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# Molecular analysis of 46,XY females and regional assignment of a new Y-chromosome-specific probe

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**Summary.** The relationship between Y-chromosome abnormalities and gonadal differentiation was investigated in six phenotypic females with a 46,XY karyotype and one patient with ambiguous genitalia secondary to apparently nonmosaic 46,XY mixed gonadal dysgenesis. No alterations were found in the Y chromosomes of six of these individuals by the use of either cytogenetic or molecular techniques. Cytogenetic analysis with high-resolution G-banding and Q-banding revealed a small deletion in the short arm of the Y chromosome in one female patient with some features of Turner syndrome. Southern hybridization with Y-specific probes showed a loss of DNA within deletion intervals 1, 2, and 3 of the Y chromosome. A new Y-chromosome-specific DNA probe that hybridizes to deletion interval 3 is described.

## Introduction

The molecular study of individuals with abnormal gonadal differentiation and sex chromosome anomalies has lead to the assignment of specific regions for sexual differentiation and gonadal function on the Y chromosome (reviews in Page 1986, 1987; Simpson et al. 1987). Until recently, genotype-phenotype correlations for gonadal differentiation were based on cytogenetic studies. More recently, investigation with DNA probes has allowed the generation of a physical deletion map dividing the Y chromosome into seven deletion intervals (Vergnaud et al. 1986). The analysis of sex-reversed individuals (46,XX males and 46,XY females) and of patients with other types of sex-chromosome anomalies has led to the development and refinement of the deletion map (Guellaen et al. 1984; Vergnaud et al. 1986; Disteche et al. 1986a; Müller et al. 1986; Affara et al. 1986, 1987; Petit et al. 1987; Ferguson-Smith et al. 1987; Müller 1987). The locus of the testis determining factor (TDF) has been shown by these techniques to map in deletion interval 1, and a candidate for the TDF gene (ZFY) has been isolated (Page et al. 1987).

DNA probe analysis of individuals with sex reversal, i.e., 46,XY females and 46,XX males, provides a genetic explanation for their sex reversal in many cases (review in de la Chapelle 1988). However, not all patients with sex reversal have detectable genetic defects and, thus, it is important to analyze additional patients and to correlate their phenotypic characteristics with their genotype.

In this study, we describe seven previously unreported phenotypic females with a 46,XY karyotype and provide an additional analysis of two previously reported 46,XY females (Disteche et al. 1986a). A new Y-linked probe specific for deletion interval 3 is also described.

## Materials and methods

### *Case reports*

The patients (Table 1) were ascertained in various ways. None had a family history of sex reversal. Chromosome analysis was performed in patients 1, 2, and 3 because of features of Turner syndrome. Patients 1 and 2 have been described previously (Disteche et al. 1986a). Patient 3 had many phenotypic features of Turner syndrome, including lymphedema of hands and feet, short neck, high-arched palate, dysplastic toenails and left ear, and hydronephrosis with duplication of the left renal pelvis. Her length at birth was normal (75th percentile). Patients 4, 5, and 6 had primary amenorrhea and lacked breast development. All three had average to tall stature. Patient 7 had ambiguous genitalia at birth, patient 8 had Down syndrome, and patient 9 had multiple anomalies (Table 1).

At the time of gonadectomy, patients 1–6 had streak gonads histologically and all but one (patient 1) had unilateral or bilateral gonadoblastoma. Patients 4–6 have phenotypes consistent with a diagnosis of "pure gonadal dysgenesis." Patient 7 has mixed gonadal dysgensis (unilateral dysgenetic testis and contralateral streak gonad). Patients 8 and 9 have bilateral streak gonads. Patient 8 has a uterus and thus is likely to have pure gonadal dysgenesis in addition to Down syndrome. Patient 9 appears to have a specific multiple congenital anomaly syndrome in which genital anomalies may be intrinsic to the syndrome and independent of sex-chromosome constitution.

