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Chromosomal Variants in Klinefelter Syndrome

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Key Words
Chromosome · Klinefelter syndrome · Sex chromosome abnormalities

Abstract
Klinefelter syndrome (KS) describes the phenotype of the most common sex chromosome abnormality in humans and occurs in one of every 600 newborn males. The typical symptoms are a tall stature, narrow shoulders, broad hips, sparse body hair, gynecomastia, small testes, absent spermatogenesis, normal to moderately reduced Leydig cell function, increased secretion of follicle-stimulating hormone, androgen deficiency, and normal to slightly decreased verbal intelligence. Apart from that, amongst others, osteoporosis, varicose veins, thromboembolic disease, or diabetes mellitus are observed. Some of the typical features can be very weakly pronounced so that the affected men often receive the diagnosis only at the adulthood by their infertility. With a frequency of 4%, KS is described to be the most common genetic reason for male infertility. The most widespread karyotype in affected patients is 47,XXY. Apart from that, various other karyotypes have been described, including 46,XX in males, 47,XXY in females, 47,XX,der(Y), 47,X,der(X),Y, or other numeric sex chromosome abnormalities (48,XXXY, 48,XXYY, and 49,XXXXY). The focus of this review was to abstract the different phenotypes, which come about by the various karyotypes and to compare them to those with a 'normal' KS karyotype. For that the patients have been divided into 6 different groups: Klinefelter patients with an additional isochromosome Xq, with additional rearrangements on 1 of the 2 X chromosomes or accordingly on the Y chromosome, as well as XX males and true hermaphrodites, 47,XXY females and Klinefelter patients with other numeric sex chromosome abnormalities. In the latter, an almost linear increase in height and developmental delay was observed. Men with an additional isochromosome Xq show infertility and other minor features of 'normal' KS but not an increased height. Aside from the infertility, in male patients with other der(X) as well as der(Y) rearrangements and in XXY women no specific phenotype is recognizable amongst others due to the small number of cases. The phenotype of XX males depends on the presence of *SRY* (sex-determining region Y) and the level of X inactivation at which *SRY*-negative patients are generally rarely observed.

Klinefelter syndrome (KS) was first described by Harry F. Klinefelter in 1942 [Klinefelter et al., 1942]. He reported 9 men with testicular abnormalities who failed to produce sperm and had gynecomastia. In 1959, this was found to be the result of an additional X chromosome [Jacobs and Strong, 1959]. About 80% of KS patients show a 47,XXY karyotype, 20% have other numeric sex chromosome abnormalities (48,XXXY, 48,XXYY, 49,XXXXY), 46,XY/47,XXY mosaicism, or structurally abnormal sex chromosomes [Lanfranco et al., 2004].

In approximately half of the Klinefelter cases the aberrant X chromosome is thought to be paternally derived, and recent evidence suggests that it may be related to advancing paternal age, although this is controversial [Ja-

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cobs et al., 1988; Lowe et al., 2001]. With a frequency of 1 out of 600 newborn males KS is described to be the most common sex chromosome abnormality [Bojesen and Gravholt, 2007]. Affected patients are characterized by an increase of the body height of about 6.5 cm, narrow shoulders, broad hips, sparse body hair, gynecomastia, small testes, absent spermatogenesis, normal to moderately reduced Leydig cell function, increased secretion of follicle-stimulating hormone (FSH), androgen deficiency, and normal to slightly decreased verbal intelligence [Bojesen and Gravholt, 2007; Wikstrom and Dunkel, 2008]. Apart from that, amongst others, osteoporosis [van den Bergh et al., 2001], varicose veins, thromboembolic disease [Igawa and Nishioka, 2003], or diabetes mellitus [Ota et al., 2002] are observed. KS is the most frequent genetic cause of male infertility, and is found in 11% of azoospermic men and 4% of infertile men [Wikstrom and Dunkel, 2008]. In most of the cases KS is not diagnosed before puberty and even in adulthood it was estimated that only a fourth of affected males receive diagnosis, mostly by their infertility [Bojesen and Gravholt, 2007], because in many cases the phenotype is not as distinct as described above.

If somebody has an additional X chromosome, there is an excess of X-chromosomal genes. Normally 1 of the 2 X chromosomes in a female is inactivated, but it has been shown that in total, about 15% of X-linked genes escape inactivation [Carrel and Willard, 2005]. The same applies for KS patients and, therefore, it is very likely that these genes are responsible for most of the KS features.

Over the last almost 50 years there have been reported many cases of KS patients with a different karyotype than 47,XXY. These variants show, amongst others, a 47,X,der(X),Y karyotype, a 47,XX,der(Y) karyotype, an additional isochromosome Xq, as well as translocations or deletions involving one of the sex chromosomes. Apart from that there have been reported a lot of male cases with a 46,XX karyotype as well as women with a 47,XXY chromosome complement. In addition to all these patients with variations on the sex chromosomes, male KS patients with 2 X and 1 Y chromosomes and an additional rearrangement on one or more autosomal chromosomes have been described.

Methods

In this review we focused on the different genetic variants of the sex chromosomes in KS patients. Therefore, we attended to male patients with 2 or more X chromosomes and women with a 47,XXY karyotype. The aim of the review is to summarize the diverse phenotypes of these different variants of KS and to compare them to that of the classical 47,XXY KS patients. For our search we used 2 different databases: First PubMed using the following search terms: 'Klinefelter' AND 'Syndrome'; 'Klinefelter' AND 'Isochromosome X'; '46 XX' AND 'Male'; '47 XXY' AND 'Female'; '48 XXYY'; '48 XXXY' and '49 XXXXY' and second for the KS cases with derivative X or Y chromosomes the online database of the Jena University Hospital, Institute of Human Genetics, Jena (Germany). All searches were restricted to articles in English and German. We were looking exclusively for studies in which additional aberrations on the sex chromosomes were described. Articles on additional autosomal chromosomes or 47,XXY/46,XY karyotypes were excluded. For 46,XX males and 47,X,der(X),Y patients we included only *SRY* (sex-determining region Y) and *XIST*- (X (inactive)-specific transcript) positive patients or those where the breakpoints were obviously distal to the *XIST* location.

In the end we found more than 300 articles of KS variant patients at which most of the studies describe KS patients with other numeric sex chromosome abnormalities and XX males. Much of the literature was published between the 60s and 80s of the last century. In these cases the used ISCN nomenclature differs from the current version. To prevent misinterpretation or even adulteration of the original karyotypes, we always took over the karyotypes as indicated in the original literature.

Klinefelter Patients with an Additional Isochromosome Xq

The prevalence of the Klinefelter variant with an additional isochromosome Xq is calculated to be between 0.3–0.9% in males with a KS phenotype [Arps et al., 1996]. The first study of a 47,X,i(Xq),Y male was reported in 1969 [Zang et al., 1969]. Apart from that, to our knowledge, 24 further cases of isochromosome Xq have been reported so far [Demirhan et al., 2009]. Most of them described a monocentric isochromosome. The clinical and laboratory data on these cases are summarized in table 1. The patients show a nearly similar phenotype with characteristic features such as infertility, elevated plasma luteinizing hormone (LH) and FSH levels, low or normal testosterone levels, sometimes gynecomastia, normal to reduced body height, and a normal to slightly reduced intelligence level [Demirhan et al., 2009]. Most of the literature indicated that the normal height is due to the presence of only one Xp carrying the growth gene *SHOX* (short stature homeobox-containing gene) [Richer et al., 1989; Stemkens et al., 2007] and other putative Xp-specific growth genes [Rao et al., 1997]. The observation of increased body height in a KS patient with an isodicentric X (pter→q22::q22→pter), with 3 copies of Xp and one distal part of Xq, is in agreement with this theory [Zelante et al., 1991].

