Human Dicentric Y Chromosomes
Case Report and Review of the Literature

MAIMON M. COHEN,* MARGARET H. MACGILLIVRAY, VINCENT J. CAPRARO, and THOMAS A. ACETO

Divisions of Human Genetics and Endocrinology, Department of Pediatrics, State University of New York at Buffalo School of Medicine and Children’s Hospital of Buffalo, Buffalo, New York, USA

Summary. A phenotypic female with histological evidence of mixed gonadal dysgenesis, and 45,X/46,X, dic(Yq) mosaicism is described. A review of the literature yielded 15 additional cases of dicentric Y chromosomes. Among the cases, a wide range of variation in phenotype, external genitalia, histology, and chromosomal findings was observed. Factors possibly contributing to such variability are discussed and include: the exact site of breakage and exchange in the Y chromosome; the timing of dicentric formation (meiotic vs mitotic); the occurrence of non-disjunction; and the presence or absence of a Y chromosome in cells of the gonadal anlage during a critical ontogenic period.

Morphologically the human Y chromosome is, probably, the most variable chromosome of the human karyotype. Extreme variations of length have been observed both in normal individuals and in individuals with physical abnormalities (Makino et al, 1963; Gripenberg, 1964; Cohen, Shaw, and MacCluer, 1966; McKenzie et al, 1972). Family studies have demonstrated that such length variation is heritable (Bishop, Blank, and Hunter, 1962; de la Chappelle et al, 1963; Borgaonkar et al, 1969; McKenzie et al, 1972). Additionally, a wide spectrum of structural rearrangements, altering Y chromosome morphology, have been observed: deletions (Conen et al, 1961; Muldal and Ockey, 1962; Nakagome et al, 1965); isochromosomes (Klevit, Mellman, and Eberlein, 1963; Jacobs and Ross, 1966; Jacobs, 1969); translocations (van den Berghe, 1965; Federman, Davidoff, and Ouellette, 1967; Nakagome, Smith, and Soukup, 1968; Schmid, 1969; Bühler, Müller, and Stalder, 1971; Caspersson et al, 1971; Noel et al, 1971); inversions (Jacobs and Ross, 1966; Sparkes, Muller, and Veomett, 1970); and dicentrics (see Table I). Comparison of 16 patients with dicentric Y chromosomes reveals a wide range of phenotypic, histological and cytogenetic variability. The possible bases for such disparity are considered in this paper.

Subjects and Methods

Case Report. L.P., an 11-year-old girl, was the product of a normal pregnancy but was born with an enlarged clitoris, rugated labia majora, absence of labia minora, and posterior labial fusion (Fig. 1a). She was delivered by breech extraction and weighed 2500 g. At birth, a buccal smear was negative; serum electrolytes and urinary 17-ketosteroids and pregnantriol were repeatedly found to be in the normal range. An intravenous pyelogram showed a double collecting system on the left with no evidence of hydrenephrosis. The initial diagnosis was probable pseudohemaphroditism.

At age 4 years, the enlarged clitoris, measuring 3 × 1 cm was totally excised (Fig. 1b). A vaginogram performed through the urogenital sinus opening confirmed the presence of a normal vagina measuring 4 cm in length. The urethra was anatomically normal. Laparotomy revealed that the uterus (2½ × 1 cm) was normally located with a normal tube and round ligament on the right side. The right ovary appeared to be a streak gonad 4 cm long and 8 mm wide.

The structures on the left, however, were distinctly abnormal in appearance. A ligamentous element, grossly resembling a fallopian tube, extended from the left cornu of the uterus. Attached to this structure at the level of the internal inguinal ring was a gonad (1½ × 1 cm) which had the appearance of a testis with a vas deferens.
The entire left gonad and ligamentous structure were removed for histological examination.

Histologically, the right gonad was diagnosed as a streak ovary with no follicles; no testicular tissue was observed. The left gonad consisted mainly of testicular elements with distinct tubules and a well formed epididymis paralleled by a well differentiated tube which had a fimbriated end. Near the epididymis was an adrenal nest, consisting of well encapsulated trabecules of vacuolated adrenal cortical cells. However, one small segment of ovarian stroma within the left gonad suggested an ovotestis.

