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Deletions within the Pseudoautosomal Region Help Map Three New Markers and Indicate a Possible Role of This Region in Linear Growth

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Summary

Short stature is consistently found in individuals with terminal deletions of Xp. In order to refine the localization of a putative locus affecting height, we analyzed two patients with a partial monosomy of the pseudoautosomal region at the molecular level. Eight pseudoautosomal probes were used for the genetic deletion analysis through dose evaluation. Three of them represent new markers (DXS415, DXS419, and DXS406) which were positioned on the pseudoautosomal map by pulsed field gel electrophoresis. Our data suggest that a locus affecting height maps in a region of about 1.5 Mbp, distal to the DXS406 locus and proximal to the DXS415 locus, a region which includes two CpG islands, and rule out an involvement of very distal sequences at the X/Y telomeres.

Introduction

Terminal deletions of the chromosomal region Xp22.3 and distal Yp of the human sex chromosomes consistently result in short stature in affected individuals (van den Berghe 1977; Zuffardi et al. 1982; Fryns and Berghe 1983; Bernstein 1985). Larger deletions in the Xp22-pter region, however, have been associated with a number of clinical features, also known as contiguous-gene syndromes (Ballabio et al. 1989). These interstitial and terminal deletions cosegregate with a variety of phenotypical X-recessive abnormalities, such as ichthyosis, Kallmann syndrome, recessive chondrodysplasia punctata, mental retardation, and short stature—which allow the construction of a deletion map (Ballabio et al. 1989). This deletion map places short stature within the pseudoautosomal region.

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In order to further refine the chromosomal location of this factor which controls growth, we analyzed two individuals having small deletions within the pseudoautosomal region. Individuals with a partial monosomy of the pseudoautosomal region seem to be rare and are only detected if the deletion happens to occur with other chromosomal (as in the two cases studied) or clinical anomalies.

We used eight pseudoautosomal probes, three of which represent new pseudoautosomal markers, to characterize the chromosomal breakpoints of the two patients. These markers were grouped with the existing markers by a genetic deletion analysis and were physically mapped by pulsed field gel electrophoresis (PFGE) analysis. Our deletion analysis suggests (*a*) that the very distal sequences at the X/Y telomeres are not involved in linear growth and (*b*) a possible role for the middle portion of the pseudoautosomal region.

Material and Methods

DNA Probes

All pseudoautosomal probes used in the genetic and PFGE analysis are listed and described in table 1. Of these, three are newly derived markers. P99, P131,

Table 1

List of Molecular Probes Used in Genetic and PFGE Mapping Analysis

Probe	Locus	Description	Size (kb)	Reference
29A24	DXYS20	*Hin*dIII	2.5	Cooke and Smith 1986
U7A	DXYS60	*Eco*RI/*Hin*dIII	.23	Rouyer et al. 1987
P99	DXS415	*Pst*I	1.0	Wapenaar et al. 1989
P131.....	DXS419	*Pst*I	1.0	Wapenaar et al. 1989
113D.....	DXYS15	*Eco*RI/*Hin*dIII	.55	Simmler et al. 1985
P12	DXS406	*Pst*I	.24	Wapenaar et al. 1989
602	DXYS17	*Eco*RI/*Hin*dIII	1.0	Simmler et al. 1985
44C1.2	MIC2	*Pst*I/*Eco*RI	1.2	Goodfellow et al. 1988

and P12 are subclones isolated from hybrid TG5sc9.1 containing the Xp21-Xpter/Xcen region as its sole human material (Wapenaar et al. 1990). They were mapped to the Xp22.3 region by using two hybrids, TG2 (Xp21-Xpter) and 445x393 (Xqter-Xp22.3), and will be described in detail elsewhere. Insert preparations and hybridization conditions have been reported elsewhere (Herrmann et al. 1987).

