boys, 16.2 (range 9.2–20.0 yr).

Four boys [47,XXY (n = 3) and 47,XYY (n = 1)] were excluded from the study due to other diseases affecting growth and development (acute lymphatic leukemia, fragile X syndrome, achondroplasia, and congenital heart disease).

Twenty-six boys and adolescents from the longitudinal follow-up were diagnosed by amniocentesis prenatally (47,XXY, n = 22; 46,XX-male, n = 2; and 47,XYY, n = 2), whereas the remaining 45 boys were referred because of aberrant childhood/adolescent behavior and/or excessive growth.

None of the boys received androgen substitution during the follow-up period.

The adult patients with 47,XXY (n = 43), 46,XX-male (n = 9), or 47,XYY (n = 7) karyotypes served as a reference for final height in these syndromes. Twenty-two of these patients (11 boys with 47,XXY karyotype, four males with 46,XX, and seven 47,XYY) were also part of the longitudinal follow-up but had reached final height as defined by age above 16 yr and a height change less than 0.1 cm on three consecutive outpatient clinic visits. The remaining 32 47,XXY and five 46,XX males aged 30.2 (range 20.2–57.2) and 24.5 yr (range 20.6–40.1), respectively, were referred to our clinic in adulthood due to infertility (n = 16), gynecomastia (n = 3), or hypogonadism (n = 18). All adults were never treated with testosterone at the time of measurement.

Chromosome analysis was performed on peripheral blood lymphocytes. Karyotypes were established on 30 metaphases from each patient. All karyotypes were nonmosaic. All XX-males were SRY positive (detected by PCR). Prenatal diagnoses were confirmed postnatally.

Data on gestational age, birth weight, and birth length were obtained from the Danish Birth Register that was established in 1973 and was available in 66 subjects.

Anthropometric measurements

Standing and sitting height was measured to the nearest 0.1 cm using a stadiometer. Individual curves of height and sitting height to height ratio were plotted on standard charts of Danish children (9, 10).

The anthropometric data were expressed as SD scores (SDSs), which allow comparing the results of patients with different ages. The height SDSs of the 46,XX-males were compared with both male and female standards (9). Birth length SDSs were calculated only for the boys born at term [47,XXY (n = 51), 46,XX-male (n = 7), and 47,XYY (n = 8)] (9).

Target height based on measurements of both parents in our outpatient clinic was available in 34 boys with 47,XXY karyotype, six 46,XX-males, and eight 47,XYY boys. Target height was calculated as 0.5 ∗(height of the mother + height of the father) + 6.5 cm.

Biochemical evaluation

IGF-I and IGFBP-3 were measured with a RIA as previously described (11). For IGF-I, inter- and intraassay variations were 8.7 and 3.9%, respectively, and the limit of detection was 21 ng/ml. Inter- and intraassay variations were 7.3 and 3.5%, respectively, and the limit of detection was 300 ng/ml for IGFBP-3.

Serum total testosterone (T) was determined by RIA (Count-a-count; Diagnostic Products, Los Angeles, CA). The detection limit was 0.23 nmol/liter, and the intra- and inter CVs were both less than 10%. FSH, LH, and SHBG were measured by time-resolved fluoroimmunoassay (DELFIA; Wallac) with detection limit of 0.23 nmol/liter. Intra- and interassay CVs in the FSH, LH, and SHBG assays were all less than 6% in the full range. Estradiol was determined by RIA (Immunodiagnostic Systems, Bolton, UK) with a sensitivity of 18 pmol/liter. Intra- and interassay CVs were 7.5 and 12.9%, respectively. Inhibin B was determined using a specific two-sided enzyme immunometric assay from Oxford Bio-Innovation Ltd. (Oxford, UK). The sensitivity of the inhibin B assay was 20 pg/ml, and the intra- and interassay CVs were less than 12 and less than 17%, respectively.

Ethics

The patients and their parents (when the patient was < 18 yr of age) gave informed consent for clinical and biochemical follow-up. Data from routine clinical visits were obtained from patient records and used for this study. Registration of clinical data were approved by the Danish Data Protection Agency (2005-41-5479).