Table 1. Clinical features in 25 patients with KS and an additional isochromosome Xq sorted by the year of publication

Case No.	Reference	Age	Age (mother)	Age (father)	Height cm	Weight kg	Beard	Gyneco-mastia	Testes	FSH ↑	LH ↑	Testoster-one level	Karyotype[a]
1	Demirhan et al., 2009	37		–	170	63	yes	no	n	yes	yes	n	47,Xi(Xq),Y
2	Höckner et al., 2008	37	30	39	180	91	no	no	small	yes	yes	n	47,XY,i(X)(q10)
3	Stabile et al., 2008	25		–	178	75	yes	–	small	yes	n	n	47,X,i(Xq),Y
4	Stemkens et al., 2007	30			174.5	89	yes	no	n	yes	yes	n	47,X,i(X)(q10),Y,9ph
5	Arps et al., 1996 (case A)	prenatal		–	–	–	–	–	–	–	–	–	47,X,i(Xq),Y
6	Arps et al., 1996 (case B)	prenatal		–	–	–	–	–	–	–	–	–	47,X,i(Xq),Y
7	Arps et al., 1996 (case 1)	28		–	175	75	–	yes	–	yes	yes	↓	47,X,i(Xq),Y
8	Arps et al., 1996 (case 2)	21		–	171	66	–	no	–	yes	yes	n	47,X,i(Xq),Y
9	Arps et al., 1996 (case 3)	41		–	170.5	77	–	no	–	yes	yes	↓	47,X,i(Xq),Y
10	Arps et al., 1996 (case 4)	37		–	181	64	–	no	–	yes	yes	↓	47,X,i(Xq),Y
11	Arps et al., 1996 (case 5)	40		–	168	–	–	no	–	yes	yes	n	47,X,i(Xq),Y
12	Zelante et al., 1991	27			178	75		no	small	yes	yes	↓	47,X,idic(Xq),Y
13	Richer et al., 1989	30	25	25	165	59	yes	no	small	yes	yes	n	47,Xi(Xq),Y
14	Kleczkowska et al., 1988; Fryns et al., 1990 (case 1)	28		–	198	89	–	yes	small	yes	n	↑	47,Xi(Xq),Y
15	Bleau et al., 1987	30		–	165	59	yes	–	small	yes	yes	n	47,X,i(Xq),Y
16	McDermott, 1978	29		–	163	52.7	–	–	small	–	–	–	47,X,i(Xq),Y
17	Donlan et al., 1987	17	27	33	160	60	no	yes	small	yes	yes	↓	47,X,i(Xq),Y
18	Geneix et al., 1983	31	20	30	166	57	no	–	small	yes	yes	n	47,X,i(Xq),Y
19	Ponzio et al., 1980	33	33	35	168	63	–	yes	small	yes	yes	↓	47,X,i(Xq),Y
20	Trunca et al., 1979	32		–	n	n	–	yes		yes	yes	↓	47,X,i(Xq),Y
21	Kalousek et al., 1978	24		–	166.4	77.7	no	–	small	yes	yes	↓	47,X,i(Xq),Y
22	Gardiner et al., 1978	36		–	164.5	–	yes	no	small	yes	yes	↓	47,X,i(Xq),Y
23	Zang et al., 1969	44 31.3	36 28.5	36 33	176 172	84 70.9	no yes: 6/11	yes yes: 6/16	small small: 13/15	– yes: 19/19	– yes: 17/19	– n: 9/19 ↓: 9/19 ↑: 1/19	47,X,i(Xq),Y
24	Alliet et al., 1989	prenatal	38	29	–	–	–	–	–	–	–	–	46,XY/47,X,i(Xq)Y
25	Kleczkowska et al., 1988; Fryns et al., 1990 (case 2)	18	–	–	164.5	57	–	–	small	–	–	–	47,XXY/48,XXi(Xq),Y

FSH = Follicle-stimulating hormone; LH = luteinizing hormone; n = normal; ↑ = increased; ↓ = decreased.

[a]All karyotypes are indicated like in the corresponding literature.

All references not mentioned in the text are available in an online supplementary reference list (for all online supplementary material, see www.karger.com/doi/10.1159/000327324).

Zang et al. [1969] described the origin of an additional isochromosome Xq as an unusual event, because it would require a double error during meiosis. Arps et al. [1996] proposed that the most probable origin of an additional isochromosome Xq is a misdivision of the centromere or a sister-chromatid exchange of one X chromosome. Höckner et al. [2008] investigated a male patient with a 47,X,idic(X)(p11.1),Y karyotype and found loss of heterozygosity for all informative Xq markers on the isochromosome and the presence of the other maternal allele on the normal homolog in each case of maternal heterozygosity. These results are in line with a maternal origin of a true dicentric isochromosome and not a maternal Xq/Xq translocation, and most likely postzygotic formation subsequent to a nondisjunction in maternal meiosis II [Höckner et al., 2008].

Klinefelter Patients with Additional Aberrations on One of the Two X Chromosomes

In the literature, only 5 cases with a 47,X,der(X),Y karyotype have been described. All of the cases were reported before 1981. Therefore, there is only little information about these rearrangements. The clinical and laboratory data on these cases are summarized in table 2. The first case showing such a karyotype was reported by Nielsen who described a male KS patient with terminal deleted X chromosome mosaic (10% normal 46,XY cells) [Nielsen, 1966]. At the age of 54 years, the man was just 160 cm tall and his whole body hair was scanty. He did not show gynecomastia, his penis was of normal size, and his testes were soft and measured 10 mm from pole to pole. His personality was described as childish and prim-

Table 2. Clinical features in 5 male patients with KS and a 47,XY,der(X) karyotype sorted by the year of publication

Case No.	Reference	Age	Age (mother)	Age (father)	Height cm	Weight kg	Gyneco-mastia	Testes	FSH↑	LH↑	Testoster-one level	Karyotype[a]
1	Fryns, 1981	30	–	–	172	59	no	small	yes	no	↓	47,XY,+del(Xp11)
2	Patil et al., 1981	19	37	40	181	67.5	yes	small	yes	yes	↓	47,XY,del(X)(pter→q22:)
3	Nielsen et al., 1976	18	–	–	163.5	52.9	no	4.5 cm	yes	yes	n	47,X,del(X)(p11→q13::q21→q24),del(Y)(q11)
4	Chandra et al., 1971	–	–	–	tall	–	yes	small	–	–	–	47,XXq-Y
5	Nielsen, 1966	54	33	31	160	–	no	small	–	–	–	47,XY,der(X)[63]/46,XY[6]

FSH = Follicle-stimulating hormone; LH = luteinizing hormone; n = normal; ↑ = increased; ↓ = decreased.
[a]All karyotypes are indicated like in the corresponding literature.
All references not mentioned in the text are available in an online supplementary reference list.

itive and in comparison with 'normal' Klinefelter patients he showed more marked personality defects and his sexual activity was more pronounced. The sex chromatin percentage in buccal smear was 14% which is less than usually found in patients with KS. The decreased body height in the man, stands, because of his 2 Xp arms, in contrast to the hypothesis about the relevance of the number of *SHOX* gene copies, but it should be mentioned that Nielsen et al. published the case in 1966 and it is not possible to control the correctness of the karyotype.

Chandra et al. [1971] also reported a male patient with a 47,XXq-Y karyotype. A little less than half of the long arm appears to have been deleted from one of the X chromosomes. One sex chromatin body could be seen in 40–60% of the examined cells from hair roots and buccal mucosa. The patient was described as a dull-looking boy with rather a large build for his age and bilateral gynecomastia. His body hair had a feminine distribution and the testes were small and soft. All these symptoms resemble to those of normal KS patients and are partly identical to those of Nielsen's case. The differences between these 2 cases are the gynecomastia and the body height, which supports the assertion of the *SHOX* gene hypothesis. However, it should be mentioned that Chandra et al. [1971] described a boy of unknown age and Nielsen [1966] a 54-year-old man.