DNA Sources and Analysis

DNA for PFGE analysis was prepared from human peripheral lymphocytes (from individual AH; 46,XX) in agarose blocks. The methods of PFGE, digestions, and DNA transfer have been described elsewhere (Herrmann et al. 1986, 1987). Electrophoresis was carried out in an LKB 2015 Pulsaphor equipped with an OFAGE system.

Genomic DNA isolated from peripheral lymphocytes from the following individuals was analyzed: one individual (GC) with an X/Y translocation, one individual (CC) with a psudic(X), one normal female (46,XX), one normal male (46,XY), and two Turner individuals (45,X). DNA also was isolated from two somatic cell hybrid lines, 445 x 393 and 697 x 175, with deletions involving Xp22.3 (Goodfellow et al. 1983; Wieacker et al. 1984; Mondello et al. 1987; Ballabio et al. 1990).

The hybrid 445 x 393 contains a human X chromosome with a breakpoint proximal to both DXS31 and STS (Ballabio et al. 1990). 697 x 175 contains an X chromosome with a breakpoint within Xp21; the chromosomal material distal to the breakpoints has been lost.

Description of Patients GC and CC

GC is a Klinefelter patient (age 33 years) with the karyotype 46,X,t(X;Y) (Xqter→Xp22.3:Yp11→Yqter), clinically described by Zuffardi et al. (1982). The patient has three sex chromosomes with an X/Y translocation. Despite the Klinefelter syndrome, normally associated with an increase in height, he exhibits short stature (height 155 cm) which might be due to a monosomy of distal Xp and Yp. The father's height was 165 cm, and the mother's was 154 cm; all of his brothers were taller than the father, and all of his sisters were taller than the mother (Zuffardi et al. 1982). X-specific probes defining loci on Xp22.3 have already been tested and are all present in double or triple doses. The pseudoautosomal marker MIC2 represents the most distal probe used in this analysis and is present in triple or double doses (Ballabio et al. 1989).

CC is a girl born at term from healthy and nonconsanguineous parents. Birth weight was 2,090 g (<3d %-centile). She is the second of a sibship of two, and her older sister died at 3 mo of age from meningitis.

At the first examination (3 mo of age) her length was 53 cm, her weight was 3,800 g, and her head circumference (OFC) was 35 cm (all <3d %-centile). At the second examination (8 mo of age) her length was 67 cm and her weight was 7,700 g (both 25th–50th %-centile), while her OFC was 41 cm (<3d %-centile). Clinical examination showed microcephaly, antimongoloid slant, hypertelorism, hypoplastic inferior maxilla, low-set ears, and umbilical hernia. At the last examinations (6 and 6½ years of age) her height was noted to be 114 cm between 25th–50th %-centile). Her mother's height was 155 cm. The father was not available for analysis.

Endocrinological investigations gave the following results: T3 = 224 ng/100 ml, T4 = 7.0 μg/100 ml, TSH = 3,5 μn/ml, cortisol = 7.9 μg/100 ml, LH = 1.4 mU/ml, FSH = 26.5 mU/ml, PRL = 29.5 ng/ml, progesterone = 4.7 ng/ml, 17-ketosteroids = 0.5

mg/320 ml, and 17-corticosteroids = 1.5 mg/320 ml, which indicates that both FSH and PRL are raised.

Chromosome investigations were performed on cultured lymphocytes and on fibroblasts from a skin biopsy. The karyotype was 45,X/46,Xpsudic(X) (Xqter→Xp22.3:p22.3→qter). The cells with monosomy X were seven (29%) of the 24 in blood and four (3%) of 121 in fibroblasts. Studies of chromosome replication patterns by autoradiography after BrdU treatment showed that the abnormal chromosome was consistently late replicating. The mother had a normal karyotype.

Results

DNA from the two patients GC and CC, one with an X/Y translocation and short stature and one with a psudic(X) chromosome and normal size was digested with *Eco*RI and analyzed by Southern blotting. It is assumed that both carry a deletion of a portion of the pseudoautosomal region.