Statistics

Clinical and biochemical characteristics of the whole group are provided as median and 2.7 and 97.5 percentiles if not otherwise indicated. SDSs of anthropometric measurements were statistically compared with zero using the one-sample *t* test. All statistical analyses were carried out using the statistical software SPSS (version 13; SPSS, Inc., Chicago, IL).

Results

Anthropometric measurements

The individual growth curves of all subjects are presented in Fig. 1, including the final height of the adult patients. When comparing the height SDSs of prenatally and postnatally diagnosed 47,XXY and 46,XX-males, respectively, we found no difference (data not shown), and we therefore found it justifiable not to divide the boys according to the time of diagnosis, thereby creating bigger individual groups divided by karyotypes only.

Median gestational age (GA) at birth was 40 (34–42), 36.5 (28–40), and 39.5 (32–42) wk in 47,XXY boys, 46,XX-males, and 47,XYY, respectively. Four of 50 boys with 47,XXY karyo-

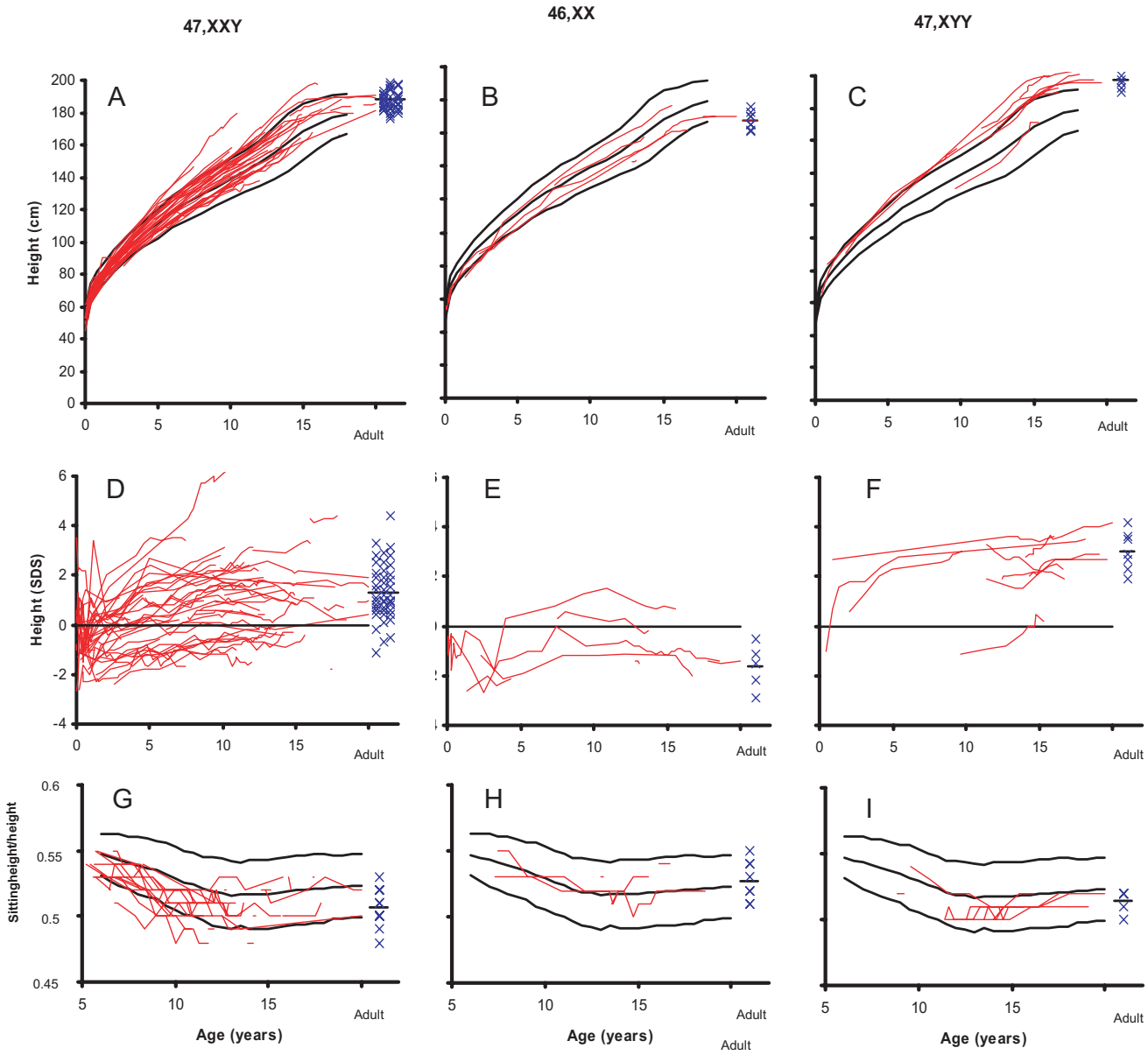

FIG. 1. Longitudinal growth charts and sitting height to height ratios in relation to chronological age in patients with Klinefelter syndrome (A and D), 46,XX male karyotype (B and E), and double Y syndrome (C and F). Final height and sitting height to height ratios of adult patients are indicated by *blue crosses*. The *lines on the crosses* indicate mean height for the adults. *Lines* represent mean ± 2 SD in healthy boys (9, 10).

type (7.8%) were born less than 37 GA, whereas three of six 46,XX-males (50%) and one of eight 47,XYY boys (12.5%) were born less than 37 GA.

There was a trend toward longer birth length in the 47,XXY and 47,XYY boys and shorter birth length in 46,XX-males, although none of these estimates reached statistical significance (Table 1).

47,XXY and 47,XYY boys exhibited accelerated growth from early infancy through childhood and adolescence (Fig. 1, A, C, D, and F). In Table 1 the individual measurements of these boys are divided into intervals of 2 yr of age. In one individual the mean value of all the measurements in each interval was calculated and used for comparisons. This revealed higher height SDSs than expected from the age of 6 yr and onward in 47,XXY, whereas height SDSs were increased at all ages in the boys with 47,XYY karyotype (Table 1 and Fig. 1, D and F).

