Localisation of male determining factors in man: a thorough review of structural anomalies of the Y chromosome

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SUMMARY It is widely accepted that male determination in man depends on the presence of a factor or factors on the Y chromosome. These factors may be localised within the Y chromosome through the study of structural anomalies of the Y. A thorough review of seven different structural anomalies of the Y is presented: dicentric Y chromosomes, Y isochromosomes, ring Y chromosomes, Y;autosome, Y;X, and Y;Y translocations, and Y deletions. The evidence from these studies indicates that a gene or genes on the short arm of the Y near the centromere play a crucial role in the development of the testes. A few studies indicate that one or more factors on the long arm of the Y may also influence testicular development. If such a factor is present on the long arm, then it too must be very near the centromere. The theory that separate genes independently control the initial development and maturation of the testes (on the long and short arms of the Y, respectively) may be premature. Recently proposed arguments in its favour are examined. Some evidence also indicates the presence of a fertility factor on the non-fluorescent segment of the long arm. Relevant information on the H-Y antigen is discussed.

The function of the human Y chromosome in sex determination was not elucidated until 1959 when a 47,XXY subject was found to be male¹ and a 45,X subject was found to be female.² At about this time, the same was found to be true in the mouse.³⁻⁵ From further studies of sex chromosome anomalies, it soon became apparent that, with rare exceptions, the presence of the Y chromosome is always associated with testicular formation. Conversely, development of ovaries occurs in its absence. Indeed, it was soon discovered that the Y chromosome results in maleness regardless of how many X chromosomes are present. Studies of various forms of Klinefelter's syndrome revealed that not only XXY but also XXXY⁶ and XXXXY^{7/8} sex chromosome constitutions lead to an unmistakably male phenotype, even though such males are sterile and often display female breast development. On the other hand, patients with Turner's syndrome (45,X) are phenotypically female, although almost always sterile (see Kohn *et al*⁹ for a review of reports of fertile 45,X females).

Apparent exceptions to this model have been described in man, including 46,XY females and 46,XX males and true hermaphrodites. Dewhurst^{10 11} and de la Chapelle,¹² respectively, discuss possible factors involved in the aetiology of these conditions. Those proposed for the latter two might similarly explain the rare reports of 45,X males.¹³ (patient BN)^{14 15/16} Nevertheless, this vital role of the Y chromosome in sex determination remains universally accepted. Moreover, it seems to apply to nearly all mammalian species, as evidenced by the virtual absence of XO males.¹⁷ One exception, however, is the mole-vole *Ellobius lutescens*, in which both the male and female are normally XO, and thus must endure a 50% zygotic lethality.¹⁸

Male determining factors can be localised within the Y chromosome through the study of structural anomalies of the Y. A review of seven different published structural anomalies of the Y, including information most relevant to this consideration, is presented in appendices 1 to 7. These are: dicentric Y chromosomes, Y isochromosomes, ring Y chromosomes, Y;autosome, Y;X, and Y;Y translocations, and Y deletions. Pericentric inversions of the Y are not considered here since they do not disturb male determination.¹⁹ The terminal synapsis between the

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Note: A solidus (/) is used to separate reference numbers of articles dealing with the same patient.

X and the Y during meiosis²⁰ precludes a meiotic disruption from such an anomaly, and thus a deleterious effect would only be expected to occur if the loss of important chromosomal material results from the breaks. Duplications of the long arm of the Y are also not included here. Interested readers may consult Borgaonkar^{21,22} for references of duplications and pericentric inversions of the Y.

The localisation of male determining factors is most easily accomplished by a step-by-step analysis of these studies. It should be kept in mind that karyotypic analyses using current staining techniques developed within the last decade are more reliable than those reported earlier. These studies are thus more valuable in localising male determining factors, and comprise the majority of those cited below.

Localisation of male determining factors

EVIDENCE THAT MALE DETERMINING FACTORS ARE NOT ON THE DISTAL PORTION OF THE LONG ARM OF THE Y

A wealth of evidence exists which indicates a lack of any male determining effect of the distal portion of the long arm of the Y (Yq). Normal male development of the external genitalia with the formation of testes has been reported in the absence of the brightly fluorescent region of the Yq in cases of ring Y chromosomes,^{23–28} Y;autosome translocations,^{29,30} and Y deletions.^{31 (case 7)–42,251} In most of these cases it is difficult to determine how much, if any, of the non-fluorescent segment of the Yq may have been deleted. Thus, this evidence rules out the presence of testis determinants in the fluorescent Yq but not necessarily in the non-fluorescent Yq. However, besides those cases described in the next section, an exception is the detailed study of Tishler *et al.*⁴³ This revealed the loss of the fluorescent and three-quarters of the non-fluorescent segments of the Yq in a male (subject 'Short Y-e') with "normal sexual development".

In addition, normal female development takes place when the brightly fluorescent portion of the Yq is present in otherwise normal female karyotypes as Y;autosome^{44/45 47–56} or Y;X^{57/58 60–62 69} (subject 6) translocations. Including relatives of the probands, these studies comprise a total of at least 36 normal females with Yq;autosome translocations and six normal females (two with some Turner stigmata) with Yq;X translocations (appendices 4 and 5). Again, it is unclear how much non-fluorescent Yq material may have been present in the translocations. Thus, these cases do not reveal precisely how much distal Yq material may be devoid of masculinising effect.

It should be pointed out that some of these trans-

locations involving the D and G group chromosomes could actually be intensely fluorescent enlarged satellites. Nielsen and Rasmussen⁵⁰ mentioned having discovered examples of this. Also, a new staining technique used by Spowart⁶³ showed a previously reported Y;22 translocation to be an enlarged satellite. However, some studies provided evidence in favour of a Y;D or G translocation in addition to morphological and fluorescence findings, including the following: autoradiography,⁴⁹ satellite association frequencies,⁵⁰ the presence of the male specific 2.2 kilobase⁶⁴ or 3.5 kilobase⁵¹ DNA fragments, and DA-DAPI staining.^{56,63}

Lastly, the Y;X translocations must be interpreted with caution, since the translocated X (X_t) seems to be preferentially inactivated in five of the six reported cases. Thus, male determining factors possibly present on the translocated Yq material would not be expressed. It is possible, though, that random inactivation occurred embryonically but cells with an active X_t had a decreased growth capacity. One of the cases^{61 (case 1)} did demonstrate apparently random inactivation. In any event, the overall evidence is sufficiently convincing that the Y;X translocations need not be considered here, except as an interesting sidelight.

EVIDENCE THAT THE MALE DETERMINING FACTORS ARE NEAR THE CENTROMERE ON EITHER THE SHORT OR LONG ARM OF THE Y

The ring Y chromosomes described by German *et al.*²⁴ and Wilson *et al.*²⁷ and the minute Y chromosomes reported by Nakagome *et al.*,⁶⁵ Nielsen *et al.*,³³ and Langmaid and Laurence³⁶ each represented a mass no greater than that of the normal short arm of the Y (Yp). Thus, they must have consisted of little more than the centromere (except possibly the fragment described by Nielsen *et al.*,³³ which was presumed to be acentric: see next section) and either (1) most of the short arm and almost none of the long arm, (2) almost none of the short arm and a greater portion of the proximal long arm, or (3) relatively equal portions of the long and short arms. Since no consistently reproducible bands are present in either the short arm or the proximal long arm, the relative contribution of each is difficult to ascertain. Each of these patients had normal male genitalia and testes. Surana *et al.*⁶⁶ describe a similar minute Y chromosome in a 9-month-old mentally defective boy with a normal phallus but a hypoplastic and empty scrotum. They initially describe the minute Y as approximately the size of the short arm of a G group chromosome, which would put it in the same category as those mentioned above. However, they later suggest that it may represent a Yp isochromosome, which is twice the size of a G short arm.

Further evidence is offered by Ohno *et al.*⁶⁷ They mention a personal communication from Harold Klinger reporting a minute Y, representing no more than a tiny pericentric region of the Y, which was found in three generations of perfectly fertile men (including presumably the case reported by Fraccaro and Lindsten²⁷⁷).

EVIDENCE THAT THE MALE DETERMINING FACTORS ARE ON THE SHORT ARM OF THE Y
Cases of Yq isochromosomes (appendix 2) in females without mosaicism and with no signs of masculinisation suggest that the male determining factors are on the Yp. At least seven such cases have been reported,⁶⁸ (cases 1 and 2), ⁶⁹ (subject 1)/70 71 (case 5) 72–74 and the two cases studied by Jacobs and Ross⁶⁸ in 1966 have since been confirmed karyotypically by fluorescence study.⁷⁵ The gonads in two of these cases ⁶⁸ (case 2) ⁷³ were not examined.