The size of their deletions on Xp22.3 was characterized by hybridization with eight different pseudoautosomal probes (see table 1). All of the probes were consecutively hybridized on the same filter. Figure 1 shows the result of this experiment, demonstrating the breakpoint regions in both GC and CC. This figure was used for the densitometric analysis (see table 2). Dosage comparison reveals two copies of the locus DXS406 (probe P12) in patient GC compared with controls (see fig. 1*A*). All loci distal to DXS406 are present in one dose in individual GC (data of DXYS20 and DXYS60 are shown in fig. 1*B*). This suggests that GC (the patient with short stature) has a terminal deletion distal to DXS406 and that the breakpoint of this deletion resides between DXS406 (P12) and DXS419 (P131).

Of all tested pseudoautosomal markers only locus DXYS20 is present in single doses in patient CC, as shown in figure 1*A* and *B*, with markers DXS406 (P12), DXS419 (P131), DXYS60 (U7A), and DXYS20 (29A24). The breakpoint on the X chromosome of patient CC therefore resides between DXYS60 (U7A) and DXYS20 (29A24). Because of the normal height of patient CC this argues against a contribution by the most distal loci at the X/Y telomere in the generation of short stature.

In order to position the three newly derived markers DXS415, DXS419, and DXS406 on the physical map of the pseudoautosomal region, long-range PFGE

