Del(Yq) Syndrome

Contents

In 1976, Tiepolo and Zuffardi (1976) first recognized the deletions of the long arm of the Y chromosome, large enough to be recognized by light microscopy, in six azoospermic men. Large structural rearrangements of the Y chromosome are known to be commonly associated with a 45, X/46,XY chromosomal mosaicism (Siffroi et al. 2000). Majority of Yq deletions are microdeletions and, therefore, require analysis by molecular means (Martin 2008).

Synonyms and Related Disorders

Chromosome Yq deletion syndrome

Genetics/Basic Defects

1. Role of Yq deletions in male infertility (Ma et al. 2000)
    1. Factors controlling human spermatogenesis: postulated to be located on the distal portion of the euchromatin segment of the long arm of the Y chromosome, Yq11 (Tiepolo and Zuffardi 1976).
    2. This spermatogenesis locus at Yq11.23, as demonstrated with high-resolution banding techniques, has since come to be known as the "azoospermia factor" or "AZF" (Bühler 1985).
    3. Further molecular investigations into genotype-phenotype correlation in azoospermic men led to the localization of the *AZF* locus to interval 6 of the Y chromosome (Vergnaud et al. 1986; Affara et al. 1986; Andersson et al. 1988).
    4. Microdeletions of the long arm of the Y chromosome.
        1. Represents the most frequent molecular genetic cause of severe male infertility (Ferlin et al. 2006; Krausz and Degl'Innocenti 2006)
        2. The first solid molecular evidence that failure of spermatogenesis may be caused by cytologically undetectable deletions on the Y chromosome: identification of two nonoverlapping microdeletions mapped to the distal region of intervals 5 and 6, carried by two azoospermic otherwise normal men (Ma et al. 1992)
        3. Further studies led to the proposal of the existence of three *AZF* subregions

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termed *AZFa* (formerly JOLAR region), *AZFb*, and *AZFc* (formerly KLARD region), respectively (Vogt et al. 1996).
   1. Deletion of AZFa: associated with lack of germ cells or Sertoli cell-only syndrome.
   2. Deletion of *AZFb*: associated with spermatogenesis arrest.
   3. *AZFc* gene products: involved in the maturation process of postmeiotic germ cells (Vogt et al. 1996).
   4. The above hypothesis remains controversial and it is generally accepted that the completion of spermatogenesis requires multiple genes not only on the Y chromosome but elsewhere as well.
4. Recent description of another *AZF* subregion further complicated the issue: *AZFd*: localized between *AZFb* and *AZFc* (Kent-First et al. 1999).
5. The discovery of the two separate microdeletions on the Yq in infertile men subsequently led to the identification of four candidate gene families for *AZF*:
   1. RNA-binding motif (*RBM*), previously named Y-linked RNA recognition motif (*YRRM*) (Ma et al. 1993)
   2. Deleted in azoospermia (*DAZ*) (Reijo et al. 1995)
   3. *Drosophila* fat facets related Y (*DFFRY*) (Brown et al. 1998)
   4. *C*hromodomain Y (*CDY*) (Lahn and Page 1999)
5. Male infertility: most likely result from deletions and/or mutations of one or more of the myriad of genes necessary for spermatogenesis (Krausz et al. 2003)

2. 45,X cell line associated with large cytogenetically visible Yq deletions (Hwa et al. 2004; Cui et al. 2007)
   1. Structural aberrations of the Y chromosome, such as large cytogenetically visible deletions of the long arm, ring Y, *iso*- or isodicentric short arm, are unstable and usually lost during mitosis, leading to mosaic 45,X (Hsu 1994; Kirsch et al. 2000; Siffroi et al. 2000; Bertini et al. 2005).
   2. In the presence of a 45,X cell line, a fetus has a risk of being a phenotypic female with Turner syndrome manifestations or to have ambiguous external genitalia, whether the other cell line is Yp, Yq, Yp plus Yq, or even a free Y chromosome (Hsu 1994).
   3. Patients with Turner syndrome with a Y-derived marker have milder phenotypic abnormalities than those with an X-derived marker. In general, patients with a Y-derived marker are not as short as, and have fewer somatic abnormalities than, patients with an X-derived marker chromosome (Schwartz et al. 1997).