In contrast, boys with 46,XX-male karyotypes were significantly shorter than the normative reference material (Fig. 1, B and E). This was already evident in infancy in which the height SDS was significantly reduced (Table 1). However, when comparing these males with healthy females, we found no difference (data not shown). As marked in Fig. 1, A and B, and Table 1, final height of the adult males with 47,XXY karyotype was equally increased, whereas final height in 46,XX-males was decreased.

Boys with 47,XXY karyotypes had increased leg length, whereas the XX-males and 47,XYY had normal body proportions when compared with healthy controls (Fig. 1, G–I). In 47,XYY boys, leg length was slightly increased around pubertal

TABLE 1. Height SDS in boys and adolescents with additional sex chromosomes

Age (yr)	47,XXY (n = 86)	46,XX-males (n = 14)	47,XYY (n = 9)
Birth	+0.2 (−1.4 to +2.7) [51]	−0.6 (−1.0 to +1.0) [7]	+0.4 (−1.5 to +1.8) [8]
0.1–1.9	−0.3 (−2.9 to +2.1) [35][a]	−1.0 (−2.6 to −0.8) [3]	+1.6 (+0.4 to +2.7) [2][b]
2–3.9	+0.2 (−2.2 to +2.0) [31]	−1.9 (−2.3 to −0.7) [4][a]	+1.4 (+1.0 to +1.8) [2]
4–5.9	+0.3 (−1.8 to +3.3) [30]	−1.5 (−2.1 to +0.3) [4]	+2.4 (+2.2 to +2.6) [2][b]
6–7.9	+0.5 (−1.5 to +4.5) [28][a]	−0.1 (−1.2 to +0.8) [4]	NA
8–9.9	+0.9 (−1.2 to +7.8) [29][a]	NA	NA
10–11.9	+0.9 (−1.5 to +6.2) [27][a]	−0.2 (−1.2 to +1.5) [4]	+1.9 (−1.0 to +3.2) [3]
12–13.9	+0.8 (−0.8 to +3.1) [20][a]	−0.8 (−1.5 to +0.9) [5]	+2.0 (−0.6 to +3.6) [5]
14–15.9	+1.1 (−0.6 to +4.3) [12][a]	−0.7 (−1.2 to +0.8) [4]	+2.3 (+0.2 to +3.5) [7][a]
16–17.9	+1.1 (−1.8 to +4.3) [9][a]	−1.4 (−1.8 to −1.2) [3][a]	+2.7 (+2.0 to +3.6) [7][b,c]
18–20	+1.3 (+0.2 to +2.1) [7][a]	−1.5 (−2.2 to −1.4) [3]	+3.2 (+2.7 to +4.0) [4][a,b]
Adult	+1.2 (−1.1 to +4.3) [43][a]	−1.5 (−2.9 to −0.5) [9][a]	+2.9 (+1.9 to +4.2) [7][a,b]
Target height SDS	+0.2 (−1.2 to +1.8) [34]	−0.1 (−1.8 to +2.2) [6]	+0.4 (−0.7 to +1.7) [8]