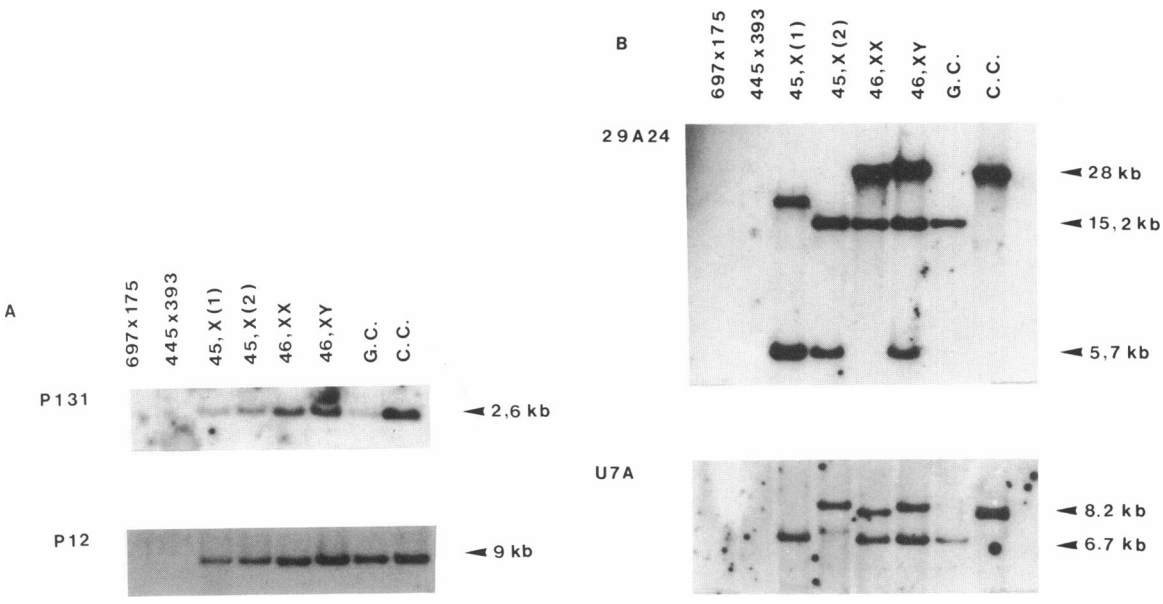


Figure 1 *A*, Pseudoautosomal probes P131 and P12 hybridized to *Eco*RI-digested DNA from two individuals, GC (G.C.) and CC (C.C.), with Xp22.3 terminal deletions. A number of controls (46,XX, 46,XY, 45,X(1), 45,X(2), 445x393, and 697x175) were included in the analysis. 46,XX, 46,XY, and 45,X represent DNA from normal male and female lymphocytes and from Turner individuals; 445x393 and 697x175 represent cell lines which lack the Xp22.3 region (Goodfellow et al. 1983; Wieacker et al. 1984; Mondello et al. 1987). P12, Results with double doses in GC. P131, Results with single doses in GC. *B*, Pseudoautosomal probe U7A present in double doses in CC, 29A24 present in single doses in CC, and 29A24 and U7A present in single doses in GC.

Table 2

Densitometric Analyses

Probe	Relative Band Intensities in					
	45,X(1)	45,X(2)	46,XX	46,XY	GC	CC
29A24	1.32	1.02	1.52	2.14	.31	.98
U7A	.93	1.08	1.64	2.34	.36	1.92
P131.....	.58	.81	1.91	2.69	.51	2.87
P12	.66	1.02	1.84	2.49	1.51	2.48

NOTE.—The autoradiographic film in fig. 1*A* and *B* was scanned using a transmission densitometer (computing densitometer model Elscript 400; Fa. Hirschman). To determine the dosage difference in hybridization, DNA of approximately equal amounts was used on each lane; however, DNA of patient GC was underloaded. The *area* under the scanned peaks of each hybridization represents the hybridization intensity of each hybridization band (band intensities). For each probe, band intensities of the control persons were summed up and divided by 6. The resulting value was taken as the standard single intensity peak value for one X or Y chromosome (270 for 29A24, 73 for U7a, 27 for P131, and 32.5 for P12). The single values were then divided by the respective standards, resulting in the relative band intensities. SDs of the relative band intensities among the controls are as follows: 29A24, .21; U7A, .16; P131, .67; and P12, .23.

mapping was carried out. Table 3 summarizes the fragment sizes obtained with *Not*I, *Bss*HII, *Sal*I, *Nru*I, *Cla*I, and *Eag*I restriction endonucleases when DNA was probed with markers 29A24 (DXYS20), P99 (DXS415), P131 (DXS419), 113D (DXYS15), P12 (DXS406), and 602 (DXYS17).

Physical linkage was detected between P12 (DXS406) and 602 (DXYS17). P12 and 602 both hybridize to the following complete or partial fragments: 900-kb *Not*I; 750-kb *Bss*HII; 1,100-kb *Sal*I; 180-, 320-, 400-, 430-, 740-, and 790-kb *Cla*I and 320-, 350-, and 750-kb *Eag*I (see table 3). The top two panels of figure 2 show several of the mentioned fragments; however, the 900-kb *Not*I and 1,100-kb *Sal*I fragments remain in the limiting mobility (LM) of the gel. The fragments derived with *Cla*I/*Sal*I are identical to the ones derived only with *Cla*I (data not shown). The smallest fragment shared between P12 and 602 represents a 180-kb *Cla*I fragment. This indicates that P12 and 602 are maximally 180 kb apart.

Physical linkage was also determined between 113D (DXYS15) and P131 (DXS419). They share the following fragments: 800-kb *Not*I; 800-kb *Bss*HII; 260- and 680-kb *Sal*I; 590- and 800-kb *Nru*I; 650- and 800-kb *Cla*I; and 350-, 610-, 700-, and 800-kb *Eag*I (see table 3). *Cla*I and *Eag*I, however, also distinguish between both loci, as a 190-kb *Cla*I fragment and a 170-kb *Eag*I fragment of P131 are not seen with 113D and a 90-kb *Eag*I fragment of 113D is not seen with P131. This indicates that P131 is located 500–670 kb from the telomere, and it independently confirms previous assignments of 113D to bp 670–760 (Brown 1988; Petit et al. 1988).