Clinical Features

1. Deletion/microdeletion of the long arm of the Y chromosome
   1. Men with deletions, in general, are infertile and therefore deletions are not transmitted to sons unless in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) are performed.
   2. Associated with severe oligozoospermia.
2. Phenotype-genotype correlative analyses (Cram et al. 2000)
   1. Identified four subregions within AZF, called AZFa, b, d, and c
   2. Most deletions observed in infertile men occur in the AZFc region (Totonchi et al. 2012; Elfateh et al. 2014): associated with severe oligospermia or azoospermia and occasionally oligozoospermia
   3. Men with more extensive deletions in the AZFb region that extend into the AZFa region: commonly exhibit histologic phenotypes such as germ cell arrest or Sertoli cell-only syndrome and as a result are usually azoospermic
   4. Men with deletions localized exclusively to AZFd: present with mild oligozoospermia or even normal sperm counts

associated with abnormal sperm morphology (Kent-First et al. 1999)

3. Phenotypes of 45,X/46,X,del(Y)(q11) (Werner et al. 1985; Hwa et al. 2004)
    1. Phenotypic males (34.2%): small testes, short stature, small penis, hypospadias, azoospermia, Turner syndrome, and gonadoblastoma (Hsu 1994).
    2. Intersex (47.4%).
    3. Phenotypic females (18.4%).
    4. Only a few cases of mos45,X/46,X,del(Y) reported with normal male external genitalia (Bühler 1980; Hoshi et al. 1998).
    5. The deletions of Y chromosomes are associated with abnormalities of the external genitalia, secondary sexual characteristics, and/or gonadal function.
    6. These phenotypic differences are related not only to the presence or absence of the *SRY* gene on Yp but also to the proportion of 45,X line in gonadal tissue.
        1. A sufficient SRY transcript level is necessary to trigger testes formation: once testes differentiate, male endocrine function is responsible for the rest of the events involving male phenotypic sexual differentiation.
        2. When the 45,X line is predominant in gonadal tissue, the phenotype of Turner syndrome would appear.
4. A case of Y chromosome with terminal deletion associated with nondisjunction, leading to mosaicism of three cell lines, has been reported (Cui et al. 2007): an azoospermic male with complete masculinization associated with karyotype 45,X/46,X,del(Y)/ 47,X,del(Y),del(Y)

Diagnostic Investigations

1. Diagnostic investigations of all infertile men (Bhasin 2007)
    1. Several semen analyses
        1. Sperm count
        2. Sperm motility
        3. Sperm morphology
    2. Hormone measurements (testosterone, LH, and FSH levels) to help determine:
        1. Low testosterone and low or inappropriately normal LH and FSH: gonadotropin deficiency: hypogonadotropic hypogonadism (Gnoth et al. 2005)
        2. Low testosterone, elevated LH, and FSH: obtain karyotype: primary testicular failure
        3. Normal testosterone and LH, elevated FSH: spermatogenic failure, test for Yq microdeletion
        4. High testosterone, elevated LH: androgen resistance
        5. Normal testosterone, normal LH, and FSH (Templeton 2000)
            1. Majority of infertile men: have normal testosterone, LH, and FSH levels
            2. Azoospermia: rule out obstruction by postejaculatory urine and seminal fructose and screen for Yq microdeletions
            3. Oligo/asthenozoospermia: exclude antisperm antibodies
2. Genetic testing of infertile couples and the offspring: important, especially in couples who are being considered for ICSI
    1. All infertile men with nonobstructive azoospermia, severe oligozoospermia, or very small testes should be offered a karyotype (Simpson and Lamb 2001; Allen et al. 2006).
    2. Screen infertile men with azoospermia or severe oligozoospermia for Yq microdeletions (Cram et al. 2006; Ferlin et al. 2007).
    3. Azoospermic men with at least one absent vas deferens or with evidence of normal spermatogenesis should be tested for CFTR mutations (Anguiano et al. 1992).
    4. Consider CREM mutations in men with postmeiotic maturation arrest (Blendy et al. 1996; Peri et al. 1998; Weinbauer et al. 1998).
    5. Genetic testing is indicated in men in whom personal or family history suggests disorders that have a genetic basis such as hemoglobinopathies and myotonic dystrophy (Takeda and Ueda 1977; Kletzky et al. 1979; Marchini et al. 2000); these patients also need genetic counseling.