Rosenfeld *et al.*⁷⁶ reported a 9-year-old female with normal external genitalia and undifferentiated gonads with an apparently male karyotype, except for a “clearly demonstrable” deletion of the short arm of the Y chromosome. The authors postulated the loss of male determining genes from the Yp.

Nielsen *et al.*³³ described a phenotypically normal 22-year-old male with normal testes and a non-fluorescent acentric fragment presumed to be derived from the Yp. Siebers *et al.*⁷⁷ suggest that the centromere and presumably a very small portion of the Yq are actually present, but not visible because of the small size of the fragment. To support this, they point out that (1) their case of a Yp isochromosome appeared acentric in nearly half the metaphases examined, and (2) that acentric fragments, because of their instability, are lost during the following division. However, the inherent instability of acentric fragments, rather than proving the presence of a centromere in this fragment, may simply explain why it was found in only 30 of 62 cells examined. Ruthner and Golob⁷⁸ also described a presumptive acentric Yp fragment. If the fragment is indeed acentric, it is more likely that it is derived from the short arm rather than from the non-fluorescent segment of the long arm, since the latter would require two breaks.

Two cases of 45,X/46,X,i(Yp) and partial masculinisation have been reported.^{79–80} However, the evidence offered to distinguish the i(Yp) from a del(Yq) is not substantial in either case. In one,⁷⁹ it is based on a ‘double positive’ H-Y antigen level. In the other,⁸⁰ the reason given is the ‘perfect symmetry’ of the Y, in spite of the presence of a small pericentric C band which Jalal *et al.*⁸¹ report to be on the Yq.

Three cases of apparently 46,XX males were reported in which a small additional band of non-

fluorescent material about the size of the Yp was found on another chromosome. It was found on the end of the short arm of an X chromosome in two cases^{82/83} ⁸⁴ (case 1) and on the short arm of chromosome 17 in the other.^{85/86} A male with a 45,X karyotype and additional non-fluorescent material on the long arm of chromosome 22 in two-thirds of the cells examined has also been described.⁶⁹ (case 8)/71 (case 7) All four of these subjects had male external genitalia including testes, although small ones. The extra chromosomal material in each case was presumably derived from the Y, and was probably responsible for the development of testes in at least three of the four. In one case,^{85/86} one of 201 cells examined was 47,XXY. Thus, masculine development might conceivably have resulted from this cell line. It is more likely that the additional material was from the Yp than from the non-fluorescent segment of the Yq, since the latter would require two breaks. In the first two cases, this is supported by the fact that the short arms of the X and Y chromosomes terminally synapse during meiosis.⁸⁷

Recently, Evans *et al.*⁸⁸ provided detailed evidence that nine of 13 cases (including the case cited in the addendum) of 46,XX males were actually 46,XXp+, presumably a product of Xp–Yp exchange. However, de la Chapelle *et al.*⁸⁹ found no conclusive evidence for the Xp+ phenomenon in five 46,XX males studied by a similar analysis.

EVIDENCE THAT THE MALE DETERMINING FACTORS ARE NOT ON THE DISTAL PORTION OF THE SHORT ARM OF THE Y

Certain cases of dicentric Yq chromosomes (appendix 1) provide evidence that the male determining factors are not on the telomeric Yp. Three cases of phenotypically normal males with testes have been reported with the karyotype 45,X/46,X,dic(Yq).⁹⁰ (case 12) ⁹¹ (case 3) ⁹² Several other cases of dicentric Yq chromosomes (excluding those with a 46,XY or 47,XXY cell line) with ambiguous external genitalia and testicular tissue have been reported.⁹¹ (case 1) ^{93–105} Since the formation of the dicentric Yq chromosome involves a break in the short arms and loss of the segment distal to the break (see footnote a, appendix 1), at least the most distal portion of the Yp may be excluded as the carrier of the male determining factors.

The formation of a ring chromosome requires breaks in both arms, usually with the loss of at least the most telomeric portions of each. Cases of ring Y chromosomes with normal male development and testes^{23–28} and in less than normal patients with testicular tissue⁷¹ ^{106–110} (observation 3) ²³¹ (case 1) have been reported.

Male development with testes has also been reported in Y;autosome^{29 111/112 113} and Y;Y¹¹⁴ translocations with loss of the distal Yp in a total of seven males, including relatives of the probands. Dalla-piccola *et al*¹¹⁵ reported a similar Y;autosome translocation in a male child with a hypoplastic scrotum and cryptorchidism.

EVIDENCE THAT MALE DETERMINING

FACTORS ARE ON THE LONG ARM OF THE Y

Cases of Yq deletions in females with no evidence of masculinisation and no detectable mosaicism would suggest male determining factors on the Yq. Only two such cases have been reported, both before the development of banding techniques. Nuzzo *et al*¹¹⁶ (case 1) reported a 17-year-old female with female external genitalia (but absent vaginal cavity), dysgenetic gonads, and a deletion presumed to be of the long arm of the Y. Fraccaro *et al*¹³ (patient KT) described a 33-year-old female with normal external genitalia, undifferentiated gonads, and a deleted Y, apparently of the long arm according to the measurements. However, two points should be raised regarding this case. Firstly, remnants of gonadal tissue "resembling to some extent totally obliterated hyalinised testicular tubules" were found, suggesting that gonadal tissue may once have been present. Secondly, it is possible that the fragment is X derived. The authors only 'tentatively' interpreted it as a deficient Y, and state that "measurements and autoradiographic studies do not contradict this hypothesis". Unfortunately, the authors do not provide control autoradiography data on the X chromosomes of normal female cells. This might have shown compatibility with X derivation as well as with Y derivation. The same possibility may also apply to the case of Nuzzo *et al*,¹¹⁶ in which the authors only claim that "morphologic and autoradiographic data do not contradict the hypothesis that the small abnormal chromosome is a deleted Y" (my translation). If the abnormal chromosomes in these two cases were derived from the X, though, the occurrence of two breaks would be necessary to account for their small size.

Ferguson-Smith *et al*¹¹⁷ described a 66-year-old female with Turner's syndrome and the karyotype 45,X/46,X,i(Yq). Based on the finding of clitoral enlargement, rudimentary epididymis, and mesonephric tubules, they suggest that factors on the long arm as well as on the short arm may play a role in male determination.

Three cases of translocations involving the long arm of the Y associated with masculinisation indicate that testis determinants are on the Yq. Hillman *et al*¹¹⁸ reported a newborn female with a translocation of the long arm of the Y to the short arm of

chromosome 21. They suggest that the finding of gonads with persistent sex cords indicates that the Yq is not totally devoid of male determining effects. It is curious, though, that according to the authors the breakpoint in the Y was at band q12.1, and thus only brightly fluorescent Yq material was present presumably. However, an abundance of evidence indicates that the brightly fluorescent segment of the Yq has no effect on male determination (above).

Bühler and Stalder¹¹⁹ reported a female with a translocation of the distal Yq to chromosome 8. Since her streak gonads showed remnants of Wolffian ducts, the authors conclude that a small portion of the non-fluorescent segment of the Yq must have been present, and that it contains male determinants.

Perhaps the most striking evidence is the case of Bernstein *et al*.¹²⁰ They reported a mentally retarded boy with normal external genitalia and testes with the brightly fluorescent and presumably some of the non-fluorescent segments of the Yq translocated to the short arm of an X chromosome.

Recently, Rary *et al*¹²¹ reported a Y;17 reciprocal translocation in a female with streak gonads and a gonadoblastoma. The break in the Y chromosome occurred in the non-fluorescent portion of the Yq with both segments maintained in the genome. The lack of virilisation could be attributed to the loss of male determinants at the breakage point.

EVIDENCE THAT A FERTILITY FACTOR IS ON THE DISTAL PORTION OF THE NON-FLUORESCENT SEGMENT OF THE LONG ARM OF THE Y

Evidence for a fertility factor on the distal portion of the non-fluorescent segment of the Yq is based on the finding of azoospermia in normal males with testes and deletions of the Yq in which the fluorescent and distal portion of the non-fluorescent segments have been lost. Azoospermia in a total of nine such males has been reported.^{34 40 41 110} (observation 1) The azoospermic patients with Yq deletions reported by Pierson *et al*¹²² (case NH) and Devictor-Vuillet *et al*¹²³ (case AF) may also fall into this category, although fluorescence data are not available.