Patil et al. [1981] reported a case of a 19-year-old KS patient with gynecomastia, small testes, and azoospermia. The analysis of the chromosomes showed a deletion of parts of the long arm of the X chromosome with the breakpoint in q22. The authors interpreted the karyotype as 47,X,del(X)(pter→q22:),Y. Growth, weight and intellectual development were normal. Just the FSH and LH levels were increased. These symptoms were consistent with those reported in the case by Chandra et al. [1971]. Patil et al. [1981] suggested that the region q11→22 might be associated with the phenotype of the KS, but this was revised in the same year by Fryns. He described a case of a 30-year-old male with completely normal phenotype without gynecomastia and normal sexual development [Fryns, 1981]. Both testes were small and sperm analysis revealed azoospermia. According to the study, his testosterone and LH levels were normal but FSH levels were elevated. The karyotype was 47,XY,+del(Xp11). Buccal smear analysis showed a small Barr body in 20% of the cells.

In comparison, we can say that a terminal deletion of the X chromosome shows a nearly similar phenotype to 'normal' KS. Just the body height differs from the typical KS phenotype and is normal to slightly reduced in the patients. The only reported case of a del(Xp) differs from all the other cases and did not even show affinity to the cases with an additional isochromosome Xq.

Klinefelter Patients with Additional Aberrations on the Y Chromosome

Eleven cases of KS patients with a 47,XX,der(Y) karyotype were found, but only 7 of them were described in detail (table 3). As the individual cases differ greatly from each other, we must consider them separately.

The most recent case we found was reported in 2009. The group presented a case of an unborn boy with a 47,XX,mar(Y) karyotype [Sheth et al., 2009]. Using different FISH clones for the *SRY* gene and for the centromeric and the subtelomeric region of the Y chromosome they found the presence of a neocentric inv dup (Y) (pter→Yp11.2::Yp11.2→pter). Spinner et al. [2008] presented a case of a newborn infant with ovotesticular disorder of sex development and sex chromosome mosaicism. The karyotype was defined as 46,XXr(Y) [10]/46,XX[40]. The patient showed ambiguous genitalia and a micropenis. After an exploratory laparotomy the

Table 3. Clinical features in 11 male patients with KS and a 47,XX,der(Y) karyotype sorted by the year of publication

Case No.	Reference	Age	Age (mother)	Age (father)	Height cm	Weight kg	Gyneco-mastia	Testes	FSH↑	LH↑	Testoster-one level	Karyotype[a]
1	Sheth et al., 2009	fetus	–	–	–	–	–	–	–	–	–	47,XX,+mar(Y)
2	Spinner et al., 2008	infant	–	–	–	–	–	present	–	–	–	47,XXr(Y)[10]/46,XX[40]
3	Manvelyan et al., 2008 (case 106)	–	–	–	–	–	–	–	–	–	–	47,XX,+r(Y)
4	Manvelyan et al., 2008 (case 109)	–	–	–	–	–	–	–	–	–	–	47,XX,+dic(Y;15)
5	Weimer et al., 2006	15	17	–	182	121	yes	6 ml	yes	no	↓	48,XX,+r(Y),+r(8)[68]/47,XX,+r(Y)[19]/47,XX,r(8)[6]/46,XX[8]
6	Karaman et al., 2006 (case 14)	2	18	–	–	–	–	–	–	–	–	46/47,+mar.ish r(Y)(DXZ1/DYZ3+,mcpY)[10/10]
7	Samli et al., 2006	24	–	–	–	–	–	–	yes	yes	↓	47,XXY
8	Heinritz et al., 2005	31			198	–	yes	small	yes	yes	↓	47,XX,+idic(Y)(q12)
9	Arnedo et al., 2005	3	36	33	–	–	–	n	–	–	–	47,XX,r(Y)/46,XX
10	Arnedo et al., 2005	33	–	–	169	–	no	n	–	–	–	46,X,r(Y)/45,X
11	Nielsen et al., 1976	18	–	–	163.5	52.9	no	4.5 cm	yes	yes	n	47,X,del(X)(p11→q13::q21→q24),del(Y)(q11)

FSH = Follicle-stimulating hormone; LH = luteinizing hormone; n = normal; ↑ = increased; ↓ = decreased.
[a] All karyotypes are indicated like in the corresponding literature.
All references not mentioned in the text are available in an online supplementary reference list.

right gonad could be identified as an ovotestis and the left gonad as an undescended dysgenetic testis and a uterus lacking endothelial uterine glands. The r(Y) chromosome was transmitted via ICSI from the oligospermic but otherwise unremarkable father to the child. Apart from this article we found another one which described a case of an additional r(Y) chromosome [Weimer et al., 2006]. The patient showed signs of KS including gynecomastia, decreased body hair, hypergonadotropic hypogonadism, learning difficulties, an increased value of FSH, and a decreased value of testosterone. His sex development was male, consistent with the presence of the *SRY* locus on the r(Y) chromosome. At the age of 15 years, the boy presented with a mild overgrowth (182 cm), obesity (121 kg), and a slight outsized head circumference (59 cm). The karyotype was described as 48,XX,r(Y),+r(8)[68]/47,XX,+r(Y)[19]/47,XX,r(8)[6]/46,XX[8]. In 2006, a case of a 24-year-old man with a KS karyotype and an additional microdeletion on the Y chromosome was presented [Samli et al., 2006]. The man was infertile and showed abnormally high LH and FSH levels but a lower testosterone level than usual. The group found a deletion in the *AZFa* region on the Y chromosome. The phenotype of the patient did not differ from those of KS patients without microdeletions in this region. Microdeletions in *AZFa* are often associated with Sertoli-cell-only syndrome and azoospermia and with a frequency of 1–2% they are one of the most frequent reasons of spermatogenetic failure and infertility [Poongothai et al., 2009].

An interesting case about a 31-year-old male patient with an in part Klinefelter phenotype and an isodicentric Y-chromosome was reported by Heinritz et al. [2005]. The karyotype was indicated as 47,XX,+idic(Y)(q12). The man showed a tall stature, unproportionally long slender legs, a normal male body hair patterning, but slightly reduced growth of his facial hair, gynecomastia, genitalia with hypoplastic, soft testes, and a small penis. The behavior of the man was described as aggressive with rapid alterations of the mood and a naive and inappropriate social performance. The LH and FSH levels were increased, but testosterone levels were lower than normal [Heinritz et al., 2005]. Normally, psychological and behavioral problems like violence, aggressiveness, and a low IQ are the main features of males with 48,XXYY and are very untypical for KS patients [Heinritz et al., 2005]. In earlier studies, the presence of an additional Y chromosome, as in men with 47,XYY, was discussed to be related to personality problems and mainly a quick-tempered behavior, but the molecular basis for the behavioral anomalies in patients with structural rearrangements of the sex chromosomes is not fully understood [Heinritz et al., 2005].

Arnedo et al. [2005] reported a case of a transmitted *SRY*-positive ring Y chromosome from the father to his KS son. The frequency of ring chromosomes in clinically detected conceptions is 1:25,000 and has been reported for all human chromosomes [Arnedo et al., 2005]. In most of the cases a mosaic is presented and only ≤1% of

all the ring chromosomes are inherited. In the study of Arnedo et al. [2005], the boy had a 47,XX,r(Y)/46,XX karyotype and his father a 46,X,r(Y)/45,X karyotype. All men with a r(Y) studied so far were infertile and also the father showed a moderate oligozoospermia (4.5×10^6 sperm/ml) which could be explained by the arrest of the spermatocytes during meiosis [Arnedo et al., 2005]. However, his wife became pregnant by natural conception. Both the father and his son showed no phenotype abnormalities and their intelligence level was reported as normal. Because of the normal body height of the father the group suggested that the loss of genetic material implicated in ring Y formation may not have included the *SHOX* locus on Yp. Via microsatellite DNA markers the paternal origin of the additional X chromosome could also be detected. Further information like the hormonal status was not provided in the study.