### *Cytogenetics*

The Y chromosomes of patients 3–9 were reexamined for small deletions using prometaphase G-banding (Yunis 1976). To examine the possibility of mosaicism, mitotic cells were obtained from peripheral blood lymphocyte cultures and when

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**Table 1.** Phenotypic and karyotypic characteristics of the patients

| Patient | Age (years) | Phenotype | Height[a] | Genitalia[b] | Gonads[c] | | Karyotype | Number of cells | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | R | L | | Blood | Skin | Gonads | |
| | | | | | | | | | | R | L |
| 1 | 4 | Turner features | 75th | F | S | S | 46,XYp- | 105 | 50 | 50 | 51 |
| 2 | 15 | Turner features | N | F | G | G | 46,XYp- | 120 | – | 54 | 58 |
| 3 | NB[d] | Turner features | 75th | F | S | G | 46,XYp- | 111 | 100 | 110 | 100 |
| 4 | 18 | Primary amenorrhea without breast development | N | Enlarged clitoris | G | S | 46,XY | 24 | 20 | 14 | – |
| 5 | 16 | Primary amenorrhea without breast development | 60th | F | G | S | 46,XY | 57 | – | – | – |
| 6 | 24 | Primary amenorrhea without breast development | 95th | F | G | S | 46,XY | 101 | 21 | – | – |
| 7 | NB | Ambiguous genitalia | N | Small phallus, hypospadias | D | S | 46,XY | 100 | 100 | 59 | 50 |
| 8 | NB | Down syndrome | 50th[e] | F | S | S | 47,XY,+21 | 25 | 55 | 20 | – |
| 9 | 5 | Coloboma, heart defect, cup-shaped ears, seizures, developmental delay | 50th | F | S | S | 46,XY | 55 | – | – | – |

[a] Percentile; N, normal height, no percentile available
[b] F, Female
[c] R, Right; L, left; S, streak; G, gonadoblastoma; D, dysgenetic testis
[d] NB, Newborn
[e] For Down syndrome

possible from fibroblast cells established from skin biopsies or gonadal tissue. Slides were stained by G-banding or Q-banding using standard procedures.

*Southern hybridization*

DNA was prepared from peripheral blood leukocytes, cultured skin fibroblasts, or Epstein-Barr virus-transformed lymphoblastoid cell lines and then submitted to restriction digestion, electrophoresis, and Southern hybridization by standard techniques (Maniatis et al. 1982). Each hybridization probe was used at either "reduced" stringency or "high" stringency. Reduced stringency means that hybridizations were performed at 42°C and that the final wash was in 0.1 × SSC (1 × SSC is 0.15 *M* NaCl, 15 m*M* sodium citrate, pH 7), 0.1% sodium dodecyl sulfate (SDS) at 55°C. High stringency means that hybridizations were carried out at 42° or 47°C and the final wash was in 0.1 × SSC, 0.1% SDS at 65°C.

The probes pDP61 (D. C. Page, unpublished, subcloned from plasmid 115 of Geldwerth et al. 1985), pDP105 (D. C. Page, unpublished), pDP34 (Page et al. 1982, 1984; Vergnaud et al. 1986), and pDP97 (D. C. Page, unpublished, subcloned from cosmid Y97 of Wolfe et al. 1985) were hybridized as previously described by Disteche et al. (1986b). The following describes the other probes used:

Probe pDP132 (D. C. Page, unpublished results) detects a Y-linked *Taq*I fragment of 4.4 or 7.0 kb, specific for deletion interval 1 and an X-linked fragment of 3.2 kb when hybridized at high stringency.

Probe pDP1007 (Page et al. 1987) detects a Y-linked *Taq*I fragment of 2.8 kb, specific for deletion interval 1 and an X-linked *Taq*I fragment of 2.3 kb, when hybridized at high stringency. This probe recognizes the ZFY locus which is a candidate for the TDF gene (Page et al. 1987).

Probe 52d (Bishop et al. 1984) detects multiple loci on the X and Y chromosomes. A Y-linked *Taq*I fragment of 3 kb (52d/B), specific for deletion interval 3 (Vergnaud et al. 1986) is seen after hybridization at reduced stringency.