The many small fragments that 29A24 (DXYS20) and P99 (DXS415) exhibit with different infrequently cutting restriction enzymes place them within the most distal 500 kb next to the telomere (Brown 1988; Petit et al. 1988; Rappold and Lehrach 1988). In agreement with those data they share several partial fragments, e.g., 470-kb *Not*I, 470-kb *Sal*I, a 470-kb *Nru*I, and 420- and 470-kb *Cla*I (see fig. 2, *top two panels*). No physical linkage can be detected between the *Eag*I fragments of both markers. 29A24 was positioned 25–30 kb from the telomere (Cooke and Smith 1986). P99 does not share either a 300-kb *Cla*I and any of the small *Not*I, *Sal*I, and *Bss*HIII fragments with 29A24. It detects two small *Cla*I fragments of 50 and 130 kb, a 300-kb *Sal*I fragment, a 250-kb *Bss*HII fragment, and a 220-kb *Nru*I fragment. Our data therefore position P99 (DXS415) 350–470 kb from the telomere.

Discussion

In order to more precisely define, at the molecular level, the Xp region of a stature-controlling factor, dosage analysis has been used for the characterization of two patients having a partial monosomy of the pseudoautosomal region. Patients with small terminal deletions of the sex chromosomes are very rare and are available only if the deletion happens to occur together with other chromosomal (or clinical) anomalies (Kalousek 1979; Zuffardi et al. 1982; Kaffe et al. 1983; Geller et al. 1986; Mondello et al. 1987; Ballabio et al. 1989), as observed in the two patients analyzed in the present study.

We used eight pseudoautosomal probes to characterize the chromosomal breakpoints of the two patients GC and CC. Three of the probes (P99, P12, and P131) represent new markers which have been grouped with existing markers by the genetic deletion analysis. The physical mapping of these new markers has been achieved by PFGE. Physical linkage of P99 to 29A24, P12 to 602, and P131 to 113D could be demonstrated through several shared fragments. Our data position P99 (DXS415) at 350–470 kb, P131 (DXS419) at 500–670 kb and P12 (DXS406) at