The patient's development and health to the present are normal. Her linear growth has progressed along the 10th centile but intellectually she is in the dull normal range. At age 11 years, the patient manifests no obvious phenotypical stigmata of Turner's syndrome other than multiple naevi, and her external genitalia are those of a normal prepubertal girl.

Cytogenetic Studies

X-chromatin determination from buccal smears was performed on the proposita and her parents using cresyl echt violet staining. Chromosome preparations from cultures of phytohaemagglutinin stimulated peripheral lymphocytes were made following a modification of the technique of Moorhead et al (1960). Fibroblasts derived from a skin biopsy obtained at laparotomy were also examined. Autoradiography was performed on lymphocyte cultures of the patient by conventional techniques with exposure of the cells to 0.1 μc/ml of tritiated thymidine for the last 4.5 to 5 hours of culture (Schmid, 1963). More precise chromosome identification was achieved by fluorescent staining using the method of Lin, Uchida, and Byrnes (1971).

Results

The X-chromatin patterns of the parents were compatible with the phenotypic sex; however, the proposita showed a chromatin negative buccal smear. The karyotypes of the parents were morphologically and numerically normal. The father possessed a Y chromosome slightly smaller than the members of group G (21-22) (Fig. 2b).

The patient's chromosomes revealed two stem lines of cells: one with 45 chromosomes, lacking a member of the C group and the other with 46 chromosomes and a morphologically abnormal element (Fig. 2a). This marker chromosome was similar in size to a member of group E (16-18) and possessed two obvious centromeres in close proximity to each other (dicentric). Of 100 leucocyte metaphases studied, 52% contained 46 chromosomes with marker, the remainder being cells with 45 chromosomes. In skin fibroblasts, 28% of the cells had 46 chromosomes (with the marker) and 72% had 45 chromosomes. The X-chromatin negative buccal smear suggested that the missing

Fig. 1. The external genitalia of the proposita. Fig. 1a—before surgery. Note the clitoral enlargement, scrotalized labia majora, posterior perineal fusion, and a urogenital sinus. Fig. 1b—following total clitoridectomy.
chromosome of group C, in the cells with 45 chromosomes, was an X chromosome.

Autoradiographic analysis demonstrated that the dicentric marker was indeed late replicating, but more definitive identification came from fluorescent studies. The dicentric chromosome showed a brightly fluorescent area, characteristic of a Y chromosome (Fig. 2a), at each end. The brightly fluorescent regions were greatly reduced in size when compared with the more commonly observed human Y chromosome. This observation is understandable following fluorescence of the father’s small Y which also exhibited only a small fluorescent distal portion (Fig. 2b). Therefore, the karyotype of the patient is interpreted as 45,X/46,X, dic(Yq).

Discussion

Dicentric chromosomes are generally considered unstable elements since improper alignment of two centromeres on the metaphase spindle might lead to the formation of a bridge during anaphase. Nonetheless, some dicentrics do persist and replicate normally (Darlington and Wiley, 1953) since the proximity of the two centromeres is such that they may behave as monocentric elements (Sears and Camera, 1952). Dicentric chromosomes are perhaps the most frequently encountered example of structural rearrangements of the Y chromosome and 16 such cases have been reported (Table I). In marked contrast, dicentric autosomes are extremely rare.

Dicentric Y chromosome formation may occur in three alternative ways. (1) By a break in the short arm of the Y followed by reunion of the proximal ends of the chromatids in meiosis I, resulting in a dicentric following meiosis II and the reduction of the centromere. (2) By a break in either arm of the Y followed by sister-strand reunion leading to duplication-deficiency chromosomes of short or long arm material, depending on the location of the breaks. (3) By breaks in either arm of the two Y chromosomes in an XYY individual, followed by exchange. The most likely mechanism for the origin of the dicentric Y is either alternative 1 or 2. The fact that all but one of the patients thus far reported are mosaics, each possessing an 45,X cell line, would suggest a post-zygotic origin of the dicentric Y. However, since this particular abnormality may be unstable and therefore selected against, mosaicism alone should not be used as a criterion for temporal aetiology and a distinction between alternatives 1 and 2 cannot readily be made.