3. Yq microdeletions are detected by PCR-based mapping of several conserved molecular markers or genes located within and outside the AZF region; these tests are available from commercial laboratories. With the availability of precise Y chromosome maps, more specific molecular markers have been developed, and guidelines for standardized testing of Yq microdeletions have been published by the European Molecular Genetics Network (Simoni et al. 2004). A novel universal multiplex PCR improves detection of AZFc Y-chromosome microdeletions (Zheng et al. 2014).
4. Array comparative genomic hybridization approach: a reliable high-resolution alternative to multiplex polymerase chain reaction for the discovery of pathogenic chromosome Y microdeletions in male infertility (Osborne 2007; Yuen et al. 2014).
5. GENOSEARCHTM AZF Deletion kit for the detection of a panel of AZF deletions using Luminex xMAP arrays: provides a routine tool for the diagnosis of AZF deletions in male infertility in Japan and also be useful for the detection of atypical microdeletions (Iijima et al. 2014).

Genetic Counseling

1. Recurrence risk
    1. Patient's sib
        1. Father without Yq deletion: since most Yq microdeletions occur de novo, the recurrence risk to the male sibling is not significantly increased.
        2. Father with Yq deletion: Father's Yq deletion will be transmitted to the male sibling.
    2. Patient's offspring
        1. The genetic defects responsible for infertility in the parent may be transmitted to the offspring through ICSI: Yq deletions will be transmitted to male offspring (Page et al. 1999; Cram et al. 2000; Simpson and Lamb 2001; Ferlin et al. 2007).
        2. Children born through ICSI have increased risk of sex chromosome aneuploidy (45,X and 47,XXY embryos) (Palermo et al. 1999; Ferlin et al. 2007).
        3. Children born through ICSI to infertile couples may have a higher risk of being infertile or subfertile (Cram et al. 2006): may need counseling upon reaching adulthood and surveillance of their reproductive function.
2. Prenatal diagnosis
    1. Prenatal testing, including chorionic villous sampling, may be appropriate in some couples undergoing ICSI.
    2. A fetus with a prenatally diagnosed mosaic 45,X/46,X,del (Y)(q11.2) karyotype from amniotic fluid, in which the deletion was defined by polymorphic microsatellite markers analysis and multiplex STS-PCR.
3. Management (Krausz and Degl'Innocenti 2006; Bhasin 2007)
    1. Gonadotropin therapy: highly effective in gonadotropin-deficient men
    2. Intracytoplasmic sperm injection (ICSI): emerges as the treatment of choice for idiopathic male factor infertility
        1. Expensive
        2. Associated with the following higher risks compared to naturally conceived pregnancies:
            1. Multiple gestation
            2. Low birth weight
            3. Preterm delivery
            4. Perinatal complications
            5. Chromosome aneuploidy
    3. Men with Yq microdeletions considering ICSI should be offered:
        1. Karyotyping
        2. Yq microdeletion testing
        3. Genetic counseling
            1. Obligatory transmission of Yq deletion to male offspring
            2. The phenotype of son: varies substantially and the extent of spermatogenic failure cannot be predicted entirely due to different genetic background and the presence or absence of

environmental factors with potential toxicity to reproductive function
3. A significant proportion of spermatozoa from men with Y microdeletion are nullisomic for sex chromosomes (Siffroi et al. 2000; Jaruzelska et al. 2001), indicating a potential risk for the offspring to develop 45, X Turner syndrome and other phenotypic anomalies associated with sex chromosome mosaicism, including ambiguous genitalia.
4. Screening for Y chromosome microdeletions in patients bearing a mosaic 45,X/46,XY karyotype with sexual ambiguity and/or Turner stigmata has shown a relatively high incidence of AZFc deletions (33%) (Patsalis et al. 2002).
5. Yq microdeletions could be associated with an overall Y chromosomal instability leading to the formation of 45,X cell lines (Le Bourhis et al. 2000; Jaruzelska et al. 2001; Patsalis et al. 2005).
6. Despite this theoretical risk, the 36 babies (18 male and 18 female) born from fathers affected by Yq microdeletions are phenotypically normal (Krausz et al. 2003). This could be due to the reduced implantation rate and a likely higher risk of spontaneous abortions of embryos bearing a 45,X karyotype.
7. In order to avoid the transfer of embryos with sex chromosome mosaicism, preimplantation diagnosis could be offered to the couple. This analysis, together with the abortion rate, would provide a more realistic estimation about the real risks of 45, X/46,XY mosaicism and Turner syndrome.