A number of cases of reduced fertility associated with various anomalies of the Y chromosome provide circumstantial evidence for such a factor. A deleted Y chromosome and oligospermia were reported in a normal male with testes¹²⁴ and in a hypospadic male^{125/126} whose childless paternal uncle had the same deleted Y. Retief and van Niekerk¹²⁷ also reported a male with primary infertility, a low sperm count, and a non-fluorescent Y chromosome presumed to be either a pericentric inversion or Yq deletion. This may be the same case as the one later reported by van Zyl *et al*,¹²⁸ of an

azoospermic male with the karyotype 46,XYq—. Laurent *et al*¹²⁹ reported azoospermia (case 9) and oligospermia (case 8) in cases of a pericentric inversion of the Y and Yq—, respectively. Further support is offered by the finding of azoospermia in three normal males with non-fluorescent ring Y chromosomes.^{23 26 28} The azoospermia in these three cases is probably not attributable to the presence of a 45,X cell line since the ring Y chromosomes were widespread enough to induce testicular formation and normal male development. German *et al*²⁴ reported hypogonadism in an otherwise normal male with testes and a very small non-fluorescent ring Y chromosome from whom there was no semen analysis. Tiepolo and Zuffardi⁴⁰ suspect azoospermia based on the hypogonadism.

Six cases of infertility have been reported in Yq;autosome translocations. Three of these were normal males with small testes and azoospermia.^{130–132} One was a 15-year-old boy with a small penis, small testes, and spermatogenic arrest.¹³³ Another was a 29-year-old man with normal external genitalia and hypotrophic testes with spermatogenic arrest.¹³⁴ Both fragments of the Y chromosome were present within the genome in each of these cases (see appendix 4 for karyotypes). One last patient, presumably male (presence of Ypter→Yq12:), has been reported with sterility.¹³⁵ (observation 21) The breaks occurred in the non-fluorescent segment of the Yq in the first two,^{130 131} but in the brightly fluorescent segment in the last four.^{132–135} Thus, infertility in the first two may be associated with loss of such a fertility factor at the break. In the last four, however, it is probably coincidental, since the brightly fluorescent segment is not necessary for fertility.³¹ (case 7) 32 37

Van Zyl *et al*¹²⁸ also reported an oligospermic male with a Y;21 translocation, although it was not indicated where the break in the Y occurred. Dutrillaux²³² reported azoospermia in two cases of '47,X,inv(Y)' and '47,XYq—?' and oligospermia in the following cases: 46,X,inv(Y),22s+; 46,X,inv(Y); 46,XYq—? (3 cases); 46,XYq—?,16qh+; 46,XYq—?,22p+. Although these cases of reduced fertility might be associated with loss of Yq material, the paucity of information provided limits their value here.

Possibly contradictory evidence is offered by three studies. Meisner and Inhorn³² described a mentally retarded, but otherwise normal, 36-year-old male with testes and a Yq deletion. The deleted Y chromosome was described as less than half the length of the G group chromosomes, and according to Tiepolo and Zuffardi⁴⁰ was 'morphologically identical' to their own six cases. The reproductive capacity of the proband was not known, but his brother, with an identical small Y, was normal and fertile. The father

presumably had the same Y also. Tiepolo and Zuffardi⁴⁰ suggest that the deleted portion of the Yq in this case must have been slightly smaller than that of their own cases, thereby excluding the proposed fertility factor.

Also, Nielsen *et al*³³ reported a male with normal external genitalia and testes. They discovered a small non-fluorescent fragment which they presumed to be acentric and derived from the short arm of the Y. If it is indeed acentric (see p 163) it is more likely derived from the Yp than the Yq, since the latter would require two chromosomal breaks. If it is not acentric, as Siebers *et al*⁷⁷ suggest, probably only a very small portion of the proximal Yq is present. Otherwise, it is doubtful that it would have appeared acentric in all 30 cells in which it was found. In either case, a fertility factor on the distal part of the non-fluorescent Yq would have been excluded. Yet the authors report that the subject always achieved 'sperm emission' on masturbation. Unfortunately, they do not say whether they in fact ever examined the ejaculate. If they did not, and if the patient happened to be azoospermic, then he may have succeeded in achieving 'semen emission' but not 'sperm emission'.

Finally, Ohno *et al*⁶⁷ cited a personal communication from Harold Klinger reporting a minute Y, representing no more than a tiny pericentric region of the Y, which was found in three generations of perfectly fertile men. No additional information was provided (see p 163).

Discussion

Jacobs and Ross⁶⁸ were among the first to propose that the male determining factors in man are on the short arm of the Y. A few years later, Jacobs⁹⁶ presented further evidence indicating that the male determining factors must be near the centromere on the short arm. As seen from the analysis above, most of the evidence since then favours this theory. Simpson^{136 137} arrived at the same conclusion by a similar analysis. This is perhaps most vividly illustrated by comparing cases of 46,X,i(Yq)⁶⁸ (cases 1 and 2)⁶⁹ (subject 1)/70 71 (case 5) 72–74 with certain cases of dicentric Yq chromosomes.⁹⁰ (case 12) 91 (case 3) 92 The former were female, with no evidence of masculinisation, and with duplicated long arms of the Y. The latter were normal males (two of whom were azoospermic⁹⁰ and oligospermic⁹¹) with testes, duplicated long arms of the Y, and duplicated pericentromeric region of the short arm of the Y (figure). Thus, the vital role of the short arm of the Y, particularly the pericentromeric region, in testicular development is unquestionable. If the short arm were dispensable in this regard, then 46,X,i(Yq) subjects would be male.

FIGURE Contrasting phenotypes in several cases of Yq isochromosomes (A) and 3 cases of dicentric Yq chromosomes (B) (see text). The former were females with no evidence of masculinisation and varying degrees of Turner's syndrome; the latter were normal males with testes (azoospermic and oligospermic in 2 of the 3 cases). The only difference between them is the presence of the pericentromeric region of the short arm of the Y. It follows that this segment plays a crucial role in male determination.

Boczkowski¹³⁸ suggests that two distinct genes on the Yp are responsible for testicular development: one near the centromere initiating development of the testes, and one on the distal portion causing further maturation of the testes. Thus, dysgenetic testes in cases of Yp deletions, for example, dic(Yq) or r(Y), could result from loss of the more distal gene. However, the effects of a 45,X cell line, if present, in preventing full testicular maturation cannot be ruled out. This is discussed in more detail below. Also, the loss of some multiple equivalent testis determinants (that is, H-Y genes) is also possible (see pp 168, 171). Moreover, cases of dic(Yq) and r(Y) chromosomes with the presence of at least one mature testis^{23 90 (case 12) 91 (case 3) 92 139} would

have to be assumed to result from breaks distal to the supposed gene. This, in addition to the evidence presented on pp 162–164, suggests that the gene (assuming that separate 'initiation' and 'maturation' genes do exist) would probably be located more proximally on the Yp.

The evidence suggesting the presence of testis determinants on the long arm of the Y is less clear, and therefore needs to be examined in detail. Since as a whole it is less conclusive than the evidence regarding the role of the short arm, alternative cytological interpretations are often presented so that the reader may decide for himself as to its strength.

The cases of Fraccaro *et al*¹³ and Nuzzo *et al*¹¹⁶ were two of the first studies to suggest possible testis determinants on the Yq. These are discussed on p 164. In addition to the alternative interpretations presented there, two others are conceivable. One is the occurrence of gonadal failure similar to that which occurs in 46,XY females with pure gonadal dysgenesis.^{10 11 140} Also, there is the possibility which is so often raised of an undetectable 45,X cell line. The question of undetectable mosaic cell lines is problematical. It has been used to explain inconsistencies in countless hypotheses, often in some which oppose one another. Ford²⁴⁴ points out that a minor cell line with a frequency of 0.05 will not be detected in a 50 cell sample 8% of the time.

Federman *et al*¹⁴¹ described a 23-year-old intersex patient with an enlarged non-patent phallus and mixed gonadal dysgenesis (streak and testis). They found an abnormal chromosome interpreted as a translocation of a Yq segment to the short arm of a D group chromosome. They suggest that the masculinisation was the result of testis determinants on the Yq. However, Jacobs's hypothesis⁹⁶ that the long arm of the D group chromosome was translocated to the short arm of the Y is just as likely, perhaps more so since the long arm of the abnormal chromosome appears longer (by the length of the Yp?) than that of the other D group chromosomes.

Sarto *et al*²³¹ reported an intersex patient with the karyotype 46,XX/47,XX,r(Y), and reviewed several other structural anomalies of the Y. They suggested on the basis of their case and two males with presumed Yq isochromosomes^{142 143} that the male determining factors are on the long arm of the Y. In the first place, the latter two cases are probably not Yq isochromosomes (see footnote a, appendix 2). Also their own case adds no support to a Yq male determining factor, since a ring Y chromosome does not require (and would rarely include) loss of the entire Yp. Finally, their suggestion that the Yq isochromosomes reported by Jacobs and Ross⁶⁸ were actually deleted X chromosomes was ruled out by subsequent

fluorescence study⁷⁵ which confirmed an i(Yq) in each case.