The apparent morphological similarity of many of the human dicentric Ys may be due to a specific location(s) on the Y chromosome which might be highly vulnerable to breakage. In most cases, the original breakage event in the Yq dicentrics must occur in the proximal region of the short arm, since breaks in the proximal region of the long arm would lead to a dic(Yp) (Starkman and Jaffe, 1967). The more distal the break in either arm, the greater will be the distance between centromeres, and those breaks beyond a critical distance from the centromere might lead to structural rearrangements which may be incapable of undergoing mitosis. Therefore, by selection, the long arm dicentric Ys as a group and the short arm dicentric Ys as a group should appear relatively morphologically similar.

The mosaicism observed in the patients in Table I could have arisen by either a prezygotic or a post-
TABLE I

PATIENTS POSSESSING DICENTRIC Y CHROMOSOMES

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Ascertainment</th>
<th>Karyotype</th>
<th>External Genitalia</th>
<th>Gonadal Findings</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>Turner's syndrome</td>
<td>X/X,dic(Y)</td>
<td>Infantile female</td>
<td>Bilateral streaks</td>
<td>Angell and Polani (cited by McIlree et al, 1966)</td>
</tr>
<tr>
<td>Female</td>
<td>Turner's syndrome</td>
<td>X/X,dic(Y)</td>
<td>Infantile female</td>
<td></td>
<td>Angell and Polani (cited by McIlree et al, 1966)</td>
</tr>
<tr>
<td>Male</td>
<td>Azoospermia</td>
<td>X/X,dic(Yq)</td>
<td>Normal male</td>
<td></td>
<td>McIlree et al (1966)</td>
</tr>
<tr>
<td>Female</td>
<td>Turner's syndrome</td>
<td>X/X,dic(Yp)</td>
<td>Infantile female</td>
<td>Ovarian stroma</td>
<td>Starkman and Jaffe (1967)</td>
</tr>
<tr>
<td>Female</td>
<td>Turner's syndrome</td>
<td>X/X,dic(Yp)</td>
<td>Infantile female</td>
<td>Ovarian stroma</td>
<td>Starkman and Jaffe (1967)</td>
</tr>
<tr>
<td>Male</td>
<td>Hypospadias; cryptorchidism</td>
<td>X/X,dic(Yq)/XYq</td>
<td>Male</td>
<td>Undifferentiated testis</td>
<td>Boschetti et al (1968)</td>
</tr>
<tr>
<td>Male</td>
<td>Hypospadias</td>
<td>X/X,dic(Yq)</td>
<td>Male</td>
<td>Streak (left); testis (right)</td>
<td>Ferrier et al (1968)</td>
</tr>
<tr>
<td>Male</td>
<td>Ambiguous genitalia</td>
<td>X/X,Y,X(X;X,dic(Y)/XX,dic(Yq))</td>
<td>Ambiguous</td>
<td>Testicular tissue</td>
<td>Yunis (1965)</td>
</tr>
<tr>
<td>Male</td>
<td>Ambiguous genitalia</td>
<td>X/X,Y(X;X,dic(Yq))/XX,dic(Yq)</td>
<td>Ambiguous</td>
<td>Testicular tissue</td>
<td>Talbert et al (1969)</td>
</tr>
<tr>
<td>Female</td>
<td>Turner's syndrome</td>
<td>X/X,dic(Yq)</td>
<td>Infantile female</td>
<td>Bilateral streaks</td>
<td>Angell et al (1970)</td>
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<tr>
<td>Female</td>
<td>Turner's syndrome</td>
<td>X/X,dic(Yq)</td>
<td>Infantile female</td>
<td>Testicular</td>
<td>Angell et al (1970)</td>
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<td>Female</td>
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<td>Angell et al (1970)</td>
</tr>
<tr>
<td>Male</td>
<td>Ambiguous genitalia</td>
<td>X/X,Y,X(X;X,dic(Yq)/XX,dic(Yq))</td>
<td>Ambiguous</td>
<td>Ovotestis</td>
<td>Ying and Ives (1971)</td>
</tr>
<tr>
<td>Female</td>
<td>Turner's syndrome</td>
<td>X/dic(Yq)</td>
<td>Female</td>
<td>Streak ovaries; ovarian stroma</td>
<td>Armendares et al (1972)</td>
</tr>
<tr>
<td>Female</td>
<td>Ambiguous genitalia</td>
<td>X/X,dic(Yq)</td>
<td>Ambiguous</td>
<td>Ovotestis</td>
<td>Present case</td>
</tr>
</tbody>
</table>