Results are presented as median (2.5 to 97.5 percentiles). *Brackets* indicate number of boys in each interval. NA, Not available.

[a] $P < 0.05$.

[b] $P < 0.05$, comparing SDSs of 47,XXY and 47,XYY boys (Mann-Whitney *U* test).

[c] $P < 0.0001$, when compared with healthy boys (one sample *t* test).

onset, but this seemed to change in adolescence during which the boys had normal sitting height to height ratios. However, we had only limited number of measurements of sitting height in 47,XYY boys.

The height SDSs at the last follow-up were significantly higher than target height SDSs in boys with 47,XXY and 47,XYY karyotypes ($P = 0.001$ and $P < 0.0001$, respectively), whereas height SDS in 46,XX-males was lower than the target height SDS ($P = 0.06$). There was no difference between the reference material and the target height SDS or between the target height SDSs of the three groups (Table 1).

Biochemical evaluation

Longitudinal evaluation of serum concentrations of IGF-I (SDS) and IGFBP-3 (SDS) is presented in Table 2. The individual measurements of these boys were divided into intervals of 2 yr of age. In one individual the mean value of all the measurements in each interval was calculated and used for comparison. At all ages 47,XXY, 46,XX, and 47,XYY boys had concentrations within the reference range.

Serum levels of T, FSH, LH, and estradiol in relation to chronological age are shown in Fig. 2, A–L. Until the time of puberty, the hormone levels of all subjects were within normal ranges

TABLE 2. IGF-I and IGFBP-3 (SDS)

Age (yr)	47,XXY (n = 86)	46,XX-males (n = 14)	47,XYY (n = 9)
IGF-I			
0–1.9	+0.1 (−2.2 to +2.8) [9]	NA	−1.0 (−1.0 to −1.0) [1]
2–3.9	+0.6 (−1.2 to +2.2) [8]	NA	NA
4–5.9	+0.4 (−1.3 to +1.5) [12]	NA	+1.3 (+0.4 to +2.2) [2]
6–7.9	+0.7 (−0.7 to +1.9) [11][a]	NA	+0.6 (+0.6 to +0.6) [1]
8–9.9	0.0 (−1.2 to +2.0) [19]	−1.4 (−1.4 to −1.4) [1]	+0.5 (−1.7 to +1.9) [6]
10–11.9	−0.6 (−2.2 to +1.1) [23][a]	−0.8 (−0.8 to −0.8) [1]	−0.2 (−1.0 to +1.1) [5]
12–13.9	−0.4 (−1.4 to +2.2) [17]	−0.3 (−0.7 to +0.5) [3]	+0.2 (−0.5 to +3.5) [9]
14–15.9	−0.8 (−2.1 to +0.9) [8]	−1.4 (−1.4 to +0.4) [2]	+0.5 (+0.8 to +0.8) [6]
16–17.9	−2.0 (−2.2 to −1.8) [2]	+1.4 (+1.4 to +1.4) [1]	+1.1 (−2.2 to +2.0) [7]
18–20	−0.9 (−2.6 to +0.6) [4]	−0.3 (−0.3 to −0.3) [1]	+1.0 (−0.6 to +1.1) [3]
IGFBP-3			
0–1.9	+0.3 (−0.6 to +1.8) 8]	NA	−0.4 (−0.4 to −0.4) [1]
2–3.9	+1.1 (−0.9 to +2.9) [8]	NA	NA
4–5.9	+0.5 (−0.6 to +1.8) [12][a]	NA	+2.5 (+1.7 to +3.3) [2]
6–7.9	+0.4 (−0.7 to +1.3) [11]	NA	+2.3 (+2.3 to +2.3) [1]
8–9.9	+0.3 (−1.6 to +1.9) [18]	−2.5 (−2.5 to −2.5) [1]	+0.9 (−1.4 to +1.8) [6]
10–11.9	−0.4 (−1.9 to +2.4) [23][a]	−1.3 (−1.3 to −1.3) [1]	−0.1 (−1.4 to +1.6) [5]
12–13.9	0.0 (−2.3 to +2.6) [19]	−1.5 (−3.4 to −0.6) [3]	+1.3 (−0.4 to +3.4) [9][a]
14–15.9	−0.9 (−2.0 to +2.1) [8]	+0.1 (−0.1 to +0.4) [2]	+1.4 (+0.1 to +3.6) [6][a]
16–17.9	−0.6 (−0.9 to −0.4) [2]	+0.2 (+0.2 to +0.2) [1]	+1.3 (−3.0 to +2.4) [7]
18–20	−0.9 (−1.2 to +1.3 [4]	−0.1 (−0.1 to −0.1) [1]	+1.1 (+1.1 to +1.1) [1]