4. The screening for Yq deletions: of additional clinical utility in azoospermic men in which the type of deletion may have prognostic value for testicular sperm retrieval
5. Testicular sperm extraction (TESE): not recommended for complete AZFa or AZFb deletions since the probability of the presence of mature sperm is virtually zero
6. Advice cryoconservation of sperm as a preventive therapy since it is a noninvasive procedure.
7. The development of assisted reproductive techniques (intracytoplasmic sperm injection and testicular sperm extraction) helps to bypass the natural barriers of fertilization, but it increases the concern about the transmission of genetic defects such as Y chromosome microdeletions (Suganthi et al. 2014).

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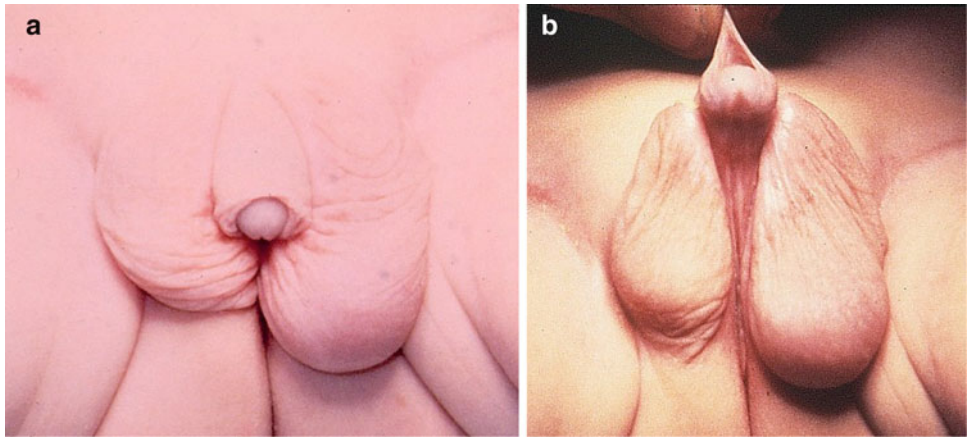

Fig. 1 (**a**, **b**) An infant with del(Yq) showing ambiguous genitalia with a palpable gonad in the left scrotal sac