Siebers *et al*⁷⁷ reported a case of 45,X/46,X,i(Yp), and also reviewed published reports. They proposed that regulatory genes on the proximal Yq are responsible for the initiation of testicular development, and that genes on the short arm cause maturation of the testes (for the sake of convenience, these genes are hereafter referred to as the 'initiation' and 'maturation' genes). As this study has received a considerable amount of attention (for example, Bühler and Stalder¹¹⁹), it merits close scrutiny.

The authors base their theory on two major conclusions. Each will be dealt with separately, and it will soon be seen that certain problems are associated with each.

One conclusion is that "a deletion of the short arm usually results in immature testicular tissue (46,X,i(Yq);46,X,dic i(Yq))." * First let us consider cases of Yq isochromosomes (appendix 2). Five cases should be eliminated from this discussion: that of Kelvit *et al*¹⁴⁴ for its complex karyotype, of Latt *et al*¹⁴⁵ for the limited information offered as well as the authors' doubts as to whether the abnormal Y was dicentric, of Kaluzewski *et al*¹⁴⁶ for the presence of a 49,XXXXY cell line, and those of Taylor *et al*¹⁴⁷ and Mattei *et al*¹¹⁰ (observation 4) for the presence of a 46,XY cell line. This leaves seven cases of 46,X,i(Yq) and one case of 45,X/46,X,i(Yq). All seven cases of 46,X,i(Yq) were females with no signs of masculinisation. Of these, five included histological examination of the gonads⁶⁸ (case 1)⁶⁹ (subject 1)/⁷⁰ ⁷¹ (case 5)⁷² ⁷⁴ while two did not.⁶⁸ (case 2)⁷³ The case of 45,X/46,X,i(Yq)¹¹⁷ was the only one which showed signs of masculinisation. This was a woman with infantile female external genitalia, an enlarged clitoris, a streak gonad, fimbrial cysts, a rudimentary epididymis, and a few mesonephric tubules.

To explain absence of masculinisation in cases of 46,X,i(Yq), Siebers *et al*⁷⁷ suggest that females with bilateral streaks and 46,X,i(Yq) had developed rudimentary testes which degenerated during further development into fibrous tissue (owing to the absence of the 'maturation' gene). Admittedly, the possibility of this occurrence is suggested by the degeneration of ovarian germ cells during embryogenesis of 45,X fetuses.¹⁴⁸ However, it seems unlikely that testicular degeneration would be complete in all five of the reported cases of 46,X,i(Yq) in which the gonads were examined histologically. Assuming that this degeneration took place, it is ironic that the only case of i(Yq) with detected masculinisation¹¹⁷ was the only one in which a 45,X

cell line was found (a finding which otherwise could have been put forth to explain a lack of masculinisation). More importantly, it seems doubtful that an 'initiation' gene on the Yq would cause masculinisation in a 45,X/46,X,i(Yq) condition, in which the 45,X cell line might be expected to 'dilute' its effect, but not in any of the five cases of 'undiluted' 46,X,i(Yq). The recent report by Rosenfeld *et al*⁷⁶ of undifferentiated gonads in a phenotypic female with a Yp deletion (46,X,del(Y)(pl)) offers further evidence along the same line of reasoning. Bühler and Stalder¹¹⁹ offer one possible explanation to make these cases conform to the theory of Siebers *et al*⁷⁷: that the presence of testicular elements may not have been detected because of failure to section serially biopsy material from the gonads.

As for the case of Ferguson-Smith *et al*,¹¹⁷ two explanations have been offered to make it conform to the absence of testis determinants on the Yq. Magnelli *et al*⁷³ suggest that a transverse fission of the Y centromere in a 46,XY zygote resulted in two cell lines, one with an i(Yp), the other with an i(Yq). The former persisted during development only long enough to influence the gonads slightly. In addition, although Ferguson-Smith *et al*¹¹⁷ argued against it, Simpson¹³⁶ ¹³⁷ suggests that the abnormal Y may have been a pericentric inversion, since this case was reported before the development of banding techniques. It would then follow that the 45,X cell line prevented full male development. If this is so, the original Y would have been a long variant of the Y, since the abnormal chromosome was slightly larger than the F group chromosomes. It would be informative in this case to know how prevalent a Y chromosome of that size is. Unfortunately, estimates on this differ. The percentage of males with Y chromosomes as long as or longer than the F group chromosomes (Y/F index ≥ 1) has been reported to be 1.5%,¹⁴⁹ 5%,¹⁵⁰ and as much as 50%.¹⁵¹ Moreover, Cohen *et al*¹⁵² found the length of the Y to vary among five different racial and ethnic groups, from mean Y/F values of 0.86 (non-Jewish Anglo-Saxons) to 1.00 (Japanese).

Now let us consider the second half of the first main conclusion of Siebers *et al*,⁷⁷ namely, cases of dicentric Yq chromosomes (appendix 1). The authors suggest that the formation of dic(Yq) chromosomes involves deletion of the short arm, including the loss of the 'maturation' gene, which thus prevents maturation of the testes. However, two factors complicate this issue and make it very difficult to use these cases as evidence here. The first is the fact that it is virtually impossible to determine how much Yp material was deleted. Thus, one would not be able to determine if the 'maturation' gene, wherever one might choose to localise it along the

*The forms dic i(Yq), idic(Yq), or variations thereof are occasionally used instead of the simpler and more commonly seen form, dic(Yq). See footnote a, appendix 1.

Yp, was deleted. Secondly, every published case of dicentric Y chromosomes with the one exception of Armendares *et al*⁹⁸ has shown mosaicism with a 45,X cell line. As a result, we are left with two possibilities. In the case of a dic(Yq) associated with at least one mature testis (and there have been at least four cases of this^{90 (case 12) 91 (case 3) 92 94}) proponents of this theory are forced to conclude that the deletion of the Yp must have been small so as to exclude the 'maturation' gene. In the case of a dic(Yq) subject with less than mature testicular tissue, it is impossible to determine if the reduced masculinisation is the result of a deletion of the 'maturation' gene, or of the 45,X cell line, or both. Although Siebers *et al*⁷⁷ as well as other investigators have sought to rule out the influence of the 45,X cell line in certain studies because of its low frequency, this is not necessarily valid.

Conclusions based on the predominance of a mosaic cell line are difficult for several reasons. The distribution of cell lines may vary not only from one tissue type to another, but also between segments of the same tissue, as well as from one stage of development to another. Moreover, the proportion of different cell lines in a tissue culture does not necessarily reflect the in vivo conditions. Selective advantage or disadvantage of one or more cell lines may occur. The only valid consideration is the question of which cell line predominated in the gonadal anlage, which is of course impossible to determine. Although the 45,X cell line might be found at a lower incidence in postnatal tissue, it may very well have predominated in the primordial gonadal tissue at the onset of gonadal differentiation. If so, masculinisation would have been reduced (or completely absent), even though the 45,X cell line could have subsequently become confined to a minority of cells. Two illustrative examples are the cases reported by Russell *et al*¹⁵³ and Mellman *et al*.¹⁵⁴ Russell *et al*¹⁵³ described an 8-year-old monozygotic twin with a right testis of karyotype 45,X/46,XY. Of 73 testicular cells, 67 were 45,X while only three were 46,XY. Mellman *et al*¹⁵⁴ reported a patient with a right testis of the same karyotype from which only one of 141 testicular cells was 46,XY. Thus, conclusions concerning sex determination cannot legitimately be based on the predominance of mosaic cell lines in gonadal tissue, much less on their predominance among blood cells or any other tissue.

Consequently, we are left with the case of Armendares *et al*⁹⁸ among cases of dic(Yq), hardly enough from which to make any firm conclusions. They reported a 16-year-old female with slight clitoral enlargement, streak gonads, and epididymis. Although this case is compatible with the theory of Siebers *et al*,⁷⁷ it should be pointed out that, besides the possibility of an undetectable 45,X cell line, it

is also compatible with another prominent theory. Ohno *et al*⁶⁷ favour the existence of multiple copies of the H-Y structural gene on the pericentromeric region of the Y. Since the H-Y antigen probably directs formation of the testes (see p 171), a Yp deletion during the formation of a dic(Yq) could conceivably include some but not all copies of the H-Y gene. This then might permit partial, but not complete, testicular development. Böök *et al*⁷² suggested this earlier, although without specific reference to the H-Y genes, since the importance of the latter in male determination had not yet been elucidated. Thus, it should be emphasised that evidence compatible with a certain theory does not necessarily offer direct support for it.

This same point also applies to the case of a 46,X,r(Y) female with streak gonads and dysgenetic testicular tissue.¹⁵⁵ The authors explain this finding on the basis of the theory of Siebers *et al*.⁷⁷ However, it could just as easily be explained by the suggestion in the preceding paragraph, as well as by the theory of Devictor-Vuillet *et al*¹²³ (see p 170). They also assume that the 'maturation' gene is on the distal part of the Yp. Evidence against this has already been discussed (pp 165–166).