In conclusion, most of the patients show some typical phenotype features of KS like small testes or increased FSH and LH levels. In one of the patients an increased aggressive and primitive behavior could be determined, whereas all other patients presented with normal behavior and intelligence levels despite from their aberration on the Y chromosome. A comparison of the cases is not possible because the rearrangements are located on diverse parts of the Y chromosome.

Men with a 46,XX Karyotype Including Patients with Ambiguous Genitalia

Sex reversal syndrome (SRS) is a human genetic disease, which is characterized by inconsistency between gonadal sexuality and chromosome sexuality and includes 46,XY females and 46,XX males [Wang et al., 2009]. The XX male SRS, also called de la Chapelle syndrome, was first characterized in 1972 [de la Chapelle, 1972]. With an incidence of 1:20,000–25,000 the syndrome is rare [Rajender et al., 2006]. Most XX men result from an abnormal X-Y interchange while spermatogenesis. During meiosis the human X and Y chromosomes pair in homologous regions named pseudoautosomal region 1 *(PAR1)* on Xp22.3 and Yp11.3 and pseudoautosomal region 2 *(PAR2)* on Xq28 and Yq12. *PAR1* spans about 2.7 Mb and *PAR2* about 0.33 Mb on each chromosome. A translocation of Y material, which includes the key sex-determining region *(SRY)* that is located centromeric to *PAR1*, to the X chromosome during paternal meiosis results in 46,XX males, with normal male sexual development [Ferguson-Smith, 1966; Rigola et al., 2002].

Individuals with 46,XX maleness can be classified as Y-positive or Y-negative according to the presence or absence of the *SRY* gene [Valetto et al., 2005]. Approximately 90% of the patients without ambiguous genitalia carry Y-derived material, particularly the *SRY* gene caused by an X/Y or Y/autosome rearrangement [Ramos et al., 1996]. In agreement most XX males with ambiguous genitalia are *SRY* negative [Ramos et al., 1996]. In XX individuals 1 of the 2 X chromosomes is inactivated in early embryonic development as a mechanism of dosage compensation for sex-linked genes [Sharp et al., 2005]. A skewed X inactivation was found in XX males with complete masculinization. Also, XX sex-reversed individuals with incomplete masculinization commonly show nonrandom inactivation, preferentially of the *SRY*-carrying X chromosome [Bouayed Abdelmoula et al., 2003]. Sharp et al. [2005] suggested that incomplete masculinization in cases of X/Y translocations is a result of abnormal *SRY* gene expression by a positional effect, rather than X chromosome inactivation.

While the clinical symptoms of XX male patients often show some degree of heterogeneity [Ergun-Longmire et al., 2005], usually, the development of genitalia is normal and masculinity signs are obvious in *SRY* gene-positive patients [Wang et al., 2009]. Development of the genitals and sex psychology was described to be normal as well as erection and ejaculation, and there are almost no significant signs except cryptorchidism before puberty in most of the patients [Wang et al., 2009]. In most of the cases the patients are found by chromosome analysis for the reason of infertility. The clinical and laboratory data on XX male patients are summarized in table 4.

Only 3 cases have been described in the literature about 46,XX men with *SRY* located on an autosomal chromosome [Dauwerse et al., 2006; Queralt et al., 2008; Chien et al., 2009]. It was postulated that the translocation between the *SRY* carrying Y chromosome and an autosomal chromosome was due to nonhomologous recombination between the autosomal chromosome and Ypter (containing SRY locus) during paternal meiosis [Queralt et al., 2008; Chien et al., 2009]. Regarding the phenotype there are no differences between the patients with the *SRY* gene on the X chromosome and the patients carrying the *SRY* gene on an autosomal chromosome.

On the contrary, *SRY* gene-negative patients can often be easily discriminated due to abnormality of genitalia shortly after birth. Some patients even show genital ambiguity [Ergun-Longmire et al., 2005] and belong to the group of true hermaphrodites and in some cases the patients have normal male genitalia in face of *SRY*-negative

Table 4. Clinical features in 149 patients with KS and a 46,XX karyotype sorted by the year of publication

Case No.	Reference	Gender	Age	Testes	Ovaries	Penis	Beard	Hair	Gyneco-mastia	Sperm	*SRY*	FSH	LH	Testo-sterone level	Karyotype[a]
	***SRY* positive**														
1	Wang et al., 2009	male	20	left: 0.8 × 1.6 cm right: 1.0 × 1.2 cm	no	n	sparse	n	no	no	on X	↑	↑	↑	46,XX
2	Chernykh et al., 2009	male	37	2 ml	no	n	sparse	sparse	mild	0.15×10^6	on X	↑	↑	↓	46,XX.ishder(X)t(X;Y)(p22.3;p11.3) (SRY+,DXZ1+) nucish(DXZ1 × 2,SRY × 1)[474]/ (DXZ1 × 1,SRY × 1)[19]/ (DXZ1 × 3;SRY × 2)[7]
3	Chien et al., 2009 (case 2)	male	1	n	no	n	–	–	–	–	on 3	–	–	–	46,XX
4	Queralt et al., 2008	male	31	–	no	–	n	n	no	no	on 1	↑	↑	n	46,XX.ish der(1),t(Y;1)(p11.31;q44)
5	Ali et al., 2008	male	33	small	no	–	–	–	–	no	on X	↑	↑	↓	46,XX
6	Pepene et al., 2008	male	28	small	–	–	–	female pattern	yes	no	on X	↑	↑	n	46,XX
7	Velissariou et al., 2006	male	29	<10 mm	no	–	–	–	no	no	on Y	↑	↑	↓	47,XXY/46,XX
8	Dauwerse et al., 2006	male	61	1 cm	no	n	–	–	no	no	on 16	↑	n	low	46,XX
9	Sharp et al., 2005 (case 6)	male	–	–		–	–	–	–	–	on X	–	–	–	46,XX
10	Sharp et al., 2005 (case 8)	male	–	–		–	–	–	–	–	on X	–	–	–	46,XX
11	Sharp et al., 2005 (case 9)	male	–	–		–	–	–	–	–	on X	–	–	–	46,XX
12	Sharp et al., 2005 (case 10)	male	–	–		–	–	–	–	–	on X	–	–	–	46,XX
13	Sharp et al., 2005 (case 11)	male	–	–		–	–	–	–	–	on X	–	–	–	46,XX
14	Sharp et al., 2005 (case 12)	male	–	testicular atrophy		–	–	–	–	–	on X	–	–	–	46,XX
15	Sharp et al., 2005 (case 13)	male	–	–		–	–	–	–	–	on X	–	–	–	46,XX
16	Sharp et al., 2005 (case 14)	hermaphrodite	–	–		–	–	–	–	–	on X	–	–	–	46,XX
17	Grigorescu-Sido et al., 2005 (case 1)	male	10	2 ml	no	–	–	–	–	–	on X	n	n	–	46,X,der(X)t(X;Y)(p22.33;q11.2)
18	Grigorescu-Sido et al., 2005 (case 2)	male	13	5 ml	no	–	–	–	–	–	on X	n	n	–	46,X,der(X)t(X;Y)(p22.3;p11.2)
19	Ergun-Longmire et al., 2005 (case 1)	male	3 weeks	palpable	no	4 cm × 1.5 cm	–	–	–	–	on X	n	↓	↓	46,XX
20	Domenice et al., 2004 (2 patients)	males	–	–	–	–	–	–	–	–	pos	–	–	–	46,XX
21	Moreeno-Garcia et al., 2003	male	4	cryptorchi-dism left: 1.2 × 1 cm right: 1 × 1 cm	no	–	–	–	–	–	on X	–	–	–	46,XX
22	Bouayed Abdelmoula et al., 2003	male	32	18.4 and 16.2 mm	no	8.5 cm	sparse	n	no	no	on X	↑	↑	↓	46,XX
23	Rigola et al., 2002	male	33	n	no	n	–	–	no	no	on X	–	–	–	46,XX
24	Suzuki et al., 2000 (case 1)	male	11	right: atrophic	–	buried	–	–	–	–	on X	–	–	–	46,XX
25	Suzuki et al., 2000 (case 2)	male	31	atrophic	–	–	–	–	–	–	on X	–	–	–	46,XX
26	Margarit et al., 2000	hermaphrodite	34	no	yes + ovotestis	penile hypospadias	–	–	–	no	on X	–	–	–	46,XX
27	Ginsberg et al., 1999 (case 1)	male	fetus	–	–	–	–	–	–	–	pos	–	–	–	46,XX
28	Ginsberg et al., 1999 (case 2)	male	fetus	n	–	–	–	–	–	–	pos	–	–	–	46,XX
29	Kusz et al., 1999 (case JW); Sharp et al., 2005 (case 4)	male	15	n		present	–	–	–	–	on X	–	–	n	