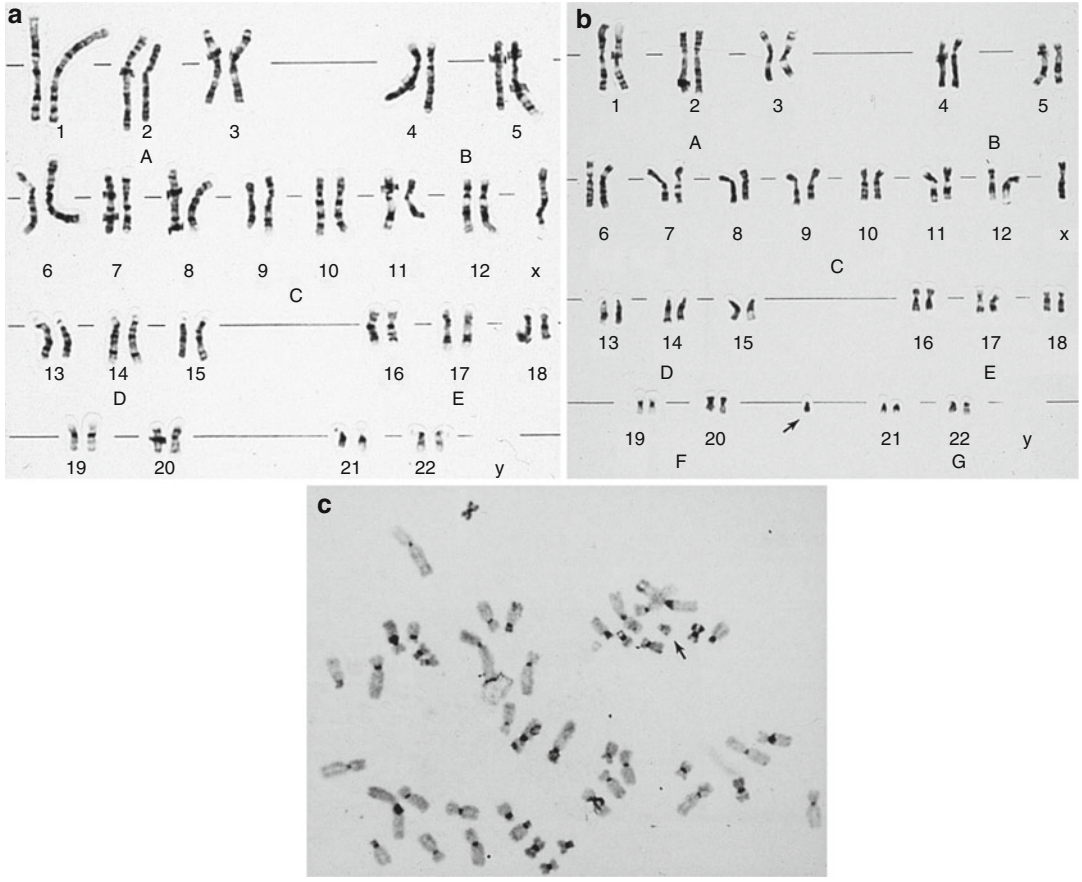

Fig. 2 (**a**–**c**) G-banding karyotypes showed mosaic 45,X/46,X,del(Yq). The del(Yq) (*arrow*) is shown in a C-banded metaphase

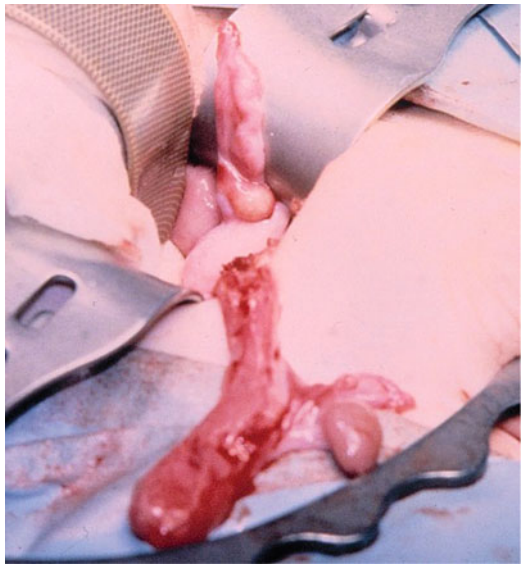

Fig. 3 A gonad is noted at the surgery

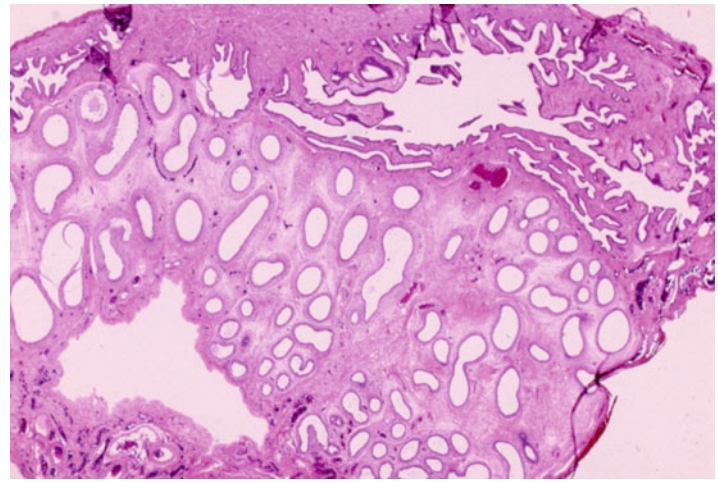

Fig. 4 Fallopian tube-epididymus is shown here on the histologic examination of the specimen