The second major conclusion upon which Siebers *et al*⁷⁷ base their theory is that "complete or almost complete loss of the long arm does not permit any gonadal differentiation (dic i(Yp);i(Yp))". Initially, one should recall the case of Neilsen *et al*⁸³ and those of possible Yp;X or Yp;autosome translocations which might contradict this statement (see p 163). With respect to dic(Yp) chromosomes, they cite three cases, none of which showed signs of masculinisation: Starkman and Jaffe¹⁵⁶ (patients SZ and MG) and Angell *et al*.¹⁵⁷ (case 3) Firstly, the cases of Starkman and Jaffe¹⁵⁶ should not be cited, since a 46,XY cell line was present and at a frequency equal to (patient MG) or greater than (patient SZ) the cell line with the dicentric Y. Otherwise, one could argue with just as much validity that the Y is not male determining. Also they claim that "in at least two of these, the absence of virilisation cannot be ascribed to the mosaic constitution, since the 46,X,dic i(Yp) cell line was predominant". We have already seen that arguments based on the predominance of mosaic cell lines are of dubious validity. Moreover, the statement itself is inaccurate. The 45,X cell line predominated in three of four tissues (including both gonads) in patient SZ,¹⁵⁶ in each of two tissues in patient MG,¹⁵⁶ and in two of three tissues in case 3 of Angell *et al*.¹⁵⁷ Also, in four more recently reported cases of dic(Yp) with absence of virilisation,^{91 (case 4) 158–160} the 46,X,dic(Yp) did not predominate in a single one (table). Thus, the influence of the 45,X cell line cannot be so easily dismissed.

TABLE Distribution of mosaic cell lines in reported cases of dic(Yp) or i(Yp) chromosomes

Reference	Karyotype	Tissue	Total cells	45,X cells	Cells with 46,X+			
					Y	dic(Yp)	del(dic Y) or del(Y)	i(Yp)
156 (patient SZ)	45,X/46,XY/46,X,dic(Yp)	Blood	53	18	26	6		
		Skin	56	50				
		L gonad	58	50				
		R gonad	57	49	1			
156 (patient MG)	45,X/46,XY/46,X,dic(Yp)/46,X,del(dic Y)	Blood	54	35	7	8		
		L gonad	60	37			13	
157 (case 3)	45,X/46,X,dic(Yp)	Blood	29	8		21		
		L skin	38	34		4		
		R skin	35	24		11 or 22*		
161 (patient 5)	45,X/46,XY/46,X,dic(Y)/†46,X,del(dic Y)	Blood						
161 (patient 6)	45,X/46,XY/46,X,dic(Y)/†46,X,del(dic Y)	Blood						
		Skin						
163	46,XY/46,X,i(Yp)/‡47,X,i(Yp),i(Yp)	Blood	168		63			82
77	45,X/46,X,i(Yp)	Skin	30					29
158	45,X/46,X,dic(Yp)	Blood	50	12				38
159	45,X/46,X,dic(Yp)/46,X,Yq— or del(dic Y)	Blood	538	379		113	28	
		Skin	31	25		43%	20%	
91 (case 4)	45,X/46,X,dic(Yp)	Blood	116	52%		5	1	
160	45,X/46,X,dic(Yp)/46,X,del(dic Y)	Blood	76	38		48%	3	
		L gonad	49	46		35	1	
79	45,X/46,X,i(Yp)	Blood		40%		2		60%
		Skin						100%
164	46,XY/46,X,dic(Yp)/46,X,del(Y)(q11)	Amniotic fluid						
110 (observation 9)	45,X/46,X,dic(Yp)	Blood	100	35%		65%		
89	45,X/46,X,i(Yp)	Blood	30	19				11
165	45,X/46,X,dic(Yp)							

*11 according to table 1 of their report, 22 according to table 3.

†These dicentric Y chromosomes were not identified by the author as either dic(Yp) or dic(Yq). They were assumed by Johnston *et al*¹⁵⁸ to be dic(Yp), and appear as such from the photographs (see Morillo-Cucci and German¹⁶² for additional photographs). No data on mosaic cell line distribution were provided.

‡See footnote d, appendix 2.

If one carefully considers the cases of dic(Yp) chromosomes, it becomes evident that they offer little useful information. Excluding cases with a 46,XY cell line,¹⁵⁶ (patients SZ and MG) 161 (patients 5 and 6) 164 a total of seven other cases of dic(Yp) have been reported⁹¹ (case 4) 110 (observation 9) 157 (case 3) 158–160 165 (table). Three of these may immediately be eliminated from this discussion, since brightly fluorescent Yq material was present between the centromeres.^{91 110 158} Thus the entire non-fluorescent segment of the Yq was present (in duplicate). It follows that any testis determinants, whether on the Yp or Yq, would have been present (since the brightly fluorescent Yq has no masculinising effect, see p 162). Therefore, the 45,X cell line must have been responsible for the absence of virilisation observed in two of these three cases.^{91 158}

Four cases of dic(Yp) remain, one with masculinisation¹⁶⁵ and three without^{157 159 160} (see footnote j, appendix 1). Let us proceed under the assumption that the testis determinants are exclusively on the Yp. One might counterargue that in spite of the presence of the 45,X cell line in all four of these cases (which could explain the lack of masculinisation in any of them individually), one would still expect to see at least partial masculinisation in more than just one of the four. According to this reasoning, the

absence of virilisation in three of the four is not consistent with testis determinants exclusively on the Yp.

Two responses to this argument can be made. Firstly, the underlying assumptions of absence of masculinisation and presence of a dic(Yp) chromosome may be incorrect. In the case of Angell *et al*,¹⁵⁷ the gonads were not examined, so it is possible that testicular tissue may have been present. Also, as Málková *et al*¹⁵⁹ point out, the finding of gonadoblastomas in the streak gonads of their case as well as that of Ying *et al*¹⁶⁰ may indicate some, though rudimentary, development in the testicular direction. And, as Johnston *et al*¹⁵⁸ suggest, the dic(Yp) reported by Angell *et al*¹⁵⁷ before the development of banding techniques may have in fact been X derived. Stevenson *et al*¹⁶⁶ found this to be true after an original interpretation of 45,X/46,XY/46,X,dic(Yp).

Secondly, the absence of virilisation in three of these four cases does not appear to be consistent with a Yq located 'initiation' gene either. If such a gene is on the Yq, then it must be located very close to the centromere. This is based on (1) the evidence presented on pp 162–163; (2) the case of a male ('Short Y-e') exhibiting 'normal sexual development' with the loss of the fluorescent and three-quarters of the non-fluorescent segments of the Yq⁴³; and (3) the

rarity of the absence of masculinisation among the multitude of reported Yq deletions (appendix 7), some of which involved loss of most of the Yq (for example, Pierson *et al*¹²² (case PP)). Thus, the isochromatid break resulting in the dic(Yp) chromosomes would have had to occur very close to the centromere in order to exclude the proposed gene. Accordingly, the dic(Yp) chromosomes would probably have included the gene in some if not all of these four cases. Thus, the absence of virilisation would again have to be ascribed to the 45,X cell line.

Turning to i(Yp) chromosomes (ignoring the one where a 46,XY cell line was found¹⁶³), three cases have been reported (all with 45,X cell lines), two with masculinisation^{79 80} and one without.⁷⁷ Again, the role of the 45,X cell line in preventing masculinisation in the latter case cannot be ruled out, even though only 12 of 50 cells examined were 45,X (especially since only blood lymphocytes were studied). Moreover, the difficulty involved in distinguishing an i(Yp) from a del(Y)(q11) makes one reluctant to use these cases as definitive evidence one way or the other (see p 163; asterisk, appendix 7; Simpson^{136 137}). Two of these cases,^{77 80} for instance, showed a pericentric C band which Jalal *et al*⁸¹ report to be on the Yq.

In summary, then, cases of dic(Yp) and i(Yp) are at present of limited usefulness in localising male determining factors for the following reasons:

- (1) a 45,X cell line is invariably present, and its role in preventing masculinisation cannot be ruled out regardless of its frequency;
- (2) it is usually difficult to determine how much Yq material is present in the dic(Yp) (although in most cases, postulated Yq testis determinants should be present); and
- (3) the distinction between an i(Yp) and a del(Y)(q11) cannot yet be made reliably.