Results are presented as median (2.5 to 97.5 percentiles). Number is in *brackets*. NA, Not available.

[a] $P < 0.05$ when compared with healthy 46,XY-males (one sample *t* test).

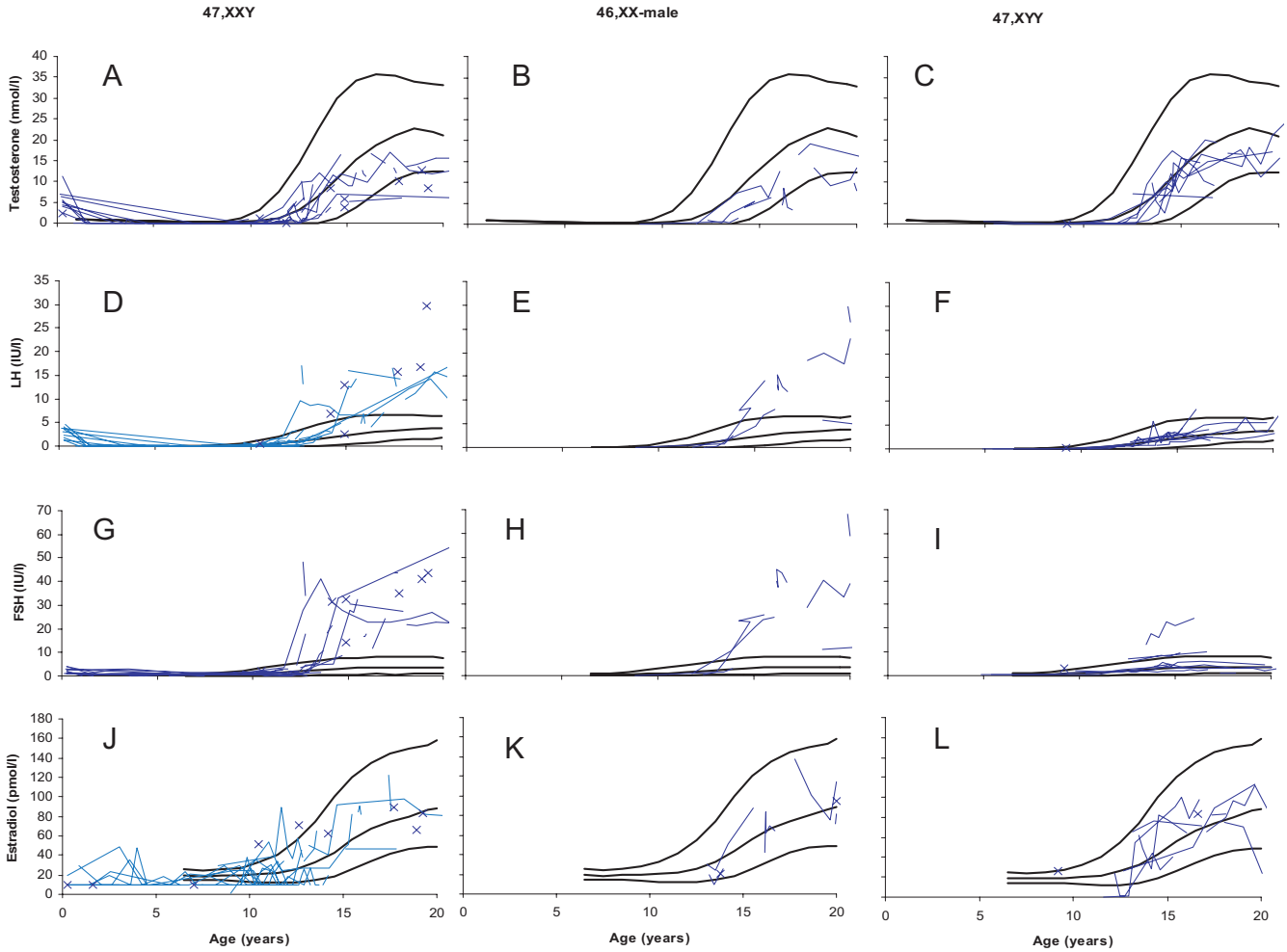

FIG. 2. Serum T, FSH, LH, and estradiol levels according to chronological age in patients with Klinefelter syndrome (A, D, G, and J), 46,XX-male syndrome (B, E, H, and K), and double Y syndrome (C, F, I, and L). *Lines* represent mean and ± 2 SD in healthy boys and adolescents (12). [Part of data on Klinefelter syndrome was previously published by Aksglaede *et al.* (44)].

when compared with our own laboratory reference for healthy children and adolescents (12). Thereafter, however, a relative hypogonadism was evident with low normal levels of T and elevated LH and FSH levels in the boys with 47,XXY and 46,XX karyotypes. In these boys inhibin B declined dramatically to undetectable levels at the time of puberty (data not shown). The levels of estradiol and SHBG were within normal ranges at all ages (data not shown).

The 47,XYY boys exhibited normal serum levels of the reproductive hormones, except one boy with extremely high FSH levels and immeasurable inhibin B.

Discussion

In our longitudinal follow-up of a large group of boys with sex chromosome abnormalities, we found accelerated growth from early childhood in boys with 47,XXY and 47,XYY karyotypes. By contrast, boys with SRY-positive 46,XX-karyotypes grew less than expected from their parental genetic potential and followed a growth pattern resembling that of healthy females. Boys with 47,XYY grew slightly faster, compared with the 47,XXY boys. These