

# Chromosomal localisation of a pseudoautosomal growth gene(s)

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## Abstract

**Although recent molecular studies in patients with sex chromosome aberrations are consistent with a growth gene(s) being present in the pseudoautosomal region (PAR), the precise location has not been determined. In this report, we describe a Japanese boy and his mother with an interstitial deletion in Xp22.3 and review the correlation between genotype and stature in six cases of partial monosomy of the PAR. The results indicate that the region from DXYS20 to DXYS15 is the critical region for the putative growth gene(s).**

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Karyotype-phenotype analysis in patients with X chromosome rearrangements suggests the presence of a growth gene(s) at the tip of Xp.<sup>1-3</sup> In particular, Curry *et al*<sup>3</sup> have shown that a deletion of Xp22.32-pter results in significant short stature. Similar analysis of Y chromosome rearrangements is also consistent with a growth gene(s) being located at the tip of Yp, distal to the testis determining gene, TDF.<sup>14</sup> As TDF has been shown to be equivalent to SRY and is located only 5 kb from the pseudoautosomal boundary,<sup>5</sup> these results argue that the growth gene(s) resides in the pseudoautosomal region (PAR). The association between short stature and terminal deletions within the PAR has provided strong support for this localisation.<sup>6-8</sup> However, the precise position of the growth gene(s) within the PAR has not been determined. Henke *et al*<sup>7</sup> have suggested that the growth gene(s) is located in the middle part of the PAR, on the basis of two patients analysed and two published cases.<sup>9,10</sup> In contrast, Ogata *et al*<sup>8</sup> have proposed that the growth gene(s) is present in the distal part of the PAR, based on the study of a subject with a terminal Xp deletion distal to DXYS15.

In this report, we describe a Japanese boy and his mother with an interstitial deletion in Xp22.3, and review the correlation between genotype and stature in six cases of partial monosomy of the PAR.

## Case report

This 11 year old boy has previously been described as suffering from a contiguous gene syndrome involving X linked recessive chondrodysplasia punctata (CDPX) and steroid sulphatase (STS) deficiency.<sup>11</sup> His clinical manifestations included nasal hypoplasia, short digits, and ichthyosis. The diagnosis of CDPX was established by the neonatal radio-

graphs showing stippled calcifications of multiple epiphyseal centres. The diagnosis of STS deficiency was confirmed by the absence of STS activity in lymphocytes. Kallman syndrome was excluded by the lack of anosmia and hypogonadism. Mental retardation was equivocal. Biochemical studies and ophthalmological examinations were normal.

The parents and the younger brother were clinically normal. STS activity detected in the mother's lymphocytes was 110 pmol DHEA/h/mg protein (normal female value 227 ± 64), being consistent with heterozygosity for STS deficiency.

## Methods

### GROWTH ASSESSMENT

The heights of the patient and his brother were assessed by the cross sectional centile growth curve for normal Japanese boys based on the 1980 national survey.<sup>12</sup> Target height (TH, a child's final height as predicted from the parental height) and target range (TR, 95% confidence interval of TH) were obtained from the following equations for Japanese boys:  $TH = \{PH + (MH + 13)\} / 2 + 2$  and  $TR = TH \pm 9$  (cm), where PH is paternal height and MH maternal height.<sup>13</sup> The parental height was estimated by the age adjusted normal Japanese standards based on the annual growth survey of the Ministry of Education, to allow for the positive secular trend in the adult height of the Japanese.<sup>13</sup>

### CYTOGENETIC STUDIES

Chromosome analysis was performed by G banding<sup>14</sup> on spreads from 40 peripheral blood lymphocytes. The fine structure of the X chromosome was examined by high resolution G banding with ethidium bromide.<sup>15</sup>

### SOUTHERN BLOT ANALYSIS

Genomic DNA was extracted from the peripheral leucocytes of the patient and his mother and from those of normal subjects. Southern transfer, probe hybridisation, and autoradiography were carried out by the standard methods.<sup>16</sup> The genomic DNA was digested with *EcoRI*, *HindIII*, *TaqI*, and *SstI*, and hybridised with 13 probes defining loci in the terminal part of Xp (table 1). The copy number of each locus was determined by the pattern of restriction fragment length polymorphisms (RFLPs) or by the comparison of band intensity. Band intensity was measured by a laser densitometer (Ultrascan, LKB), using the autosomal TK gene<sup>30</sup> as an internal control.