The cases of Hillman *et al*¹¹⁸ and Bühler and Stalder¹¹⁹ suggest the presence of testis determining factors on the Yq. This is based on the finding of 'persistent sex cords' and 'remnants of Wolffian ducts', respectively, in two females with Yq;auto-some translocations. It should be mentioned, though, that incompletely obliterated Wolffian elements are not necessarily associated with Y material. Vestiges of the mesonephric (Wolffian) tubules and duct often remain recognisable in normal females as the opoöphoron and canals of Gartner. A less complete obliteration would be expected in females with only one X chromosome, such as in these two cases. Greenblatt *et al*¹⁶⁷ found mesonephric rests (tubules and ducts) in all cases of 45,X in their survey of gonadal dysgenesis. Also, at least vaguely defined sex cords are present in the indifferent gonad of a

6-week embryo,²⁴⁶ and could conceivably survive in a poorly differentiated gonad (only one degenerating follicle was found on multiple sections). Thus, it is possible that the finding of Yq material and Wolffian remnants in these two cases is coincidental. This is supported by the fact that the proximal portion of the non-fluorescent segment of the Yq, in which any testis determinants on the Yq would most probably be located (above), appears to be missing in both of these cases.

The case of Bernstein *et al*¹²⁰ seems to provide the strongest evidence for testis determinants on the Yq. They reported normal sexual development in a boy with part of the Yq translocated to the short arm of one of two X chromosomes. However, they believe that this does not further elucidate the localisation of testis determinants on the Y, presumably because some investigators favour a pericentric inversion of the Y as part of the mechanism leading to such a translocation.

Interestingly, Devictor-Vuillet *et al*¹²³ concluded that the primary male determinants influencing testicular differentiation are on the Yp, near the centromere, and that factors controlling the further development of the testis are on the Yq, near the centromere. This is just the opposite of what Siebers *et al*⁷⁷ proposed. This theory is compatible with the absence of masculinisation in 46,X,i(Yq) subjects. However, it is not compatible with reports of masculinisation in the absence of the Yp¹¹⁷⁻¹²⁰ or with the absence of masculinisation with Yq deletions¹³ (patient KT)¹¹⁶ (case 1) (see pp 164, 166) unless (1) one accepts alternative interpretations such as those suggested above, or (2) one proposes, in the case of the latter, a 'degeneration' hypothesis like that of Siebers *et al*⁷⁷ (p 167). Moreover, Devictor-Vuillet *et al*¹²³ often assume that small metacentric Y chromosomes are Yp isochromosomes. Using conventional karyotyping techniques, though, these are indistinguishable from metacentric Yq deletions (above). In addition, they overlook the significance of mosaicism, making karyotype-phenotype correlations on the basis of only one cell line. Thus, some of the evidence they present should be viewed with scepticism.

Most, if not all, of the available evidence in favour of testis determinants on the Yq has now been presented and discussed. Although in most cases other interpretations are possible, it may be more reasonable to conclude that multiple factors are involved, some of which may be present on the Yq. The major problems with the assumption of testis determinants on the Yq are (1) the absence of masculinisation in cases of 46,X,i(Yq), and (2) well-developed masculinisation presumably in the presence of only Yp material (p 163). What is most certain is that if

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such factors are on the Yq, they must be near the centromere (pp 169–170).

The easiest explanation may be that a factor or factors are present on the Yq in some subjects, but not in others. Testis determinants on the Yp could conceivably be transferred to the Yq in an unknown percentage of subjects by a pericentric inversion. This could occur with little or no change in the morphology or staining properties of the Y if the two breaks are symmetrical about the centromere. By this mechanism too, testis determinants on the Yq would have to be near the centromere, since they are pericentromeric on the Yp initially (pp 162–164).

These conclusions would agree with current theory on the H–Y antigen. Recent years have yielded an increasing amount of evidence favouring a testis organising function of the H–Y antigen.^{168–172} From studies of 17 patients with structural anomalies of the Y chromosome, Koo *et al*⁷¹ concluded that the H–Y locus is near the centromere on the short arm of the Y in most subjects, and on the long arm in at least one. They suggest that pericentric inversions may alter the position of the gene, and conclude that “there is insufficient evidence at this time to rule out a long arm location of the H–Y locus in some individuals or even to hazard a guess at the proportion of human Y chromosomes with an H–Y gene at a given location”. In addition, Ohno *et al*⁶⁷ and Wachtel¹⁷³ favour the existence of multiple copies of the H–Y structural gene on the pericentromeric region of the Y chromosome. Wachtel¹⁷³ argues that the Y linked H–Y locus is structural rather than regulatory, since males with two Y chromosomes express more H–Y antigen than 46,XY males. “At present there is no reason to believe that the products of supernumerary regulatory genes would elicit production of ‘excess’ H–Y antigen, given a single structural locus or even multiple structural loci.”

Most of the phenotypes associated with structural anomalies of the Y chromosome can be explained on the basis of multiple structural H–Y genes on the Y (for example, see pp 166, 168). They are most likely to be located predominantly on the short arm near the centromere, but may be present on the long arm near the centromere in unknown amounts and in an unknown percentage of subjects. A threshold effect could be postulated whereby a certain number of H–Y genes would have to be present on the short arm or long arm or both for the H–Y antigen to be detectable immunologically. A gradient of the degree of testicular development, and thus of masculinisation, might result from the number of H–Y genes present. The absence of masculinisation in all seven cases of 46,X,i(Yq) suggests that the H–Y genes are either not present or present in insignificant numbers on the Yq in most subjects, especially

since the long arm was present in duplicate. The few reports of masculinisation in the absence of the Yp indicate that the H–Y genes may occasionally be present on the Yq in significant numbers, although rarely enough for normal male development. This concept is simpler and has a sounder theoretical foundation than the concept of two separate genes independently controlling the initial development and the maturation of the testes, whether both are on the short arm,¹³⁸ on the short and long arms respectively,¹²³ or on the long and short arms respectively.⁷⁷

There is a fair amount of evidence that a fertility factor is present on the non-fluorescent segment of the Yq. This is not necessarily inconsistent with the cases described above of females with absence of virilisation and karyotype 46,X,i(Yq). A male fertility factor in the absence of male gonads would not be expected to cause masculinisation. Similarly, Devictor-Vuillet *et al*¹²³ suggested that factors influencing spermatogenesis are located on the long arm, adjacent to the secondary constriction. They also point out the fact that fertility factors have been found on the Y chromosome in *Drosophila melanogaster*.¹⁷⁴ Brosseau¹⁷⁵ mapped at least seven of these on both the short and long arms of the Y. However, the significance of this is questionable, since the mechanism of sex determination in *Drosophila* is very different from that in man.¹⁷⁶

Donahoe *et al*¹⁷⁷ suggest a fertility factor on the Yq by somewhat different reasoning. They first assume that 46,XX true hermaphrodites, since they are H–Y⁺, have the short arm of the Y present somewhere in their genome. This would account for the formation of testicular tissue. They then point out that the testicular elements of 46,XX true hermaphrodites show either the absence of germ cells or their failure to mature beyond the spermatogonia stage. On this basis they speculate that the missing Yq might be essential for germ cell maturation beyond the spermatogonia stage. However, they do not consider the possibility that the spermatogenic arrest may be the result of the presence of two X chromosomes. Patients with Klinefelter’s syndrome (47,XXY) are almost always sterile with absence of spermatogenesis.

Suggestive evidence for the presence of a fertility factor on an unknown region of the Y chromosome derives from the impaired spermatogenesis often seen in 47,XYY males. Such impairment could be explained by a genetic imbalance caused by the supernumerary Y chromosome (and fertility factor). Alternatively, a disruption of sex chromosome pairing may be responsible.¹⁷⁸ On the other hand Chaganti and German¹⁷⁹ postulated, on the basis of the familial incidence of infertility in males with

normal karyotypes, a gene for meiotic disturbance, spermatogenic arrest, and azoospermia with either an X linked recessive or a sex limited autosomal dominant transmission.

Conclusion

A review of structural anomalies of the Y chromosome in man reveals unequivocally that the pericentromeric region of the short arm of the Y plays an essential role in male determination. The important role of the short arm is most evident from reports of 46,X,i(Yq), which present a deletion of the entire short arm and a duplication of the entire long arm. No signs of masculinisation were noted in all seven cases of 46,X,i(Yq) so far published, five of which included histological examination of the gonads. No evidence as conclusive as this exists that testis determinants reside on the long arm. However, some findings do suggest this, and thus the possibility should be examined carefully as further evidence becomes available. If such a factor is on the Yq, it must be very near the centromere.

The theory that separate factors are responsible for the initial development and maturation of the testes (on the long and short arms, respectively) was examined in detail. Arguments in its favour are beset with considerable problems, and thus acceptance at this point would be premature.

The easiest explanation is based on the concept of multiple H-Y structural genes, located predominantly on the short arm near the centromere, but possibly present on the long arm near the centromere in unknown quantities and in an unknown percentage of subjects.

There is a fair amount of evidence that a fertility factor resides on the long arm. Unfortunately, in many potentially informative cases of structural anomalies of the Y, either the proband was pre-pubescent or no semen analysis was performed. It is suggested that semen analysis should be performed routinely in these cases, and that follow-up post-pubescent studies be conducted if possible. Again, caution is advised in the acceptance of this theory before the accumulation of further data.