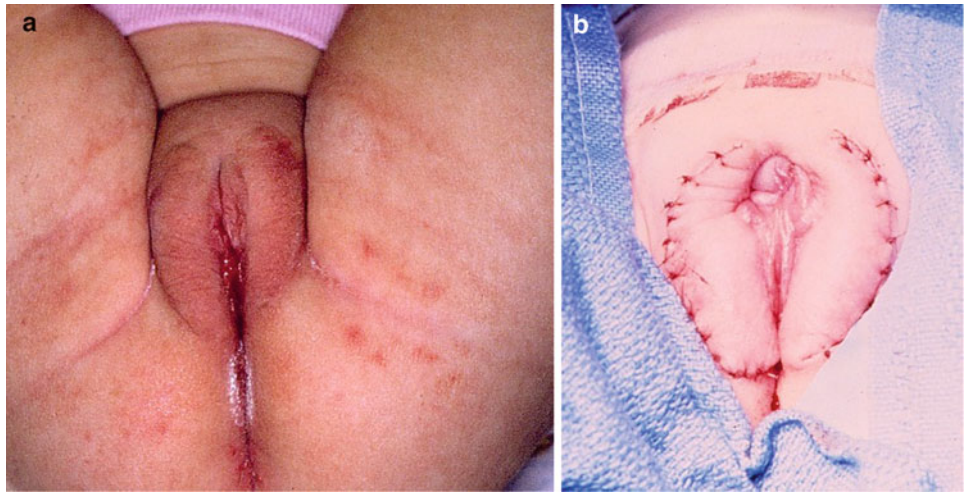

Fig. 5 (**a**, **b**) Successful vaginal reconstruction surgery

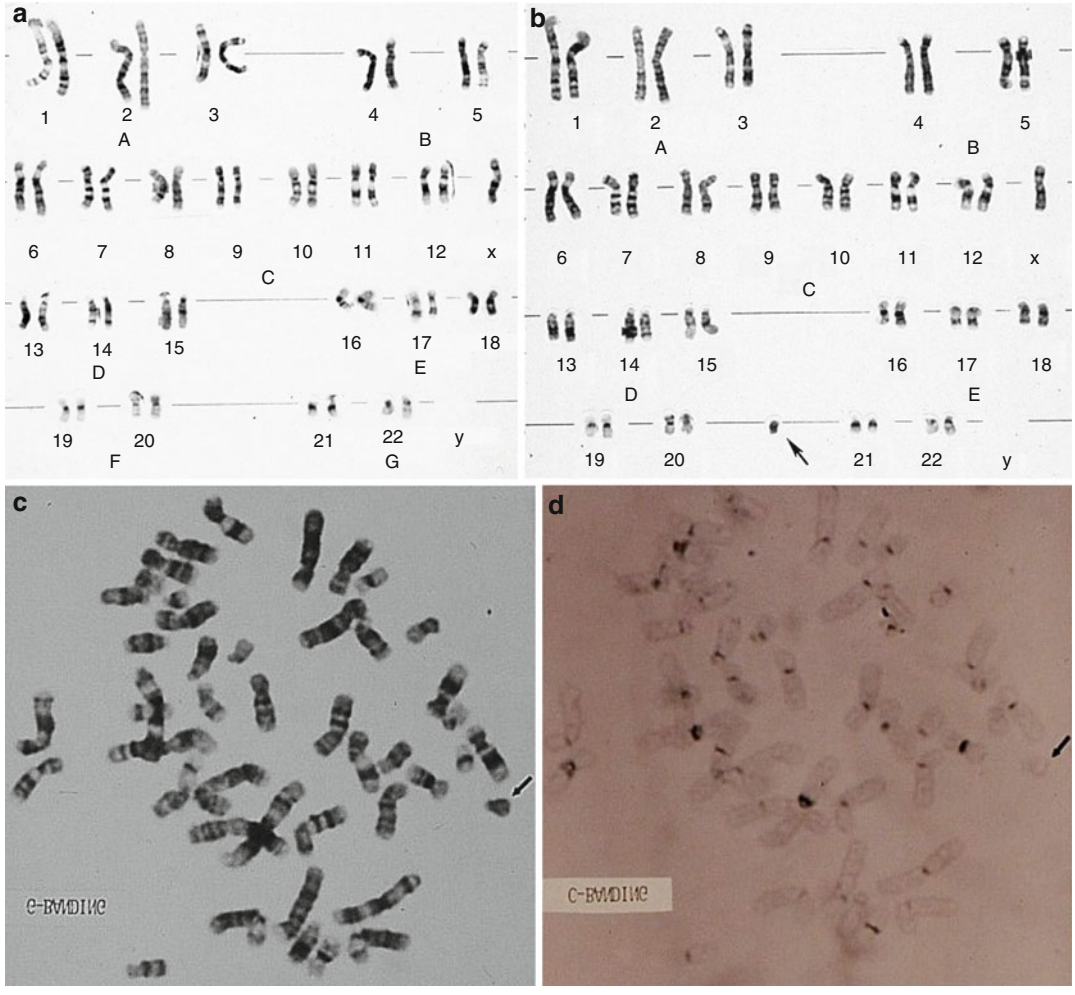

Fig. 6 (**a**–**d**) Another patient with del(Yq) with G- and C-bands showing 45,X/46,X,del(Yq)

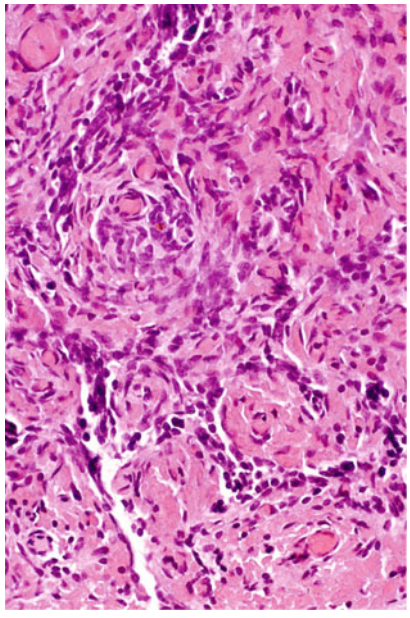