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Table 1 Band intensity ratios as compared with the autosomal TK gene.

Locus	Probe	Enzyme	Patient	Mother	Female	Male	Reference
Pseudoautosomal region							
<i>DXYS14</i>	29C1		—	—	—	—	17
<i>DXYS60</i>	U7A	<i>HindIII</i>	0.39	0.43	0.43	0.45	18
<i>DXYS28</i>	pDP411	<i>HindIII</i>	1.60	1.78	1.70	1.85	19
<i>DXYS59</i>	68A	<i>EcoRI</i>	1.25	1.30	1.20	1.33	20
<i>DXYS15</i>	113D	<i>EcoRI</i>	1.22	1.32	1.15	1.35	21
<i>CSF2RA</i>	cDNA	<i>EcoRI</i>	0.93	1.20	0.88	1.10	22
<i>DXYS17</i>	601	<i>HindIII</i>	0.71	0.77	1.52	1.55	23
<i>MIC2</i>	19B	<i>HindIII</i>	0.65	0.70	1.43	1.48	24
X specific region							
<i>PABX</i>	Hf0.2	<i>SstI</i>	0	0.58	1.20	0.61	25
<i>DXS31</i>	M1A	<i>EcoRI</i>	0	0.87	1.60	0.90	26
<i>STS</i>	ST-12	<i>EcoRI</i>	0	0.84	1.70	0.91	27
<i>DXS143</i>	dic56	<i>EcoRI</i>	0.32	0.65	0.70	0.37	28
<i>DXS69</i>	71-7A	<i>HindIII</i>	0.85	1.60	1.78	0.80	29

The loci are arranged from telomere to centromere. Non-RFLP bands were measured for the band intensity. For *DXYS14*, only RFLP bands were detected. Dosage blottings for *DXYS59*, *CSF2RA*, *DXYS17*, *MIC2*, *DXS31*, *STS*, and *DXS143* are shown in fig 2.

#### PCR ANALYSIS

PCR (polymerase chain reaction) analysis for the pseudoautosomal boundary (*PABX/PABY*)<sup>31</sup> was performed on genomic DNA of the patient under standard conditions.<sup>16</sup> Reactions were cycled 30 times with incubations at 94°C for one minute, at 54°C for one minute, and at 72°C for two minutes. Primer sequences used were: pseudoautosomal, 5'-GAATTCT-TAACAGGACCCATTTAGGATTAA-3'; X specific, 5'-CTGCAGAAACAAGCTCA-TCAGCGTGACTAT-3'; and Y specific, 5'-GTACTACCTTTAGAAAAGTAGTATT-TTCCC-3'.

#### Results

##### GROWTH ASSESSMENT

The growth charts of the patient and his brother are shown in fig 1, together with their TH/TR. The height of the patient remained between the 10th and 25th centile (mean - 1.1 SD), and that of the brother was around the 50th centile (mean + 0.3 SD). The 37 year old father measured 168 cm (mean + 0.2 SD, male standard for his age 166.8 ± 5.6 cm) and the 31 year old mother 158 cm (mean + 0.4 SD, female standard for her age 156.0 ± 4.9 cm). Thus TH was 171.5 cm (mean + 0.3 SD, 1980 male standard 169.7 ± 5.6 cm)