abnormal growth patterns were not reflected in circulating levels of IGF-I and IGFBP-3, which were normal, and the accelerated growth was apparent before any biochemical evidence of impaired testicular function during the pubertal maturation. Thus, other factors such as differences in gene expression due to the underlying chromosome aberration most likely plays a role for the excessive growth.

With the discovery of the short stature homeobox-containing gene (SHOX) in 1997 (13), a new perspective was added to the understanding of tall stature in patients with supernumerary sex chromosomes and the poor growth in Turner syndrome.

The SHOX gene is located on the distal part of the pseudoautosomal region 1 of the sex chromosomes, a region of the X chromosome escaping X inactivation (14). Because the SHOX gene is expressed from an inactive X chromosome as well as either an active X or a normal Y chromosome, it is present in two active copies in both males and females (15). It exerts the dosage effect in sex chromosome aberrations (13) and may therefore positively influence the stature in 47,XXY and 47,XYY syndromes, whereas haploinsufficiency or mutations of the SHOX gene may lead to short stature (13). SHOX is expressed in two major regions: the growth plate of the limbs and the pharyngeal

arches (16), implying that SHOX has a certain role in bone growth and maturation. Munns *et al.* (17) found expression of the SHOX gene in the growth plate from 12 wk of gestation until the fusion of the plates in late childhood suggesting that SHOX plays an important role for skeletal development and growth, especially the long bones.