Table 4 (continued)

Case No.	Reference	Gender	Age	Testes	Ovaries	Penis	Beard	Hair	Gyneco-mastia	Sperm	*SRY*	FSH	LH	Testo-sterone level	Karyotype[a]
30	Kusz et al., 1999 (case MB)	male	7	n		penile hypospadias	–	–	–	–	on X	–	–	–	46,XX
31	Kusk et al., 1999 (case KM); Sharp et al., 2005 (case 7)	male	1	n		penile hypospadias	–	–	–	–	on X	–	–	↓	46,XX
32	Kusz et al., 1999 (case AK); Sharp et al., 2004 (case AK); Sharp et al., 2005 (case 2)	hermaphrodite	17	present	yes	no	–	–	–	no	on X	–	–	–	46,XX
33	Kusk et al., 1999 (case RZ); Sharp et al., 2005 (case 3)	hermaphrodite	14	no	yes + ovotestis	no	–	–	–	–	on X	–	–	n	46,XX
34	Kusz et al., 1999 (case PG); Sharp et al., 2004 (case PG); Sharp et al., 2005 (case 1)	hermaphrodite	6 months	no	yes + ovotestis	no	–	–	–	–	on X	–	–	↓	46,XX
35	Wu et al., 1999	male	17	2 and 3 cm	no	n	n	n	–	–	on X	↑	↑	n	46,XX
36	Plöchl et al., 1999 (case 1)	male	2	0.5 ml	no	hypospadias	–	–	–	–	on X	–	–	n	46,XX
37	Plöchl et al., 1999 (case 2)	male	9	1–1.5 ml	–	n	–	–	–	–	pos	↓	↓	↓	46,XX
38	Plöchl et al., 1999 (case 3)	male	32	small	–	n	–	–	–	infertile	on X	↑	↑	↓	46,XX
39	Margarit et al., 1998 (case 1)	male	–	small, testicular atrophy	–	–	–	–	no	no	pos	–	–	–	46,XX,t(X;Y)(p33.3;p11.3)
40	Margarit et al., 1998 (case 2)	male	–	small, testicular atrophy	–	–	–	–	no	no	pos	–	–	–	46,XX,t(X;Y)(p33.3;p11.3)
41	Margarit et al., 1998 (case 3)	male	–	small, testicular atrophy	–	–	–	–	yes	no	pos	–	–	–	46,XX,t(X;Y)(p33.3;p11.3)
42	Margarit et al., 1998 (case 4)	male	–	testicular atrophy	–	–	–	–	yes	no	pos	–	–	–	46,XX,t(X;Y)(p33.3;p11.3)
43	Margarit et al., 1998 (case 5)	male	–	testicular atrophy	–	–	–	–	no	no	pos	–	–	–	46,XX,t(X;Y)(p33.3;p11.3)
44	Margarit et al., 1998 (case 6)	male	fetus	present	–	present	–	–	–	–	pos	–	–	–	46,XX,t(X;Y)(p33.3;p11)
45	Manieri et al., 1996 (case 1)	male	29	5 ml	–	n	–	–	yes	–	pos	↑	↑	n	46,XX
46	Manieri et al., 1996 (case 2)	male	19	5 ml	–	n	–	female pattern	no		pos	↑	↑	n	46,XX
47	Cooper et al., 1996	male	36	4 ml	–	–	–	–	no	no	pos	↑	↑	↓	46,XX/47,XXX (6%/94%)
48	Lim et al., 1996	hermaphrodite	5 months	cryptorchidism	ovarian histology	hypospadias	–	–	–	–	–	↑	↑	n	46,XX
49	Rego et al., 1996	male	11	2 ml	–	5.1 cm	–	no	–	no	pos	↓	↓	n	46,XX
50	Torres et al., 1996 (case 7)	hermaphrodite	2	nonpalpable	yes + ovotestis	–					pos	n	↓	n	46,XX/46,XY (70/25)
51	Torres et al., 1996 (case 8)	hermaphrodite	2	n	ovotestis 1.5 ml	2 cm	–	–	–	–	pos	n	n	n	46,XX/46,XY (68/32)
52	Torres et al., 1996 (case 9)	hermaphrodite	1	–	ovotestis	3 cm	–	–	–	–	pos	nd	nd	n	46,XX/46,XY (23/77)
53	Torres et al., 1996 (case 10)	hermaphrodite	16	nonpalpable	yes + ovotestis	3.5 cm	–	–	–	–	pos	↑	↑	↓	46,XX/46,XY (72/28)
54	Yamamoto et al., 1995	male	32	3 and 2 ml	–	n	n	n	no	no	pos	↑	↑	n	46,XX
55	Lindsay et al., 1994 (case 3) Sharp et al., 2005 (case 15)	male	10	–	–	–	–	–	–	–	on X	–	–	–	46,XX
56	Fechner et al., 1994 (case 1)	hermaphrodite	–	–	ovotestis	–	–	–	–	–	pos	–	–	–	46,X,del(X)
57	Fechner et al., 1994 (case 2)	male	–	–	–	–	–	–	–	–	on X	–	–	–	46,XX
58	Jalal et al., 1994	male	infant	–	–	–	–	–	–	–	on X	–	–	–	46,XX
59	Abbas et al., 1993 (case 1)	hermaphrodite	–	–	ovotestis	–	–	–	–	–	on X	–	–	–	46,XX
60	Abbas et al., 1993 (case 2)	male	21	–	–	–	–	–	no	no	on X	↑	↑	↓	46,XX