Table 3

Summary of Fragment Sizes

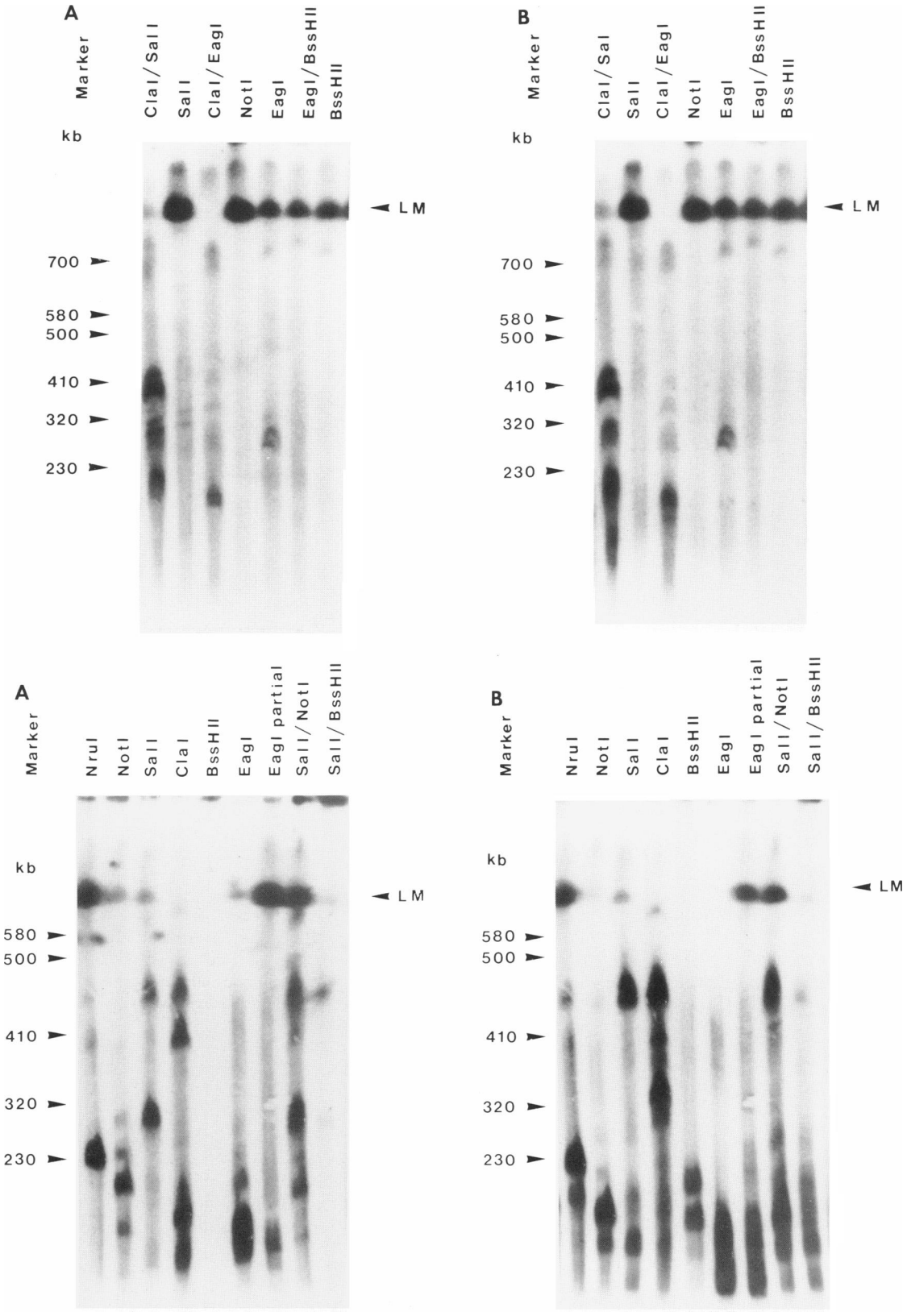
Probe (locus)	Fragment Size Resulting from Digestion With[a]					
	*Not*I	*Bss*HII	*Sal*I	*Nru*I	*Cla*I	*Eag*I
29A24 (DXYS20).....	(100)	(80)	(50)	(180)	(300)	30
	150	140	90	250	340	70
	(230)	(220)	(170)	470	(380)	120
	(280)		470		(420)	
	(470)				470	
P99 (DXS415).....	(120)	250	300	220	50	(100)
	190		470	470	130	130
	(250)				(420)	190
	(320)				470	
	(370)					
	(470)					
P131 (DXS419).....	800	800	260	590	190	170
			(680)	(800)	(650)	(260)
					(800)	(350)
						(610)
						700
						800
113D (DXYS15)	800	800	260	590	(340)	90
			(680)	(800)	430	(180)
					(470)	(350)
					(650)	440
					(800)	610
						700
						800
P12 (DXS406)	900	750	1100		180	320
					320	(350)
					400, 430	(750)
					(740)	
					(790)	
602 (DXYS17).....	900	750	1100		180	320
					320	(350)
					400, 430	(750)
					(740)	
					(790)	

[a] Fragment sizes are in kilobase pairs. Weak bands (which are considered to represent partials) are in parentheses; strong bands are not in parentheses. Fragments identified by two different probes are underlined. To confirm identity of bands recognized by two probes, several gels were run using different resolutions for different size ranges.

1,700–2,000 kb from the telomere and confirm previous assignments of 113D (DXYS15) and 602 (DXYS17) (Brown 1988; Petit et al. 1988).

As suggested by our study of individual CC, who has normal stature, the most telomeric sequences do not contribute to growth retardation. Data derived on the monosomic region found within patients GC and CC suggest that a locus affecting height maps in a region of less than 1.5 Mbp, distal to DXS406 which is present in double doses in patient GC (who has short stature) and which is proximal to the DXS415 and DXS419 loci, which are monosomic in patient GC.