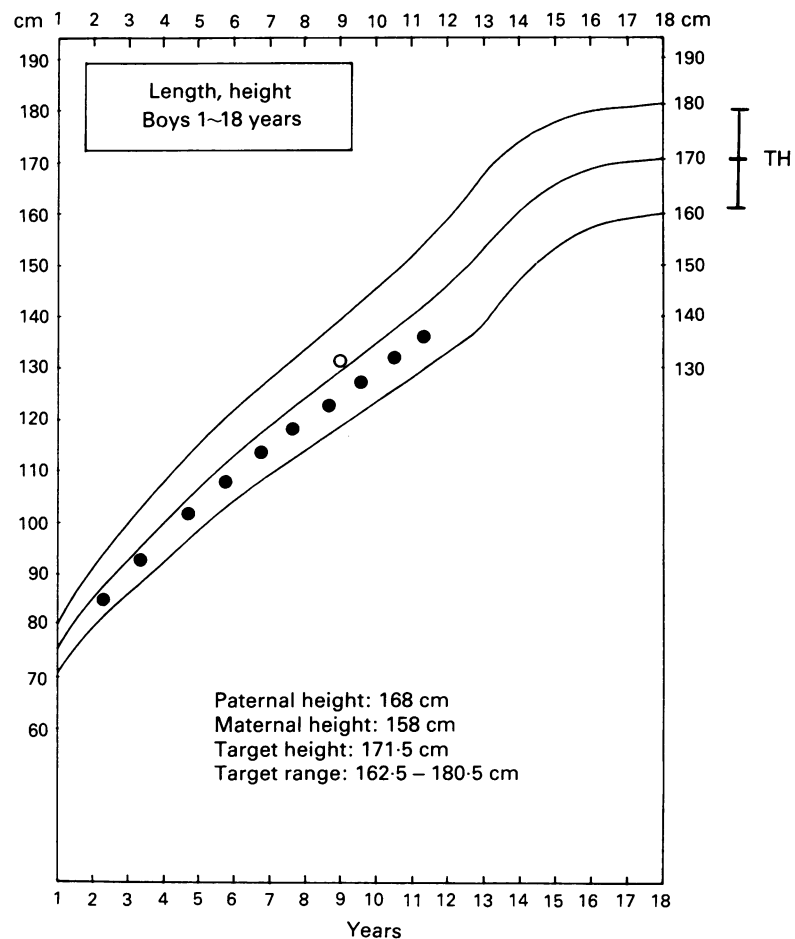


Figure 1 The growth charts of the patient (closed circles) and the brother (open circle). The upper, middle, and lower curves depict the 97th, 50th, and 3rd centile growth curves of Japanese boys, respectively.

and TR 162.5~180.5 cm (mean - 1.3 SD ~ mean + 1.9 SD). The two sisters of the mother were 156 cm and 152 cm tall.