Case No.	Reference	Gender	Age	Testes	Ovaries	Penis	Beard	Hair	Gyneco-mastia	Sperm	*SRY*	FSH	LH	Testo-sterone level	Karyotype[a]
61	Coles et al., 1992; Sharp et al., 2005 (case 5)	male	3	palpable		short	–	–	–	–	on X	–	–	–	46,XX
62	Boucekkine et al., 1992 (case 1)	hermaphrodite	24	nonpalpable	yes + ovotestis	5.5 cm	–	scanty	yes	–	pos	n	n	↓	46,XX
63	Boucekkine et al., 1992 (case 2) Palmer et al., 1989 (ZM)	male	2.5	undescended	–	small	–	–	–	–	pos	n	n	↓	46,XX
64	Boucekkine et al., 1992 (case 3) Palmer et al., 1989 (MB)	male	20	1.5 ml	–	small	–	–	yes	no	pos	↑	↑	n	46,XX
65	Boucekkine et al., 1992 (case 4) Abbas et al., 1990 (case 3)	male	14.5	4.5 ml	–	n	–	n	yes	–	pos	↑	↑	n	46,XX
	***SRY* negative**														
66	Mustafa et al., 2010	male	30	small	no	n	n	n	yes	no	neg	↑	↑	↓	46,XX
67	Dorsey et al., 2009 (case 1)	hermaphrodite	–	testicular tissue	ovarian tissue	–	–	–	–	–	neg	–	–	–	46,XX
68	Dorsey et al., 2009 (case 2)	hermaphrodite	–	undescended	ovotestis	–	–	–	–	–	neg	n	n	low	46,XX
69	Maciel-Guerra et al., 2007 (case 1)	male		present	–	1 cm	–	–	–	–	neg	n	n	n	46,XX
70	Maciel-Guerra et al., 2007 (case 2)	hermaphrodite		present	ovotestis	0.5 cm	–	–	–	–	neg	↑	↑	↓	46,XX
71	Tempel et al., 2007 (9 patients)	3 hermaphro-dites 6 males	5–15 10–33	– present	yes + ovotestis no	not present present	–	–	no no	–	neg	–	–	–	46,XX
72	Rajender et al., 2006	male	34	4.8 and 5.1 ml	no	n	n	n	–	no	neg	↑	↑	n	46,XX
73	Grigorescu-Sido et al., 2005 (case 3)	male	3	1 ml	no	2 cm	–	–	–	–	neg	n	n	–	46,XX
74	Ergun-Longmire et al., 2005 (case 2)	male	1.5 months	1 ml	no	hypospadias	–	–	–	–	neg	n	↓	n	46,XX
75	Ergun-Longmire et al., 2005 (case 3)	male	10 months	present	no	micropenis	–	–	–	–	neg: in blood pos: in some sections of gonads	↓	↓	↓	46,XX
76	Ergun-Longmire et al., 2005 (case 4)	male	2 days	2 ml	no	4 × 2 cm hypospadias	–	–	–	–	neg	↓	↓	↓	46,XX
77	Valetto et al., 2005	male	35	2 ml	–	n	n	n	–	no	neg	↑	↑	–	46,XX
78	Domenice et al., 2004 (13 patients)	hermaphrodites	–	–	–	–	–	–	–	–	neg	–	–	–	46,XX
79	Domenice et al., 2004 (2 patients)	males	–	-	–	–	–	–	–	–	neg	–	–	–	46,XX
80	Becker et al., 2001	hermaphrodite	fetus	no	no	no	–	–	–	–	neg	–	–	–	46,XX
81	Abusheikha et al., 2001	male	28	9 ml	no	n	n	n	no	no	neg	↑	↑	n	46,XX
82	Vernole et al., 2000	male	56	–	–	–	sparse	n	no	–	neg	↑	↑	↓	46,XX
83	Malavaud et al., 2000	hermaphrodite	56	no	ovarian tissue	–	–	–	yes	–	neg	–	–	–	46,XX
84	Inoue et al., 1998	hermaphrodite	28	present	ovotestis	–	–	–	–	–	neg: in blood pos: in ovotestis	↓	n	n	46,XX
85	Slaney et al., 1998 (case 1)	hermaphrodite	10	no	yes	small	–	–	–	–	neg	–	–	–	46,XX
86	Slaney et al., 1998 (case 2)	male	12	–	–	n	–	–	–	–	neg	–	–	–	46,XX
87	Slaney et al., 1998 (case 3)	male	8 months	–	ovotestis	small	–	–	–	–	neg	–	–	–	46,XX
88	Slaney et al., 1998 (case 4)	male	newborn	–	ovotestis	small	–	–	–	–	neg	–	–	–	46,XX
89	Manieri et al., 1996 (case 3)	hermaphrodite	60	no	no	hypoplastic	–	–	yes	–	neg	↑	n	↓	

Table 4 (continued)

Case No.	Reference	Gender	Age	Testes	Ovaries	Penis	Beard	Hair	Gyneco-mastia	Sperm	*SRY*	FSH	LH	Testo-sterone level	Karyotype[a]
90	Ramos et al., 1996 (case 1)	hermaphrodite	9	–	yes + ovotestis	2 cm	–	–	–	–	neg	–	–	–	46,XX
91	Ramos et al., 1996 (case 2)	hermaphrodite	35	–	ovotestis	hypospadias	–	–	–	–	neg	–	–	–	46,XX
92	Ramos et al., 1996 (case 3)	male	7	n	no	present	–	–	–	–	neg	–	–	–	46,XX
93	Torres et al., 1996 (case 1)	hermaphrodite	27	nonpalpable	yes + ovotestis	4.8 cm	–	–	–	–	neg	↑	n	↓	46,XX
94	Torres et al., 1996 (case 2)	hermaphrodite	10	1.8 ml	ovotestis	3.1 cm	–	–	–	–	neg	↑	↑	n	46,XX
95	Torres et al., 1996 (case 3)	hermaphrodite	10 months	nonpalpable	ovotestis	3.5 cm	–	–	–	–	neg	n	↓	n	46,XX
96	Torres et al., 1996 (case 4)	hermaphrodite	11 months	no	ovotestis	2.8 cm	–	–	–	–	neg	n	↓	n	46,XX
97	Torres et al., 1996 (case 5)	hermaphrodite	17	present	yes	3 cm	–	–	–	–	neg	–	–	–	46,XX
98	Torres et al., 1996 (case 6)	hermaphrodite	4	1.7 ml	yes	2.8 cm	–	–	–	–	neg	nd	nd	n	46,XX
99	Tar et al., 1995	hermaphrodite	7	–	ovotestis	present	–	–	–	–	neg	↑	n	n	46,X,del(X)(p21.1→pter)
100	Turner et al., 1995 (case 1)	male	8 weeks	present	no	3 cm	–	–	–	no	neg	n	n	n	46,XX
101	Turner et al., 1995 (case 2)	hermaphrodite	20	present	–	–	–	–	–	–	neg	–	–	–	46,XX
102	Turner et al., 1995 (case 3)	hermaphrodite	11	present	no	–	–	–	–	–	neg	↑	↑	n	46,XX
103	Kucheria et al., 1994 (case 1)	hermaphrodite	16	underdescended	ovotestis	6 × 3 cm	no	n	yes	–	neg	–	–	–	46,XX
104	Kuhnle et al., 1993 (case II-1)	hermaphrodite	20	present	yes	–	–	no facial hair	–	–	neg	–	–	n	46,XX
105	Kuhnle et al., 1993 (case II-3)	male	–	small	–	n	–	–	–	–	neg	↑	↑	n	46,XX
106	Kuhnle et al., 1993 (case II-4)	hermaphrodite	–	–	–	–	–	no facial hair	–	–	neg	n	n	n	46,XX
107	Hadjiathanasiou et al., 1994 (21 patients)	hermaphrodite	1 day–8 years	3/21	ovaries: 9/21 ovotestis: 20/21	–	–	–	–	–	analyzed in 12 patients: pos: 5/12	–	–	–	12: 46,XX 4: 46,XX/47,XXY

FSH = Follicle-stimulating hormone; LH = luteinizing hormone; n = normal; nd = not detectable; neg = negative; pos = positive; *SRY* = sex-determining region Y; ↑ = increased; ↓ = decreased.

[a] All karyotypes are indicated like in the corresponding literature.

All references not mentioned in the text are available in an online supplementary reference list.