zygotic event. If, during meiosis the dicentric were formed and non-disjunction occurred at some stage following fertilization, mosaics with different proportions of the resultant cell lines would be observed. However, another possible mechanism which does not involve non-disjunction exists. If during the first zygotic division, the dicentric Y is formed, it will behave as an attached Y chromosome after replication. Therefore, following mitosis two cell lines (X/X,dic[Y]) will occur. This mechanism will explain most of the observed cases. However, the cases of Jalbert et al (1969) and Ying and Ives (1971) must have undergone such a process later in embryonic development since multiple cell lines exist, one of which retains a normal Y chromosome. These two cases, of necessity, also involve non-disjunction. The non-mosaic case of Armendares et al (1972) most likely represents a prezygotic event, resulting in dicentric formation before the second meiotic division, and fertilization by a sperm bearing a dicentric Y chromosome without subsequent non-disjunction.

The patient described in this report does not exhibit the phenotype commonly associated with Turner's syndrome. However, the cytogenetic and histological evidence strongly suggests mixed gonadal dysgenesis. Of the 16 patients described in Table I, nine have been classified as female and six as male (one unclassified). They manifest a wide spectrum of phenotypic variation, being ascertained due to clinical manifestations of Turner's syndrome, ambiguous genitalia, hypospadias, and azoospermia. Similar variation occurs in the appearance of the external genitalia, which range from normal male or infantile female to ambiguous genitalia of varying degrees. Histological examination of the gonads of these patients exhibits multiple combinations of tissue, such as undifferentiated ovarian streaks, ovotestis, and frank testicular architecture but without evidence of spermatogenesis. It is therefore obvious that, although all the patients possess a dicentric Y chromosome, a unique phenotype cannot be ascribed to this chromosomal abnormality.

The dicentric Y chromosome is, obviously, not identical in all patients. Most cases involve the duplication of predominantly long arm material (dic[Yq]), while three patients possess a duplication
primarily of the short arm (dic(Yp)). It is interesting that histological evidence of testicular material was present in almost all cases of dic(Yq), but in none of the dic(Yp) individuals, which exhibit only ovarian stroma (see Table I). This finding, perhaps, suggests that the determinants for testicular development may reside in the long arm of the Y chromosome (Ferguson-Smith, 1965; Jacob and Ross, 1966; McClure et al., 1966). However, additional evidence that the long arm of the Y chromosome may also contain genes for testicular development exists (Federman et al., 1967; Sarto, Opitz, and Inhorn, 1969). Even among the cases of Y dicentrics, although the marker chromosomes may be morphologically similar, the sites of breakage and reunion may not be exactly the same. Therefore the presence or absence of given genes depends directly upon the point of breakage. Even though a dic(Yq) might be present, the genes necessary for testicular development may be lacking, due to the specific location of the break. Since testicular tissue might be absent, such patients might resemble females according to the studies of Jost (1947). A case in point is patient No. 2 described by Angell, Giannelli, and Polani (1970).

Finally, the fact that all cases of Y dicentrics, with the exception of the one reported by Armendares et al. (1972), are mosaic individuals must be considered. Since mosaicism most frequently indicates a postzygotic event, the precise stage at which the non-disjunction might occur would have an important bearing as to the phenotype of the patient. If the Y chromosome were present during the proper ontologic period of gonadal development, male structures might be present. If, however, the non-disjunction had occurred before this time so that a 45,X constitution existed in the critical cells of the gonadal anlage, such individuals would probably exhibit manifestations of Turner’s syndrome. The embryonic timing of such events, therefore, may also influence the phenotypic variability observed.

We thank Drs H. Jockin and J. Fisher for the histological studies; Pamela Borchert, Laurie Quinn, Geri Krypel, Terry Hartnett, and Claudia Hastings for technical assistance. Additionally, we are indebted to Drs J. Wahlman and R. G. Davidson for helpful discussion and critical reading of the manuscript. The work was supported in part by a grant from the US Department of Health Education and Welfare—Division of Maternal and Child Health Service (Project No. 417).

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