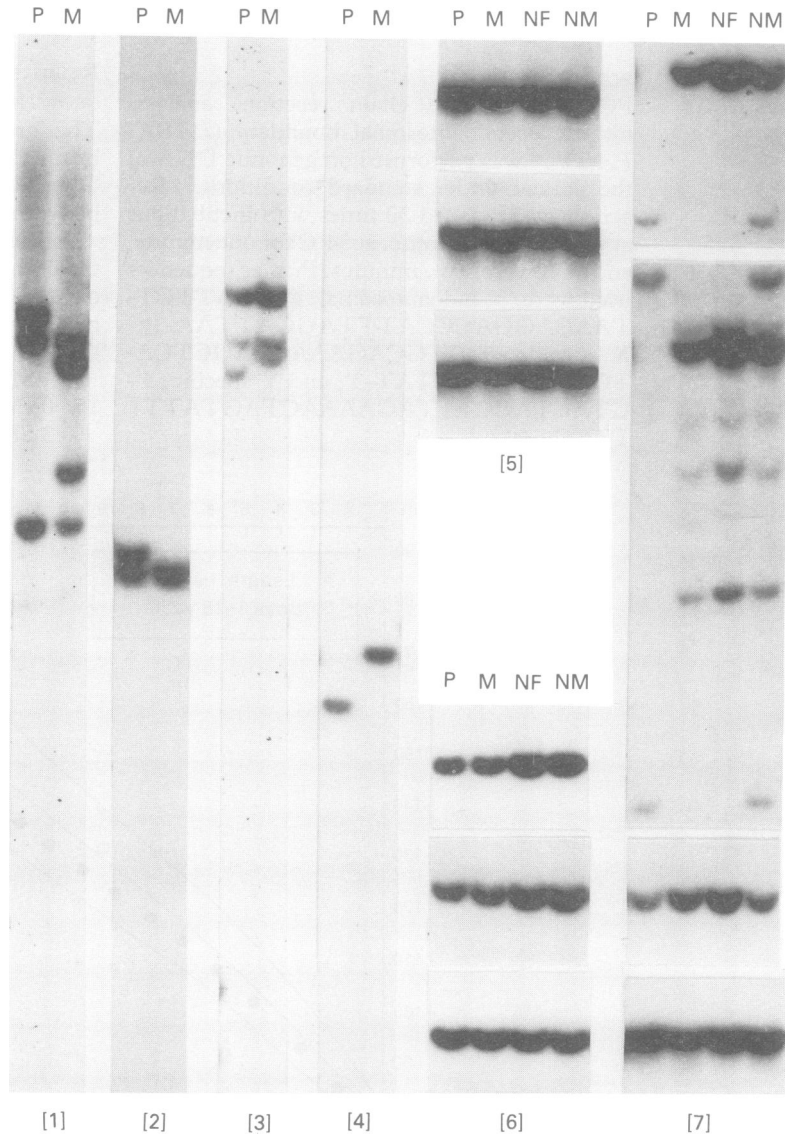
#### CYTOGENETIC STUDIES

The patient's karyotype was 46,XY. No structural abnormality of the X chromosome was detected by high resolution G banding.

#### SOUTHERN BLOT ANALYSIS

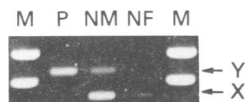
Representative results are shown in fig 2 and table 1. Probes defining *DXYS14* (*EcoRI* and

*TaqI* digests), *DXYS15* (*TaqI* digests), and *CSF2RA* (the gene locus for the receptor for the granulocyte-macrophage colony stimulating factor) (*HindIII* and *TaqI* digests) recognised bands specific to the patient and bands shared by the patient and his mother. The probe defining *DXYS17* (*TaqI* digests) failed to show a common band between the patient and his mother. Comparison of band intensity for probe-enzyme combinations which failed to detect RFLPs indicated that, in both the patient and the mother, *DXYS60*, *DXYS28*, *DXYS59*, *DXYS15*, and *CSF2RA* in the distal part of the PAR were present in two



**Figure 2** Southern blot analysis (P=patient, M=mother, NF=normal female, NM=normal male). (1) *EcoRI* digests hybridised with 29C1 (*DXYS14*). (2) *TaqI* digests hybridised with 113D (*DXYS15*). (3) *HindIII* digests hybridised with cDNA probe for GM-CSF receptor gene (*CSF2RA*). (4) *TaqI* digests hybridised with 601 (*DXYS17*). (5) *EcoRI* digests hybridised with 68A (*DXYS59*, top panel), cDNA probe for GM-CSF receptor gene (*CSF2RA*, middle panel), and the probe for autosomal TK gene (bottom panel) (same filter). (6) *HindIII* digests hybridised with 601 (*DXYS17*, top panel), 19B (*MIC2*, middle panel), and the probe for autosomal TK gene (bottom panel) (same filter). (7) *EcoRI* digests hybridised with M1A (*DXS31*, top panel), ST-12 (*STS*, second panel), *dic56* (*DXS143*, third panel), and the probe for autosomal TK gene (bottom panel) (same filter). RFLP pattern and comparison of band intensity indicate that, in both the patient and his mother, *DXYS14*, *DXYS59*, *DXYS15*, and *CSF2RA* in the distal part of the pseudoautosomal region are present in double doses, whereas a single dose is detected for *DXYS17* and *MIC2* in the proximal part of the pseudoautosomal region. *DXS31* and *STS* in the X specific region are absent in the patient and present in a single copy in the mother.

copies, whereas only a single copy was detected for *DXYS17* and *MIC2* in the proximal part of the PAR. The X specific loci from *PABX* to *STS* were absent in the patient and present in a single copy in the mother.



**Figure 3** PCR analysis of the pseudoautosomal boundary (M = DNA size marker, P = patient, NM = normal male, NF = normal female). The X specific product (771 bp) is absent in the patient, although the Y specific product (947 bp) is present. The size markers represent 1.08 and 0.87 kb  $\Phi$ X174/HaeIII fragments.

#### PCR ANALYSIS

No trace of *PABX* was detected in the patient, providing additional evidence for the absence of a normal X chromosome (fig 3). *PABY* was present as expected.

#### Discussion

The present study indicates that the patient inherited, from his mother, a submicroscopic interstitial deletion with breakpoints between *CSF2RA* and *DXYS17* and between *STS* and *DXS143*. Although the deletion explains the CDPX and *STS* deficiency of the patient,<sup>69</sup> it is not associated with short stature. The patient's height is within the normal range of Japanese boys and appropriate for the TH/TR, despite the CDPX. The mother's height is above the average height of Japanese females of her age. In addition, the normal brother's height is in close agreement with the TH/TR calculated using the mother's height. This suggests that the putative pseudoautosomal growth gene(s) is present in the region distal to *DXYS17* and preserved in the abnormal X chromosome of the patient and his mother.