46,XX karyotype [Rajender et al., 2006; Mustafa and Mehmet, 2010]. In many cases masculinity signs are not clear in *SRY*-negative patients. Mainly in adult patients, breast development and female secondary sex characteristics were found. Domenice et al. [2004] proposed that 90% of 46,XX males carried Y chromosome material including the *SRY* gene. There have been postulated 2 different theories for the remaining 10%: The first indicates that a structural gene that determines human gender could be located on an autosomal chromosome which is regulated by X chromosome inactivation and the activation of Y chromosome [Wang et al., 2009]. Due to defects in the X inactivation, which result in spontaneous activation of a downstream gene in the absence of *SRY*, 46,XX males could develop [Wang et al., 2009]. In previous studies, other genes in mouse and goat have been identified that lead, in the case of a mutation, to SRS. The corresponding homologs in human, *FOXL2* (forkhead box L2) and *WNT4* (wingless-type MMTV integration site family, member 4) were also mostly analyzed since these findings [Temel et al., 2007]. In different studies it was postulated that *NR0B1* (nuclear receptor subfamily 0, group B, member 1), also known as *DAX1* (dosage-sensitive sex reversal, adrenal hypoplasia congenital critical region on the X chromosome, gene 1) acts as an anti-testis gene by antagonizing *SRY* function and that this gene may be necessary for testis development and its effect seems to be dosage sensitive [Ergun-Longmire et al., 2005]. Domenice et al. [2004] analyzed mutations in the *DAX1* and the *WNT4* genes in sex-reversed patients and found out that the dosage of these genes was normal in their patients. With the help of these data, they proposed that the *DAX1* and *WNT4* are rarely involved in the etiology of male gonadal development in sex-reversed patients. This fact suggests the presence of other genes in the sex determination cascade.

The second hypothesis is about a *SOX9* gene (*SRY* box-related gene 9) overexpression. It was suggested that this gene might function downstream to the *SRY* gene in the sex-determination pathway. Therefore, an upregulation of *SOX9* expression caused by chromosomal abnormalities or mediated by other bypass activation mutations could lead to female-to-male sex reversal in 46,XX *SRY*-negative males [Dorsey et al., 2009; Wang et al., 2009].

Maciel-Guerra et al. [2008] identified in 2008 a case of XX maleness and XX true hermaphroditism in *SRY*-negative monozygotic twins, suggesting that these entities might represent pleomorphic manifestations of the same disorder of gonadal development. Rajender et al. [2006] also described an SRY-negative man with 46,XX karyotype who presented with normal genitalia. The group did not find a mutation in the coding region of the *SOX9* and the *DAX1* gene and no copy number variant in the *SOX9* gene. In general, the reported patients with *SRY*-negative 46,XX karyotype have small or undescended testes [Valetto et al., 2005; Rajender et al., 2006; Temel et al., 2007; Dorsey et al., 2009] and in part additional ovarian tissue [Maciel-Guerra et al., 2008; Dorsey et al., 2009]. Most of the men have normal body hair and no gynecomastia. In that part they differ from the 'normal' KS patients. However, the hormone status shows the typically increased FSH and LH values and normal to decreased testosterone levels.

Women with a 47,XXY Karyotype

Searching in PubMed we found only 13 cases describing a female phenotype with a 47,XXY karyotype and one patient with a 47,XX+der(Y) karyotype. Seven of these cases have been diagnosed as suffering from androgen insensitivity (testicular feminization) syndrome resulting from mutations in the androgen receptor *(AR)* gene [German and Vesell, 1966; Bartsch-Sandhoff et al., 1976; Gerli et al., 1979; Müller et al., 1990; Uehara et al., 1999; Saavedra-Castillo et al., 2005; Girardin et al., 2009]. Only 3 cases are reported about women with an additional or at least parts of the Y chromosome. One report describes a mother and her daughter with a 47,XXY *SRY*-negative karyotype [Röttger et al., 2000] and the other a woman with a 47,XX+mar karyotype where the extra chromosome contained centromeric DNA derived from the Y chromosome [Causio et al., 2002]. In the other two 47,XXY female cases, the cause for their femaleness could not be clarified [Schmid et al., 1992; Thangaraj et al., 1998]. The clinical and laboratory data of the reported 47,XXY women are summarized in table 5.

The complete androgen insensitivity syndrome (CAIS) describes an X-linked disorder in which affected people have normal female external genitalia, female breast development, absence of the müllerian structures and abdominal or inguinal testes, despite a normal male karyotype. At puberty, female secondary sex characteristics like breasts develop, but menstruation and fertility do not. The prevalence of CAIS is estimated between 1 in 20,000–60,000 births [Girardin et al., 2009]. It is due to mutations in the *AR* gene, which is located on the X chromosome on Xq12 and may occur de novo or be inherited.

Normally, a defect resulting from a mutant *AR* allele on one X chromosome is masked by the effect of the normal allele on the other X chromosome [Uehara et al.,

Table 5. Clinical features in 13 female patients with KS and a 47,XXY karyotype sorted by the year of publication

Case No.	Reference	Age	Age (mother)	Age (father)	Height cm	Weight kg	Testes	Uterus	FSH ↑	LH ↑	Testosterone level	*SRY* positive	Karyotype[a]	CAIS
1	Girardin et al., 2009	11	23	–	–	–	yes	no	yes	yes	↑	–	47,XXY	yes
2	Saavedra-Castillo et al., 2006	34	–	–	180	88	–	no	yes	yes	n	yes	47,XXY	yes
3	Causio et al., 2002	25	34	35	–	–	no	yes	n	n	n	no	47,XX,+der(Y)	no
4	Röttger et al., 2000 (case 1)	newborn	33	–	–	–	–	–	–	–	–	no	47,XXY	no
5	Röttger et al., 2000 (case 2)	33	–	–	–	–	–	–	–	–	–	no	47,XXY	no
6	Uehara et al., 1999	30	–	–	165	61.5		no	yes	yes	↑	–	47,XXY	yes
7	Thangaraj et al., 1998	15	–	–	–	–	no	yes	–	–	n	yes	47,XXY	no
8	Schmid et al., 1992	6	32	33	–	–	yes	yes	–	–	–	yes	47,XXY	no
9	Müller et al., 1990	11	26	30	157	34	yes	no	–	–	↑	–	47,XXY	yes
10	Gerli et al., 1979	35	40	48	167	–	no	no	yes	yes	↘	–	47,XXY	yes
11	Bartsch-Sandhoff, 1976	–	29	–	175	55	yes	no	–	–	–	–	47,XXY	yes
12	German et al., 1966 (case 1)	12	29	30	151	37.5	yes	no	–	–	–	–	47,XXY	yes
13	German et al., 1966 (case 2)	12	29	30	149	40	yes yes: 6/8	no yes: 2/9	–	–	–	–	47,XXY	yes

CAIS = Complete androgen insensitivity syndrome; FSH = follicle-stimulating hormone; LH = luteinizing hormone; n = normal; ↑ = increased; ↘ = moderately decreased.

[a] The karyotypes are indicated like in the corresponding literature.

All references not mentioned in the text are available in an online supplementary reference list.

1999]. In 2009, two different hypotheses were suggested that could explain a CAIS phenotype in a 47,XXY individual. The first is that the homozygosity for the mutated *AR* gene implies either complete or partial maternal molecular identical material. The second hypothesis involves 2 different X chromosomes with 2 different *AR* alleles but with skewed X inactivation of the nonmutated X chromosome [Girardin et al., 2009].

The external genitalia like breast development or formation of the vagina differ in the reported cases. German and Vesell [1966] described monozygotic female twins with a 47,XXY karyotype and normal female external genitalia. However, Saavedra-Castillo et al. [2005] reported a woman with the same karyotype but hypoplasia of labial folds, clitoris, and vagina. Apart from that, the internal genitalia are nearly similar. All patients are characterized by the absence of the uterus and ovaries. Most of them have no wolffian and müllerian ducts but testes. Interestingly, in most of the described cases the testosterone levels were lower than expected in androgene insensitivity. This could be explained by testicular dysgenesis due to the 47,XXY karyotype. Just in one case the testosterone and LH levels were increased as expected in CAIS [Girardin et al., 2009]. The high FSH level likely reflects testicular dysgenesis in the context of the 47,XXY karyotype. Girardin et al. [2009] found a point mutation in the *AR* gene on both X chromosomes and Uehara et al. [1999] found 2 mutations in the *AR* gene in a 30-year-old woman with severely increased hormone levels. This can explain why CAIS occurred in this XXY patient. In the other cases the *AR* gene was not sequenced.