As Bühler and Stalder¹¹⁹ point out, mapping of the human Y chromosome by karyotype-phenotype correlations or deletion mapping is a rather crude method. This is undoubtedly responsible for many of the ambiguities present while using this method to localise male determining factors. Another source of confusion is the ubiquitous spectre of mosaicism. Nevertheless, there is much hope that these issues will be clarified in the near future. Immunological or biochemical detection of the crucial gene products involved in sex determination should eventually be possible. This has already been

accomplished in the case of the X linked testicular feminisation (*tfm*) gene and the H-Y structural (see p 171) gene.²⁴⁹ However, products of other proposed genes (for example, fertility factor, H-Y regulatory and gonad specific plasma membrane receptor genes) have not yet been detected. Correlating the presence or absence of these products with structural anomalies of the Y chromosome would more easily and convincingly localise male determining genes along the Y.

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Appendices

In the following appendices, several conventions have been used by the author and deserve mention.

- (1) Karyotype nomenclature is exclusively according to the Paris Conference.¹⁸⁰ These were often converted from previous systems of nomenclature, formulated from the text or figures or both or altered from incorrect forms (occasionally pointed out). See footnote a, appendices 1 and 4.
- (2) When authors made statements such as "the physical examination was normal" or "no gross abnormalities were noted", it was assumed that the external genitalia were normal and that, in the case of males, descended testes were present.
- (3) Primary amenorrhoea and lack of breast development are not explicitly stated (but should be assumed) when the remark 'Turner's syndrome' appears, since they are present in at least 95% of the cases of 45,X Turner's syndrome.^{136 137} However, this does not apply to the remarks 'Turner stigmata' or 'features of Turner's syndrome'.
- (4) In appendix 7, deleted Y chromosomes which were not studied by banding techniques are indicated as 'del(Y)' unless the authors explicitly stated their belief that the deletion was of the long arm (indicated as 'del(Y)(q1)'). In any event, most of these are probably Yq deletions, although a few might represent normal variations in the length of the q12 segment (see footnote a).
- (5) Unpublished cases of various anomalies of the Y may also be found in Borgeonkar and Bolling.¹⁸¹

APPENDIX 1 Reported cases of dicentric Y chromosomes^a

Reference	Age	Height (cm)	External genitalia	Gonadal findings	Karyotype	Remarks
93	4 wk		Ambiguous	Testes (abdominal)	45,X/46,X,dic(Yq)	Reported as a Y;Y translocation
90	24 yr		Normal male	Testes	45,X/46,X,dic(Yq)	Azoospermia
156(patient SZ)	16 yr	157	Infantile female	Bilateral streaks with ovarian stroma	45,X/46,XY/46,X,dic(Yp)	Turner's syndrome
156(patient MG)	19 yr	150	Infantile female	Bilateral streaks, ovarian stroma (right)	45,X/46,XY/46,X,dic(Yp)/46,X,del(dic Y)	Turner's syndrome
94	13 yr	142	Ambiguous (small penis, severe hypospadias, bifid scrotum)	Streak (left), inguinal testis (right)	45,X/46,X,dic(Yq)	Features of Turner's syndrome
95	7 yr	110	Ambiguous (aplastic penis, hypospadias, bifid scrotum)	Undifferentiated testes (abdominal)	45,X/46,X,dic(Yq)/46,XXq-b	
182	8 yr		Ambiguous (penis, hypospadias, pseudovaginal orifice)	Testicular tissue	45,X/46,XY/46,XX/46,X,dic(Yq)/47,XX,dic(Yq)	
96 ^d	3 yr		Ambiguous	Testes (inguinal)	45,X/46,X,dic(Yq)	
157(case 1) ^e	14 yr	138	Infantile female	Bilateral streaks, testicular tubule (right)	45,X/46,X,dic(Yq)	Features of Turner's syndrome, lack of breast development
157(case 2) ^e	36 yr	147	Infantile female	Bilateral streaks	45,X/46,X,dic(Yq)	Features of Turner's syndrome, primary amenorrhoea, slight breast development
157(case 3)	11 yr	124	Infantile female		45,X/46,X,dic(Yp)	Features of Turner's syndrome
161(patient 5) ^e	47 yr	140	Ambiguous (infantile female except for 4 cm phallus)	Dysgenetic testes (abdominal)	45,X/46,XY/46,X,dic(Y)/46,X,del(dic Y)	Turner's syndrome
161(patient 6) ^f	21 yr	149	Ambiguous (short penis, hypospadias, pseudovaginal orifice)	Testis adjoining streak (right), gonadoblastoma (left)	45,X/46,XY/46,X,dic(Y)/46,X,del(dic Y)	Features of Turner's syndrome
97	6 yr	25th centile	Ambiguous (enlarged clitoris perineal hypospadias, small vaginal orifice)	Streak (right), ovotestis (left)	45,X/46,X,dic(Yq)	
183					dic(Yq)	
98 ^g	16 yr	138	Female (clitoral enlargement, hypoplastic labia)	Bilateral streaks with ovarian stroma, epididymis, and tiny gonadoblastoma	46,X,dic(Yq)	Features of Turner's syndrome, primary amenorrhoea, lack of breast development
184(patient 4)		144	Female	Bilateral streaks	45,X/46,X,dic(Yq)	Primary amenorrhoea, lack of breast development
99	11 yr	10th centile	Ambiguous (enlarged clitoris, scrotalised labia majora, no labia minora, posterior labial fusion)	Streak (right), ovotestis (left)	45,X/46,X,dic(Yq)	Multiple naevi
100	15 yr	134	Ambiguous (vagina, 5 cm phallus with blind urinary meatus)	Streak (left), undifferentiated testis and microscopic gonadoblastoma (right)	45,X/46,X,dic(Yq)	Features of Turner's syndrome
158 ^h	26 yr	156	Infantile female	Streak (right), no gonadal tissue on the left	45,X/46,X,dic(Yp)	Features of Turner's syndrome, primary amenorrhoea, dic(Yp) = dic(Y)(q12)
185 ⁱ	11 yr	123	Infantile female		45,X/46,X,dic(Yq)	
159	19 yr	148	Infantile female	Bilateral streaks and gonadoblastomas	45,X/46,X,dic(Yp)/46,XYq-or del(dic Y)	Primary amenorrhoea, lack of breast development
101	17 yr	150	Ambiguous (markedly enlarged phallus, perineal hypospadias, vagina 8 cm deep)	Testis (dysgenetic) and gonadoblastoma (left), no gonadal tissue on the right	45,X/46,X,dic(Yq)	Lack of breast development
103	1.5 yr	82	Ambiguous	Asymmetrical gonadal development	45,X/46,X,dic(Yq)	
165				Mixed gonadal dysgenesis (testis and streak)	45,X/46,X,dic(Yp)	
102	4 yr	3rd centile	Ambiguous (small penis, severe hypospadias, partially bifid scrotum)	Immature testis (right, abdominal)	45,X/46,X,dic(Yq)/46,X,del(dic Y)	
160	14 yr	144	Normal female	Cyst (right), streak and gonadoblastoma (left)	45,X/46,X,dic(Yp)/46,X,del(dic Y)	Cubitus valgus, no pubertal maturation
186	8 mth	-1 SD	Ambiguous (small phallus, vaginal orifice, labia majora)	Testes (right, inguinal; left, abdominal)	45,X/46,X,dic(Yq)/47,XY	