To our knowledge, only two other patients with breakpoints within the pseudoautosomal region have been analyzed (Page et al. 1990; Petit et al. 1990; table 4). In patient PORa, who has short stature and an


A
Marker
ClaI/SalI
SalI
ClaI/EagI
NotI
EagI
EagI/BssHII
BssHII
kb
700
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320
230
LM
B
Marker
ClaI/SalI
SalI
ClaI/EagI
NotI
EagI
EagI/BssHII
BssHII
kb
700
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LM
A
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NotI
SalI
ClaI
BssHII
EagI
EagI partial
SalI/NotI
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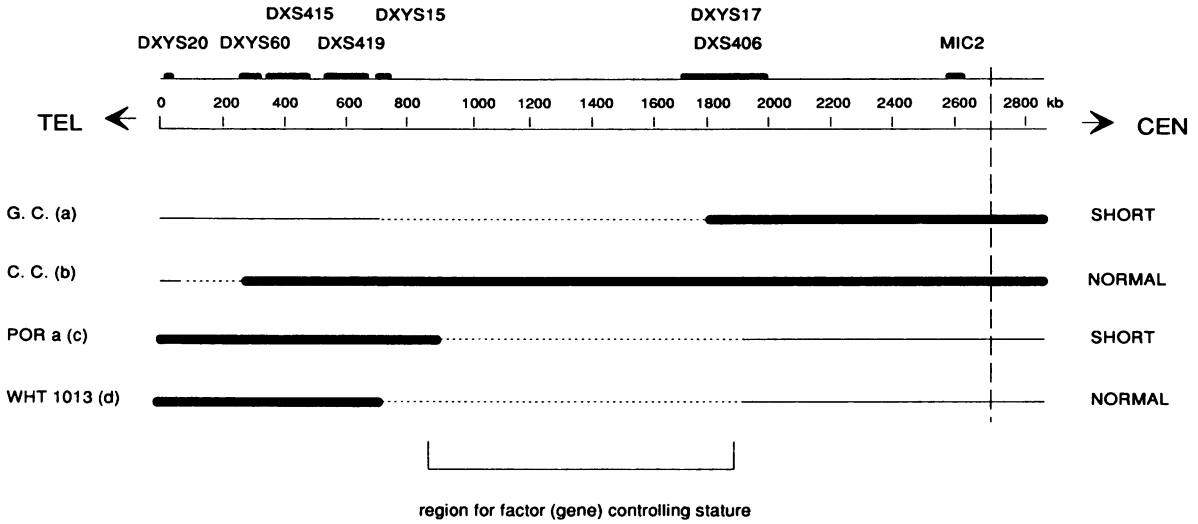

Figure 3 Diagram showing presence of pseudoautosomal probes in four different individuals with deletions within pseudoautosomal region. GC (G.C.) and CC (C.C.) represent the patients analyzed in our study. The data on patients PORa and WHT 1013 were taken from the literature (see table 3). The thick lines denote double doses of tested probes, and the fine lines denote single doses. The dotted lines mark the regions where a doses analysis has not yet been done, because of lack of markers.

Table 4

Patients with Terminal or Interstitial Deletions Involving Subregions of Pseudoautosomal Region

Case	Karyotype	Deletion
GC[a]	46 X,t(X;Y) (Xqter→Xp 22.3: Yp 11→Yqter)	Terminal
CC[b]	46,Xpsudic(X) (Xqter→Xp22.3: p22.3→qter)	Terminal
PORa IV[c]	46, XY male	Interstitial
WHT 1013[d]	46, XY female 46,X,t(Y;22)(p11.2;q11)	Interstitial

[a] Sources: Ballabio et al. (1989) and present study.
[b] Source: present study.
[c] Source: Petit et al. (1990).
[d] Source: Page et al. (1987, 1990).