Probe 50f2 detects a number of Y-specific fragments at reduced stringency (Guellaen et al. 1984). One such fragment 50f2/A or B, gives a 3.5-kb *Taq*I band specific for deletion interval 3 (Vergnaud et al. 1986).

Probe pY3.4 (Lau et al. 1984) detects highly repeated Y-specific *Taq*I fragments of less than 1 kb, specific for deletion interval 7 when hybridized at high stringency.

Probe pMC23 was isolated after hybridization by a phenol-enhanced reassociation technique (PERT) (Kunkel et al. 1985) in which *Sau*3A-digested, Y-chromosome-specific DNA was hybridized with an excess of sheared DNA from patients 1 and 2. Ligation of the resultant mixture into the *Bam*HI site of pBR322 generated a library whose clones were analyzed to identify sequences hybridizing to specific regions of the Y chromosome (Cantrell and Disteche 1987). Probe pMC23 was obtained from that library, contains a Y-specific DNA insert of approximately 140 bp, and was hybridized at high stringency.

## Results

*Cytogenetics studies*

When the chromosomes of patients 3 to 9 were examined using prometaphase banding, six of the patients appeared to have normal chromosomes. There was no evidence of mosaicism in the tissues examined (Table 1). However, patient 3 who has features of Turner syndrome was found to have a small deletion in the short arm of the Y chromosome (Fig. 1).

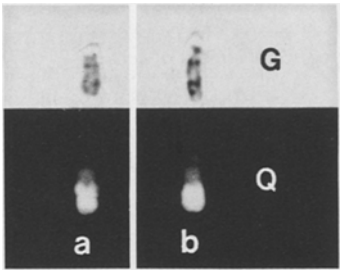


**Fig. 1a, b.** Examples of Y chromosomes from patient 3 (**a**) and a normal male control (**b**). The upper samples are Y chromosomes stained by G-banding *(G)* and the lower samples are Y chromosomes stained by Q-banding *(Q)*

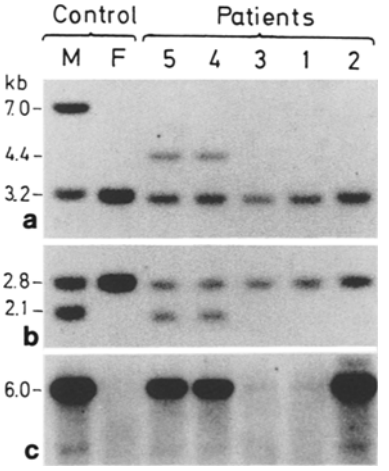


**Fig. 2a–c.** Hybridization of Y-chromosome-specific probes to Southern transfers of DNA from sex-reversed patients. DNA from a normal male *(M)*, a normal female *(F)*, patient *5*, patient *4*, patient *3*, patient *1*, and patient *2* was digested with *Taq*I, separated by electrophoresis, and blotted. The membranes were then probed with pDP132 (**a**), pDP61 (**b**), and pMC23 (**c**)

This deletion appeared to be similar to the deletions previously reported in two other XY females (patients 1 and 2) with features of Turner syndrome (Disteche et al. 1986a). Cytogenetic studies of the father of patient 3 revealed a normal Y chromosome. All three of these patients therefore have a de novo karyotype of 46,X,Yp- with no apparent mosaicism in multiple tissues examined in each patient (Table 1).

*Southern hybridization studies*

Y-specific probes were used to compare the Y-chromosome deletions in two previously reported 46,X,Yp- patients with the deletion observed in patient 3. DNA from the six patients with cytogenetically normal Y chromosomes was probed in a similar fashion to determine whether they contained cytogenetically undetectable deletions.