Röttger et al. [2000] reported the only 2 cases of women with an *SRY*-negative 47,XXY karyotype. They described these 47,XXY females resulting from an aberrant X-Y interchange with transfer of Xp material onto Yp, with concomitant loss of the *SRY* gene. The 2 patients are mother and daughter, which is very uncommon because normally XXY women are sterile. The data of Röttger et al. [2000] indicated that the Y chromosome in the mother and, by inference, in the daughter show a replacement of the Yp material that includes *SRY* and *PRKY* (protein kinase, Y-linked) by Xp material up to and including *PRKX* (protein kinase, X-linked). The absence of *SRY* explains the sex reversal in these two 47,XXY females. One X and the Y chromosome in the daughter were inherited from the mother. Her phenotype was not described. At her birth the daughter showed a female phenotype with normal external genitalia and bilateral clubbed feet. Two years later a patient was reported with a normal female karyotype but an additional marker chromosome, resembling an Y chromosome in size and QFQ-staining pattern [Causio et al., 2002]. The woman presented an apparently normal female habitus, with normal secondary sexual development. The extra chromosome contained centromeric regions of the Y. By means of sequence-tagged-sites PCR the absence of the *SRY* gene and the

presence of the *AZF* genes could be defined. In none of 2 further reports the reason of the femaleness could be determined [Schmid et al., 1992; Thangaraj et al., 1998].

A comparison between the symptoms of a Klinefelter patient and a 47,XXY female is hardly possible because most of the KS symptoms also relate to a more feminine expression of certain body parts (e.g. gynecomastia). Symptoms like a tall stature, sparse body and pubic hair development, and elevated FSH and LH levels occur in most but not all of the described women. These characteristics are similar to those of KS.

Other Numeric Sex Chromosome Abnormalities

Besides the 47,XXY karyotype, a less frequent group of KS patients have additional X and/or Y chromosomes and show karyotypes like 48,XXYY, 48,XXXY, or 49,XXXXY [Visootsak and Graham, 2009].

48,XXYY syndrome occurs in approximately 1:17,000–1:45,000 males [Borja-Santos et al., 2010]. The physical features have been described to be similar to 47,XXY but with some more pronounced phenotypic abnormalities. These are mild craniofacial dysmorphism, skeletal anomalies such as radioulnar synostosis and clinodactyly, lower IQ (typically between 70 and 80), significant developmental delays, and medical problems like neurological symptoms such as intention tremor, poor dentition, or reactive airway disease [Lenroot et al., 2009; Visootsak and Graham, 2009]. The behavior of the patients is described to be shy and reserved. It can include hyperactivity, attention problems, impulsivity, aggression, mood instability, 'autistic-like' behaviors, and poor social function [Lenroot et al., 2009; Visootsak and Graham, 2009]. In comparison to 47,XXY patients, men with 48,XXYY karyotype show a greater impairment in cognitive, verbal, and social functioning [Visootsak and Graham, 2009] and also the physical height is increased [Lenroot et al., 2009]. Tartaglia et al. [2008] reported a cohort of 95 subjects ranging from 1 to 55 years of age and having a 48,XXYY karyotype. 92% of the men showed speech/language delays and 100% received special education for learning disabilities. The group found common medical problems including allergies and asthma, congenital heart defects, radioulnar synostosis, inguinal hernia and/or cryptorchidism, and seizures in the patients [Tartaglia et al., 2008]. In the adulthood, medical features like hypogonadism, deep vein thrombosis, intention tremor, and type II diabetes were found [Tartaglia et al., 2008, 2009]. In the same year, Zhang and Li [2009] reported a case with 48,XXYY karyotype. They proposed the origin of this karyotype in a successive nondisjunction during paternal meiosis I and II. As the father of the patient was 56 years old, this case adds to the evidence that an age-related increase in sex chromosomal aneuploidies occurs in sperm.

The 48,XXXY karyotype is considered a variant of KS with features generally more pronounced than 47,XXY but less severe than 49,XXXXY and with an incidence of 1:17,000 to 1:50,000 in male births it is uncommon [Linden et al., 1995; Venkateshwari et al., 2010]. Affected males show a normal to tall stature with a decreased upper segment to lower segment ratio, hypertelorism and epicanthic folds, simplified ears and mild prognathism, skeletal anomalies including clinodactyly, abnormalities of the elbows and radioulnar synostosis, hypergonadotropic hypogonadism and testicular histology similar to 47,XXY and 48,XXYY, gynecomastia, and an abnormal glucose tolerance [Linden et al., 1995]. One fourth of these patients has a hypoplastic penis and is infertile [Linden et al., 1995]. In accordance with Zhang and Li [2009], the IQs of the patients range between 40 and 60, and a greater deficit in daily living skills, communication, and socialization in comparison to 48,XXYY cases could be detected [Visootsak et al., 2007]. Behavioral characteristics are immaturity, passivity, and irritability with temper tantrums [Visootsak and Graham, 2009]. Similarities to the 48,XXYY males are the activity level, the helpfulness, the pain tolerance, the morality, and the rejection based on the Reiss Personality Profile [Visootsak et al., 2007].

The rarest of the described variants in this review is the 49,XXXXY that shows an incidence of 1:85,000 to 1:100,000, and is in addition described to be the most severe variant of KS [Linden et al., 1995]. The extra X chromosomes in this variant accrue during maternal meiosis I and II and are the product of a double nondisjunction event [Simsek et al., 2009]. A correlation between maternal age and 49,XXXXY syndrome could not be detected in previous studies [Celik et al., 1997]. Clinical features of the syndrome are a coarse face with microcephaly, ocular hypertelorism, flat nasal bridge, upslanting palpebral fissures, bifid uvula and/or cleft palate, skeletal abnormalities including radioulnar synostosis, genu valgum, pes cavus, or clinodactyly, short stature with hypotonia, hyperextensible joints, and underdeveloped genitalia with hypergonadotropic hypogonadism [Visootsak et al., 2007]. The behavior of affected people is described as timid and shy to friendly, but the patients show a low frustration tolerance and so irritability and bout of temper can occur sometimes [Linden et al., 1995]. The IQs of the patients range between 20 to 60 points [Linden et al., 1995].

Therefore, mental retardation was long described to be a characteristic feature for the syndrome. However, recent studies have reported that cognitive delays were not as significant as described in the past and personalities and learning styles are similar to 47,XXY cases [Samango-Sprouse, 2001; Visootsak et al., 2001, 2007; Visootsak and Graham, 2006; Gropman et al., 2010]. Variability in clinical and cognitive functioning may reflect skewed X inactivation, mosaicism, or other factors that warrant further investigation [Gropman et al., 2010]. Recently, Ottesen et al. [2010] reported a study about the increased height in patients with additional sex chromosomes. In line with other reports [Bojesen and Gravholt, 2007; Tartaglia et al., 2008], they found an increased stature in subjects with 47,XXY, 47,XYY, or 48,XXYY karyotypes. In patients with a 49,XXXXY karyotype the stature was reduced and for that the group suggests a nonlinear effect of the number of sex chromosomes on height [Ottesen et al., 2010]. Altogether, the phenotypic features of 49,XXXXY patients share some characteristics with 47,XXY, but there are also other unique and distinctive traits.

In conclusion, the effects on physical and mental development increase with the number of extra X chromosomes, and each X reduces the overall IQ by 15–16 points, with language most affected [Polani, 1969]. In addition, it was found that height decreases and radioulnar synostosis becomes more frequent as the number of X chromosomes increases [Visootsak et al., 2007].

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