Fig. 7 Dysplastic ovary is shown here

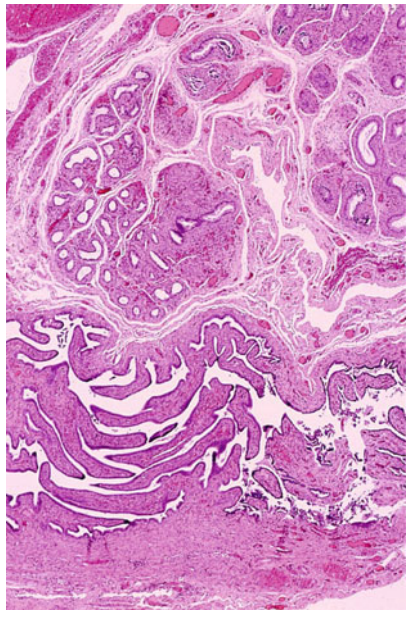

Fig. 8 Epididymus-fallopian tube is shown here

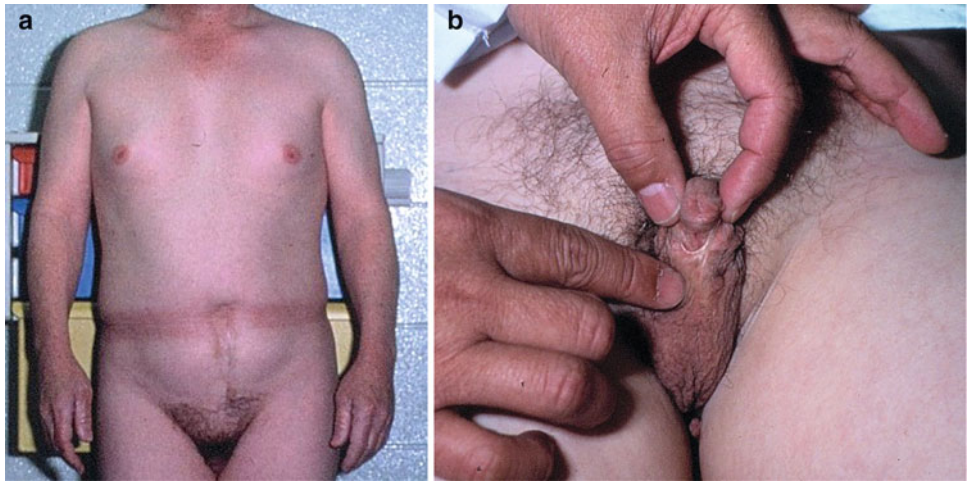

Fig. 9 (**a**, **b**) Another adult male patient with del(Yq) showing short stature, female distribution of the pubic hair, and ambiguous genitalia