Figure 2 shows the results of a Southern hybridization when *Taq*I-digested DNA from a normal male and female, three of the new patients, and the previously described patients 1 and 2 (Disteche et al. 1986a) was hybridized with three different Y-specific probes. Figure 2a shows the hybridization of pDP132, a probe specific for deletion interval 1 of the Y chromosome (Vergnaud et al. 1986; Page 1986), to either a 4.4-kb Y-specific DNA fragment or a 7.0-kb restriction fragment length polymorphism (RFLP). A 3.2-kb X-linked fragment also hybridizes to pDP132. The Y-specific fragment is deleted in patients 1, 2, and 3 but present in patients 4 and 5. Figure 2b shows hybridization of the probe pDP61 to a 2.8-kb X-linked fragment and a 2.1-kb Y-linked fragment specific for deletion interval 2 (Vergnaud et al. 1986). This Y-linked fragment is also deleted in patients 1, 2, and 3 but present in patients 4 and 5. Figure 2c shows the hybridization pattern obtained with a new probe, pMC23, which we have recently isolated by use of PERT hybridization (Cantrell and Disteche 1987). This probe detects a 6-kb Y-specific fragment that is missing in patients 1 and 3 but present in patients 2, 4, and 5. We have previously shown at least some region-3-specific DNA to be absent in patient 1 but present in patient 2 (Disteche et al. 1986a), so we tentatively consider pMC23 to be a region-3-specific probe that defines a locus deleted in patients 1 and 3.

The results shown in Fig. 2 plus the results of a large number of other hybridizations with Y-linked probes are summarized in Table 2. The DNA from patient 3 gives the same hybridization pattern to all the probes tested as was obtained with patient 1. Both patients appear to have deletions spanning the Y-chromosome deletion interval 1 when probed with

**Table 2.** Y-chromosome-specific DNA studies using DNA probes to test individuals for the presence (+) or absence (−) of indicated Y-specific restriction fragments

| DNA probe/locus | Deletion interval | Individual | | | | | | | | | Normal male | Normal female |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | | |
| pDP132 | 1 | − | − | − | + | + | + | + | + | + | + | − |
| pDP1007 | 1 | − | − | − | + | + | + | + | + | + | + | − |
| pDP61 | 2 | − | − | − | + | + | + | + | + | + | + | − |
| pMC23 | 3 | − | + | − | + | + | + | + | + | + | + | − |
| 52d/B | 3 | − | + | − | + | + | | | | + | + | − |
| pDP105/A | 3 | − | + | − | + | + | + | + | + | + | + | − |
| 50f2/A,B | 3 | − | + | − | + | | + | + | + | + | + | − |
| pDP34 | 4A | + | − | + | + | + | + | + | + | + | + | − |
| pDP97 | 4B | | | | | | + | + | + | | + | − |
| pDP105/B | 6 | + | + | + | + | + | + | + | + | + | + | − |
| pY3.4 | 7 | | | | | | + | + | + | | + | − |

pDP132 or pDP1007; interval 2 when probed with pDP61; and interval 3 when probed with pMC23, 52d, pDP105 or 50f2. The analysis of patients 1 and 2 with additional Y-linked probes not used in the previous study (Disteche et al. 1986a) corroborates the patterns of hybridization seen before. DNA from patient 2 hybridizes to probes specific for all Y-chromosome regions except 1, 2, and 4A.

The other patients (4–9) showed no deletion of the Y chromosome with any of the probes tested (Table 2). In particular, probe pDP1007 that recognizes the ZFY gene, a candidate for the TDF gene (Page et al. 1987), showed a normal male hybridization pattern on all six patients (4–9) analyzed. Further analysis of two of the patients (4 and 6) was done by using additional restriction enzymes (*Hind*III, *Pst*I, *Sau*3A, *Msp*I) with probe pDP1007 and no abnormal restriction patterns were found.

Table 2 shows that the new probe pMC23 gives the same pattern of hybridization to all of the patients as the region 3 probes – 52d (fragment A), pDP105 (fragment A), and 50f2 (fragments A or B). We conclude that pMC23 does indeed detect a locus in region 3. Upon hybridization and washing at medium stringency (data not shown), a smear indicative of hybridization to a large number of autosomal loci is seen, but washing at high stringency produces a single, extremely intense band that is Y-chromosome-specific (Fig. 2C). This indicates that pMC23 represents a single member of a dispersed family of repeated sequences and that the band seen upon high stringency washing may represent more than one locus within region 3.