For a more precise localisation of the growth gene(s), it is useful to review the correlation between genotype and stature in cases of partial monosomy of the PAR; six cases have previously been published (table 2).

The critical factor is adequate height assessment (table 3). Cases 1 and 2 are estimated to be short not only by comparison with population standards but also by comparison with

TH/TR. The latter comparison is useful in the assessment of individual height, since it is primarily determined by the genetic height potential as represented by parental height.<sup>33,36</sup> Furthermore, the size of the height decrease found in case 1 (14.5 cm) and case 2 (11 cm) is similar to the adult height difference between 13 females with 46,X,del(X)(p22.32) and nine females with 46,XX in the two pedigrees described by Curry *et al*<sup>3</sup> (about 12 cm). This is consistent with the growth gene(s) being affected and present in a single dose in the two cases. The normal stature of case 3 (the present case) is as described above. Cases 4 and 5 appear normal in height, although TH/TR is not available. Classification of case 6 is more difficult. The male patient is shorter than the two normal brothers and his height is below the normal range of French males, but this could be because of the CDPX. The four carrier females in the pedigree are short, but their heights are within the normal range of French females. Unfortunately, TH/TR is not available for the family.

Correlation of genotype with stature in the six cases is shown in fig 4 (the dosage of *CSF2RA* in cases 1, 2, and 6 and that of *DXYS15* in case 6 are unpublished data). The simplest explanation is to postulate a single growth gene in the region between the breakpoints of cases 1 and 5, and to assume that case 6 is free from pathological short stature in the context of the growth gene. The distal and proximal limits of the region are defined by *DXYS20* and *DXYS15*, respectively. It might be possible that the growth gene extends proximally and is disrupted in case 1, and even in case 2. In this case, the growth gene is located distal to *DXYS17* because of normal height in cases 3 and 4. Furthermore, unless the growth gene overlaps with *CSF2RA*, it must be located distal to *CSF2RA*. Although case 6 may be associated with pathological short stature, a simple explanation in terms of genotype-phenotype correlation is impossible because of the absence of a shared deleted region between case 6 and cases 1 and 2.

This location of the growth gene is inconsistent with that previously suggested by Henke *et al*<sup>7</sup> on the basis of the genotype-phenotype analysis of cases 2, 4, 5, and 6. The discrepancy is apparently caused by the difference in the assessment of case 6: Henke *et al*<sup>7</sup> regarded

**Table 2** Reported cases of partial monosomy of the pseudoautosomal region.

Case	Karyotype	Reference
1 Sporadic	46,X,rea(X)(Xqter→Xq26::Xp22.3→Xq26:)	8
2 Sporadic	46,X,t(X;Y)(Xqter→Xp22.3::Yp11→Yqter)	6,7
3 Familial	46,XX (n = 1) and 46,XY (n = 1)	Present case
4 Sporadic	46,X,t(Y;22)(p11.2;q11)	10
5 Sporadic	45,X/46,X,psu dic(X)(Xqter→Xp22.3::Xp22.3→Xqter)	7
6 Familial	46,XX (n = 4) and 46,XY (n = 1)	9

Cases 3 and 6 have a submicroscopic interstitial deletion in Xp22.3.

**Table 3** Height assessment for subjects with partial monosomy of the pseudoautosomal region.

No*	Sex	Age (y)	Height (cm)	Remark	Comparison with population standards	Comparison with TH/TR	Heights of normal relatives	Assessment
1	F	9.8	122		< 3rd centile	Short†	Brother 75th–90th centile	Short
2	M	33	155		< 3rd centile‡	Short§		Short
3	M	11.3	136	CDPX	- 1.1 SD	Normal	Brother + 0.3 SD	Normal
	F	31	158		+ 0.4 SD	NA		
4	F	15.8	165		Normal for XYGD	NA		Normal?
5	F	6.5	114	Mosaic	25th–50th centile	NA	Mother 10th centile‡ (155 cm)	Normal?
6	M	Adult	160	CDPX	- 2.5 SD¶	NA	Brothers - 0.5 SD¶ (172 cm) and + 1.6 SD¶ (185 cm)	Equivocal
	F	Adult	152~155	n = 4	- 2.0 SD ~ - 1.5 SD¶	NA		

TH = target height, TR = target range, NA = not available, CDPX = X linked chondrodysplasia punctata, XYGD = XY gonadal dysgenesis.