The effect of SHOX overdosage has been reported by several authors (18–21), and it seems reasonable to suspect that triplicate of the SHOX gene in 47,XXY and 47,XYY syndromes explains their characteristic tall stature. This may also explain why this feature is already present before puberty.

The existence of an additional Y-specific growth gene has long been searched for. The potential growth control gene of the Y chromosome (GCY) is located in the pericentromeric region of the long arm of the Y chromosome, but to our knowledge no specific candidate genes have yet been identified (22). The presence of such gene(s) may explain several physiological phenomena: for example, the height difference between sexes and also the fact that our patients with 47,XYY syndrome were significantly taller than the 47,XXY boys. The XYY boys express a triplicate of the SHOX gene and a duplicate of possible Y-specific growth genes, whereas 47,XXY boys express the triplicate of the SHOX but only one copy of Y-specific growth genes.

In contrast, 46,XX-males most probably exhibit only two copies of the SHOX gene and no Y-specific growth genes, leaving these patients shorter than healthy males, as reported here and by Ogata and Matsuo *et al.* (23). However, when comparing these males with healthy females, we found, like others (24, 25), no difference between height SDSs. It seems reasonable that the growth pattern of 46,XX males resembles that of females because the SHOX gene constitution is most likely the same. It must be emphasized that small sampling sizes [n = 9 and n = 10 (24)] have to be taken into account when making conclusions about these data.

47,XXY boys have usually been described as short at birth (5, 26, 27). We found normal birth length but impaired growth during the first 2 yr of life. We found no medical explanation for this failure to thrive. However, height was normal during childhood until the age of approximately 6 yr at which growth was significantly accelerated with further growth acceleration at the time of puberty. As previously reported (3–5), the height of the 47,XXY boys was significantly increased, compared with healthy boys, already before pubertal onset. As many previous authors, we found significantly higher height SDS in the adult patients with 47,XXY karyotype (Table 1 and Fig. 1).

Data on birth length in 47,XYY boys are contradicting. We, like others (28), found normal birth length, whereas others reported increased birth length (29) in 47,XYY boys. These results must be seen in the light of the small sample sizes. From birth through early infancy, these boys presented accelerated growth with an acceleration that was more aggressive and occurring earlier than in the 47,XXY boys. The 47,XYY boys were taller than controls at all ages. The early reports on 47,XYY were mainly based on studies of tall males and may therefore be biased against increased height. However, in our study only three of the nine boys with 47,XYY karyotypes were diagnosed due to excessive growth, whereas the remaining were diagnosed prenatally (n = 2) or due to aberrant childhood/adolescent behavior (n = 4), minimizing such bias.

The boys with 47,XYY karyotypes all had normal reproductive hormones except one boy with extremely high FSH levels and immeasurable inhibin B. Although testicular biopsies were not available, his biochemistry was in accordance with the presence of Sertoli-cell-only syndrome, which has been described in 30% of boys with double Y syndrome (30). His hormones were otherwise unaffected.

Short stature is a cardinal feature of the SRY-positive 46,XX-male (1, 25, 31, 32). In our 14 cases of SRY-positive 46,XX-maleness, we found growth retardation from birth to adulthood. Interestingly, we found no difference between the height of the XX-males and healthy females, although previous studies have found 46,XX-males to be taller than normal females (31, 32), whereas others confirm our finding (25).