interstitial deletion within Xp22.3, the distal extremity of the pseudoautosomal region spanning at least 900 kb is present on the deleted X chromosome. The deletion described by Petit et al. (1990) has one of the two breakpoints within the pseudoautosomal region but extends into the X-specific region (Petit et al. 1990). Individual WHT 1013, who has normal stature and has been described by Page et al. (1990), has a breakpoint between DXYS15 and DXYS17 on the deleted Y chromosome, a breakpoint which we would expect to reside within the pseudoautosomal region and proximal to a putative gene that affects linear growth (see fig. 3). The other breakpoint resides in the Y-specific region.

The results obtained by these authors, together with the data presented here, make it possible to further

Figure 2 *Top two panels,* PFGE analysis of DNA isolated from blood of female (AH 46,XX). High-molecular-weight DNA samples were digested with *Sal*I, *Not*I, *Eag*I, *Bss*HII, *Cla*I, and combinations of these. Electrophoresis was carried out for 40 h in a 0.9% agarose gel at an electric field gradient of 7.5 V/cm at 14°C. Separation of DNA fragments up to 750 kb was obtained by electrophoresis with a pulse time of 60 s. Filters were analyzed by hybridization with the probes P12 (DXS406) (*left*) and 602 (DXYS17) (*right*). *Bottom two panels,* PFGE analysis of peripheral lymphocytes of individual AH. Restriction digests by *Nru*I, *Not*I, *Sal*I, *Cla*I, *Bss*HII, *Eag*I, and combinations of these were probed by P99 (DXS415) (*left*) and 29A24 (DXYS20) (*right*). *Bss*HII-derived fragments with probe P99 remain invisible on this filter. Electrophoresis was carried out for 40 h in a 0.9% agarose gel at an electric field gradient of 7.5 V/cm at 14°C. Separation of DNA fragments up to 600 kb was obtained by electrophoresis with a pulse time of 45 s.

refine the localization of a putative locus controlling height, to within a region of about 950 kb and proximal to locus DXYS15 and distal to locus DXYS17 (see fig. 3). This region includes two CpG islands (Bird 1986) and a GM-CSF receptor gene, which has been localized to this region by genetic recombination analysis (Gough et al. 1990).

In humans, growth retardation has been associated with monosomy of a number of specific chromosomal subregions. One may, therefore, argue that short stature represents a general aspect of a partial monosomy, with a required minimal loss of DNA. In our case the loss of less than 1.5 Mbp would have been sufficient to retard growth. This argument, however, does not apply to monosomies of many other chromosomal subregions, in which the loss of DNA has no effect on growth. It is therefore possible that different, yet specific, genes—when they are monosomic—may lead into the same developmental pathway.

Fisher et al. (1990) recently suggested that the haploinsufficiency of one gene (a ribosomal protein gene) may cause (or contribute to) the overall picture of the Turner phenotype. An alternative view would see the complex and diverse phenotype of the 45,X Turner individuals (Turner 1938; Ferguson-Smith 1965; Rosenfeld 1989) as the consequence of the haploinsufficiency of a number of genes involved. One of these genes, affecting growth in Turner individuals, may reside in the pseudoautosomal region, within DXYS15 and DXYS17. This would help to explain the phenotype of a 46,XY female with true Turner stigmata and an interstitial deletion of interval 1 and 2 on the short arm of the Y chromosome (Affara et al. 1987; Levilliers et al. 1989). Despite typical Turner features, she has normal stature, which possibly reflects the existence of both intact pseudoautosomal regions. Further work in that region should help to clarify that question.

Note added in proof.—The D numbers DXS406, DXS419, and DXS415 of markers P12, P131, and P99 were changed at the recent Human Gene Mapping Conference HGM11 by the chairmen of the Y chromosome committee. The new D number of P12 is DXYS85, of P131 is DXYS86, and of P99 is DXYS87.

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