\* The case numbers correspond to those in table 2.

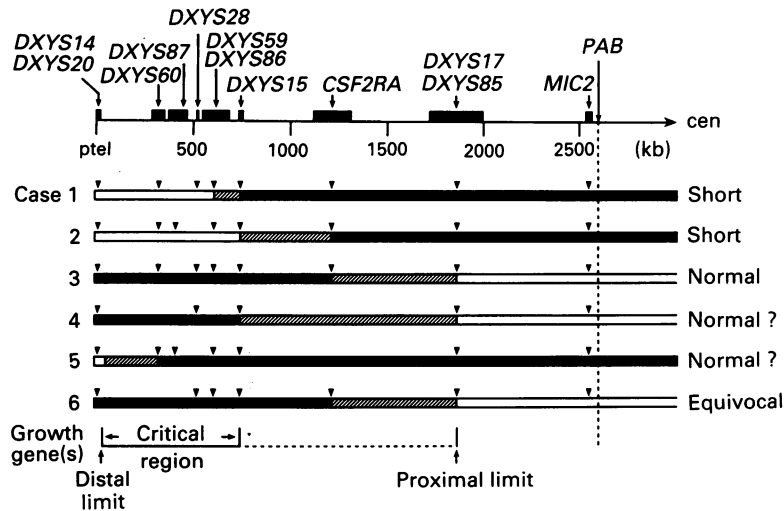
† Predicted adult height based on the biological data of this patient (148.5 cm) is below her TH (163 cm) and TR (155–171 cm).<sup>8</sup>

‡ According to the height standards of Tanner *et al*.<sup>32</sup>

§ According to Tanner's formula,<sup>33</sup> TH of this patient is 166 cm and TR 156–176 cm.

|| The mean height of adult Caucasian patients (20 to 50 years of age) with XYGD is 172.0 ± 7.0 cm.<sup>34</sup>

¶ French height standard is 163.3 ± 5.6 cm for females and 175.2 ± 6.0 cm for males.<sup>35</sup>



**Figure 4** A diagram showing the genotype-phenotype correlations in six cases of partial monosomy of the pseudoautosomal region. The case numbers correspond to those in tables 2 and 3. The white areas denote the monosomic regions and the black areas the disomic or trisomic regions. The striped areas depict the dosage unknown regions where the breakpoints should exist. For case 5 with 45,X/46,X,dic(X) mosaicism, the genotype of cells with the abnormal X chromosome is shown. The inverted black triangles represent the loci examined in each case. Dosage of CSF2RA in cases 1, 2, and 6 and that of DXYS15 in case 6 are unpublished data. The two doses of CSF2RA in case 1 have been confirmed by RFLP pattern using parental DNA. The two doses of CSF2RA in case 2 have been based on densitometric analysis. The two doses of DXYS15 and CSF2RA in case 6 have been established by the positive bands detected for DNA from a human-rodent hybrid cell line in which the abnormal X chromosome of the patient is retained but the Y chromosome is absent. The physical positions of the pseudoautosomal loci are based on the reports of Petit *et al.*,<sup>20</sup> Brown,<sup>37</sup> Henke *et al.*,<sup>7</sup> and Rappold *et al.*<sup>38</sup> DXYS14 is just distal to DXYS20, but the relative position is unknown between DXYS59 and DXYS86 and between DXYS17 and DXYS85. The critical region for the pseudoautosomal growth gene(s) is indicated, together with the distal and proximal limits.

case 6 as having pathological short stature owing to the impairment of the growth gene(s), as described in the original paper.<sup>9</sup> In addition, cases 1 and 3 were not available at that time, nor was the dosage of CSF2RA analysed.

In summary, although genotype-phenotype analysis of the pseudoautosomal growth gene(s) is still not conclusive, we propose that the region between DXYS20 and DXYS15 is the critical region for the growth gene(s) and that DXYS17 defines the proximal limit of the whole growth gene(s). Further accumulation of informative cases will permit a more precise localisation.

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