## Discussion

We have reported the cytogenetic and Southern hybridization analysis of seven new 46,XY female patients plus additional analysis of two previously described patients (Disteche et al. 1986a). DNA analysis was performed using eleven probes for regions 1, 2, 3, 4, 6, and 7 of the Y chromosome, including pMC23, a new probe for region 3 that is strictly Y-linked and moderately repeated.

One of the new patients analyzed (patient 3) has a deletion of the short arm of the Y chromosome. This deletion includes regions 1 through 3, like the deletion that had been previously found in another patient (patient 1) with a similar phenotype while a third individual (patient 2) has a deletion of region 1, 2, and 4A (Disteche et al. 1986a). This deletion of noncontiguous intervals seen in patient 2 is likely to result from an inversion in her father (Disteche et al. 1986a). Since the TDF is localized within region 1 of the Y chromosome (Vergnaud et al. 1986; Page et al. 1987), it is presumed that deletion of region 1 (or at least of a critical portion of region 1) in these three 46,XY female individuals has resulted in the failure of testicular development and in the development of streak gonads. The lack of fetal androgen production therefore resulted in female rather than male external genitalia.

Interestingly, all three patients with a Y-chromosome deletion have features of Turner syndrome, which prompted their initial evaluation. This has been reported in other cases of deletions of the short arm of the Y chromosome (Rosenfeld et al. 1979; Magenis et al. 1984). However, the normal height of these Y-chromosome-deleted patients distinguishes them from typical Turner patients (Disteche et al. 1986a). This suggests that if a gene for stature is located on the Y chromosome, it is in proximal region 4A through region 7, which are not deleted in these patients. Two of the Y-chromosome-deleted patients (patients 2 and 3) developed gonadoblastoma, a tumor frequently seen in 46,XY females (Scully 1970). A hypothetical gene predisposing to gonadoblastoma would thus be also located in proximal region 4A through region 7 of the Y chromosome (Page 1987; Disteche 1989).

The findings in patients 1–3 contrast to those in patients 4–6 who do not have the Turner syndrome phenotype, but have streak gonads secondary to "XY pure gonadal dysgenesis." These three patients (patients 4–6) have normal chromosomes and no evidence for loss of Y-specific DNA, including those DNA sequences detected by probe pDP1007, which identifies the ZFY gene, a candidate gene for the TDF (Page et al. 1987). Thus, it appears that only a small proportion of XY females have detectable deletions (Ferguson-Smith et al. 1987; Müller 1987). Patients with XY pure gonadal dysgenesis usually do not have sex-chromosome structural abnormalities, which is consistent with its presumed autosomal or X-linked recessive inheritance (German et al. 1978). Nonetheless, the analysis performed in this study does not eliminate the possibility of a small deletion or point mutation of Y-chromosome material in these patients. Continuing investigation of XY pure gonadal dysgenesis patients with Y-chromosome probes is warranted because this condition demonstrates genetic heterogeneity, suggesting that abnormalities of genes encoded on the Y chromosome may account for some patients with this phenotype.

Patient 7 has mixed gonadal dysgenesis, a condition often associated with 45X/46,XY mosaicism (Donahue et al. 1979; Robboy et al. 1982). The lack of mosaicism in a total of 309 cells from three different tissues, including both gonads, in this patient indicates than Y-chromosome mosaicism is an unlikely explanation for the phenotype of this patient. In contrast to pure gonadal dysgenesis, mixed gonadal dysgenesis is not familial. An autosomal recessive or X-linked recessive mode of inheritance for mixed gonadal dysgenesis has not been proposed, suggesting that a point mutation or small deletion of the TDF gene or some other Y locus is still very likely in such patients.

The phenotypes of patients 8 and 9 are less well-defined. Patient 8 has Down syndrome and is likely to have pure gonadal dysgenesis in addition. The abnormalities in gonadal differentiation seen in patient 9 may be the result of a multiple congenital abnormality syndrome. Nonetheless, the use of Y-specific DNA probes has excluded the possibility of a large submicroscopic deletion of the candidate TDF gene (locus ZFY) as the etiology of their sex reversal.

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