We found eunuchoid body proportions in 47,XXY boys as indicated by the low sitting height to height ratios (Fig. 1G) in accordance with previous reports (1, 2, 33–35). Long-leggedness is a well-known clinical feature of male hypogonadism. It has been suggested that growth of the upper segment in boys is mainly due to androgens (36), and the disproportion of the body segments in the 47,XXY boys might thereby theoretically be caused by an impaired growth of the trunk. On the other hand, others have suggested that the increased leg length in 47,XXY to be caused by delayed epiphyseal closure as a consequence of decreased androgen levels (37), but we and others (3, 4, 33, 38) found that the eunuchoid body proportions were present before puberty, which excludes impaired androgen secretion as the only cause of eunuchoidism. The normal body proportion in 46,XX-males in conjunction with their 47,XXY-like hormonal status adds further to the hypothesis that the long-leggedness may be a consequence of the triplicate of the SHOX gene rather than an impaired androgen secretion. However, boys with 47,XYY karyotype had normal body proportions in conjunction with the three copies of SHOX, which may indicate that the extra Y chromosome, may be the reason these boys have preservation of sitting height relative to standing height.

Estradiol plays an important role in epiphyseal maturation, normal skeleton proportions, and bone mineralization in both sexes (for review see Ref. 39). It has a biphasic effect on epiphyseal growth, with stimulation of linear growth at low concentrations and closure of the epiphyseal plates and cessation of linear growth at higher concentrations. The pubertal increase in growth velocity associated with increased GH secretion has traditionally been attributed to testicular androgen secretion in boys and to estrogens or adrenal androgen secretion in girls. It has, however, been established that androgens influence the GH axis only after aromatization into estrogens (40). Thus, estradiol is probably the principal hormone stimulating the pubertal growth spurt in boys as well as girls. The levels of estradiol in our patients were within normal ranges at all times (Fig. 2, J–L). However, this reflects only the circulating estradiol and not the actual activity of estradiol in peripheral tissues such as bone. If local aromatization of T to estradiol is impaired, this might result in a relative delay in epiphyseal closure.

It has been suggested that the increased height in 47,XXY

karyotype could be due to impaired androgen secretion and thereby delayed epiphyseal closure (37). This study, however, like others (3, 4, 41, 42), has shown that the increased height is already present before puberty and thus cannot be related to epiphyseal closure alone. Patients with 47,XXY karyotype usually enter puberty at the expected time (2, 6, 43), with an initial rise in the serum level of T, which, however, remains at a level in the low normal range in combination with hypergonadotropism soon after puberty (Fig. 2, A, D, and G).

One study revealed a significant negative correlation between serum T level and length of the lower body segment and the lower to upper segment ratio in 25 adult patients with 47,XXY karyotypes (37). Dividing the 25 47,XXY patients of that study into two groups of low serum testosterone *vs.* normal serum testosterone levels, Smals *et al.* (37) found significantly longer legs and height in the androgen-deficient group, compared with both the controls and the 47,XXY patients with normal testosterone levels. However, our patients with 47,XYY were even taller than the 47,XXY subjects and had normal T and LH secretion at all times (Fig. 2, C, F, and I), adding further to the hypothesis that factors other than androgen deficiency may influence the excessive growth rate in these patients.

Measurements of the circulating IGF-I and IGFBP-3 levels reflect the integrated GH secretion. GH and thereby IGF-I and IGFBP-3 are known to increase in puberty along with the increasing androgens and estrogens. Children with tall stature have higher IGF-I and IGFBP-3 levels, compared with normal-statured children (11). As seen in Table 2, we found normal levels of both IGF-I and IGFBP-3 in all subjects. Previous reports on GH and IGF-I secretion, including 12-h nocturnal GH profiles in four boys with 47,XXY karyotype have shown normal secretion and pulsatility of the two hormones in relation to height velocity and pubertal stage (2).

In conclusion, in our longitudinal study of a large cohort of male patients with sex chromosome abnormalities, we found increased linear growth in patients with 47,XXY and 47,XYY karyotypes and impaired growth in SRY-positive 46,XX-males. Patients with 47,XXY were eunuchoid, whereas patients with 47,XYY and 46,XX karyotypes had normal body proportions. Importantly, these abnormal growth patterns were not reflected in the circulating levels of IGF-I and IGFBP-3 and did not seem to be solely related to lowered androgen secretion because the 47,XYY boys had normal pituitary-gonadal function, whereas the 47,XXY boys developed hypogonadism after puberty. The described features are already present before puberty, giving strength to the hypothesis that the abnormal statures of these patients are results of the chromosome aberration and the abnormal expression of growth-related genes on the sex chromosomes.

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