APPENDIX 1—continued

Reference	Age	Height (cm)	External genitalia	Gonadal findings	Karyotype	Remarks
104	4 yr	93	Ambiguous (phallus with blind urinary meatus, urogenital sinus leading to urethra and rudimentary vagina)	Testis (left, descended), streak (right)	45,X/46,X,dic(Yq)	Loss of distal $\frac{1}{2}$ of Yp
91(case 1) ^k	12 yr	132	Ambiguous (enlarged clitoris, pseudoscrotum)	Testis (left), streak (right)	45,X/46,X,dic(Yq)	
91(case 2)	18 yr	135	Infantile female	Bilateral streaks	45,X/46,X,dic(Yq)	Features of Turner's syndrome, primary amenorrhoea, lack of breast development
91(case 3)	28 yr	150	Normal male	Testes	45,X/46,X,dic(Yq)	Extreme oligospermia (0.2 million/ml)
91(case 4)	14 yr	138	Infantile female	Bilateral streaks	45,X/46,X,dic(Yp)	Features of Turner's syndrome, lack of breast development, dic(Yp) = dic(Y) (q12)
187 188	6 yr	101	Normal female		dic(Y) 45,X/46,X,dic(Yq)/ 47,X,dic(Yq), dic(Yq)	A few Turner stigmata; anomalous Y appeared monocentric in many cells with one centromere presumably inactivated
189 ^l			Female		46,X,dic(Yq)	Turner's syndrome, H-Y +
105	Newborn	42.5	Ambiguous (2 cm phallus, penoscrotal hypospadias, right scrotal sac, left labium majus)	Small testis (right)	45,X/46,X,dic(Yq)	Dic(Y) appears monocentric in most cells
190 191	Newborn	10th centile	Ambiguous (fused, rugated labioscrotal folds, clitoral enlargement, urogenital sinus)	Testes (left, normal; right, dysgenetic)	45,X/46,X,dic(Y) 45,X/46,X?Y/ 46,X,dic(Yq)/ 47,X,dic(Yq), dic(Yq)/47,XY, dic(Yq)/47,X, Yq,Yq	Dic(Y) appeared monocentric in cells of 4th cell line, with one centromere presumably inactivated
192	18 yr	146.5	Normal female	Bilateral streaks and gonadoblastoma	45,X/46,XY/46,X,dic(Yq)	H-Y -
164	Aborted fetus		Male	Epididymal cyst	46,XY/46,X,dic(Yp)/46,X,del(Y)(q11)	dic(Yp) = dic(Y)(q11)
110(observation 9)	Infant	48 (at birth)	Male (hypospadias)	Testes (left: inguinal, immature)	45,X/46,X,dic(Yp)	
92	14 yr	136	Normal male	Testes	45,X/46,X,dic(Yq)	Turner stigmata

^a The often used forms dic(Yq) and dic(Yp) are used here and indicate complete duplication of the long or short arm of the Y, respectively. Assuming that the formation of the dicentric Y is the result of an isochromatid break and subsequent reunion of the proximal ends of the sister chromatids, a dic(Yq) would be designated according to the Paris Conference¹⁸⁰ as dic(Y)(p11) = short form or dic(Y)(qter→p11::p11→qter) = long form. Similarly, a dic(Yp) would be designated as dic(Y)(q12) = short form or dic(Y)(pter→q12::q12→pter) = long form if intensely fluorescent material is present between the centromeres; otherwise, as dic(Y)(q11) = short form or dic(Y)(pter→q11::q11→pter) = long form. Another possible mechanism is a Y;Y translocation, which is how Yunis⁹³ reported his case of a dicentric Y. The finding of a 47,XY cell line in the case of Roubin *et al*¹⁸⁶ supports the possibility of this mechanism, at least with respect to this study. Two cases of Y;Y translocations have been reported, although monocentric (see appendix 6). A dicentric translocation chromosome tdc(Y;15)(Ypter→Yq11::5p14→5qter) described by Vignetti *et al*³⁰ appears in appendix 4. See footnote e, appendix 2.

^b Jacobs⁹⁶ suggests that the chromosome described as Xq- is the dicentric Y in which the region between the centromeres is contracted.

^c First described (briefly) by McIlree *et al*.⁹⁰

^d Karyotype later confirmed by the fluorescence study of Robinson and Buckton.⁷⁵ (subject VI)

^e Redescribed by Morillo-Cucci and German.¹⁶² (patient 2) See footnote †, table.

^f Redescribed by Morillo-Cucci and German,¹⁶² (patient 3) who indicated an additional cell line of 47,XY,dic(Y). See footnote †, table.

^g Also cited by Márquez-Monter *et al*.¹⁹⁴

^h Fluorescence study reported earlier by Robinson and Buckton.⁷⁵ (subject VIII)

ⁱ Fluorescence study reported earlier by Bühler *et al*.¹⁹⁵

^j The authors state that the dic(Yp) resulted from a break in the proximal part of the Yq12 region. However, since no intensely fluorescent material was present in the dic(Y), the break probably occurred in the distal Yq11 region.

^k Some inaccuracies appear in tables 1 and 2 of Giraud *et al*,⁹¹ including references to their own case histories (their case 4 was listed as dic(Yq) when actually it was dic(Yp)). These have been corrected here. Subsequently reported by Mattei *et al*.¹¹⁰ (observations 5-8)

^l This case was first described by Koo *et al*.⁷¹ (case 6) as a slightly asymmetrical Y with duplicated long arms and additional non-fluorescent material adjacent to the centromere. This additional material was assumed to be derived from the short arm of the Y. Buchanan and colleagues¹⁸⁹ have since identified a second, small centromere between the additional material and one of the long arms, thus establishing this as a dic(Yq) chromosome. That the patient is female is an enigma. The possibility that the testis determinants were lost from the isochromatid break in the short arm is doubtful, since she is H-Y+. In addition, no 45,X cell line was detected in over 500 blood and skin cells studied. If present, it would have to be at an extremely low frequency. The dicentric Y is thus very stable, presumably because of the fact that the centromeres, which are very close

APPENDIX 1—continued

to one another, do not seem to behave independently. This is only the second case of a dicentric Y chromosome without detectable mosaicism. It is possible, since her gonads were not examined, that testicular tissue is present, or that a 45,X cell line might be found in the gonadal tissue. Wachtel¹⁷³ suggests that such a situation may result from a mutation of the H-Y antigen receptor gene. The presence of the H-Y structural gene would account for H-Y expression, but the mutant H-Y antigen receptor site would allow little or no testicular development.

APPENDIX 2 Reported cases of Y isochromosomes^a

Reference	Age	Height (cm)	External genitalia	Gonadal findings	Karyotype	Remarks
144	10 yr	Normal	Male (short penis, 3rd degree hypospadias, empty scrotum resembling fused labia)	Testis (left), streak (right)	45,X/46,X,i(Yq-)/ ^b i(Yq-)	i(Yq-) is metacentric, with arms = 90–100% of length of normal Yq
68(case 1) ^c	34 yr	155	Infantile female	Bilateral streaks	46,X,i(Yq)	Primary amenorrhoea, suggestion of webbed neck
68(case 2) ^c	62 yr	163	Infantile female		46,X,i(Yq)	Primary amenorrhoea, bilateral chorioretinitis
117	66 yr	147	Infantile female except for enlarged clitoris	Streak with ovarian stroma and a few mesonephric tubules (left), fimbrial cysts and epididymal tubules (right)	45,X/46,X,i(Yq)	Turner's syndrome
163	50 yr	163	Normal male	Testes (hypotrophic)	46,XY/46,X,i(Yp)/ ^d 47,X,i(Yp),i(Yp)	Azoospermia
77	20 yr	138	Female	Bilateral streaks	45,X/46,X,i(Yp)	Turner's syndrome; faint, symmetrical G bands seen on each arm of i(Yp)
72	26 yr	152	Normal female	Bilateral streaks	46,X,i(Yq)	Primary amenorrhoea, lack of breast development
145 73 ^f	8 yr	112	Female Infantile female		45,X/46,X,i(Yq) ^e 46,X,i(Yq)	Turner's syndrome Turner's syndrome, H-Y-
74	28 yr	165	Normal female	Bilateral streaks	46,X,i(Yq)	A few Turner stigmata, amenorrhoea, lack of breast development
71(case 5) 146	3 yr		Female Male (short penis, empty hypoplastic scrotum)	Bilateral streaks Small palpable gonads in inguinal canal	46,X,i(Yq) 48,XXXXX/49,XXXXX/49,XXXXX,i(Yq)	Turner's syndrome Severe congenital defects, normal twin brother
147	37 yr	168	Normal male	Testes (small)	45,X/46,XY/46,X,i(Yq)	Gynaecomastia, infertility
70 ^g	11 yr	143	Normal female	Streak (left), malignant teratoma (right)	46,X,i(Yq)	H-Y-
80			Male (3rd degree hypospadias)	Testis and streak (spermatogenic arrest in testis)	45,X/46,X,i(Yp)	H-Y+
79	5 dy		Ambiguous (small penis, hypospadias, small vaginal orifice)	Testis (right, normal; left, inguinal and small)	45,X/46,X,i(Yp) ^h	Nearly normal sized uterus, fallopian tube, H-Y+ ('double positive')
110(observation 4)	14 yr	151	Male	Testes (infantile)	45,X/46,XY/ 46,X,i(Yq)	Scanty axillary and pubic hair

^a Yp isochromosomes are difficult to distinguish cytologically from Yq deletions (see asterisks in appendix 7). Metacentric chromosomes resulting from pericentric inversion may also have been confused with Y isochromosomes before the development of current banding techniques. Stoeckenius¹⁹⁶ describes one case (also described by Lenz and Pfeiffer¹⁴³) and cites two others^{142,197} (subject JB) which he suggests are Yq isochromosomes. However, they probably represent pericentric inversions. One of these cases¹⁹⁷ has since been described as a pericentric inversion.⁶⁸ (case 3) Moreover, the authors of the other two cases^{196,142} state that the anomalous chromosome does not correspond in size to a Yq isochromosome. Unfortunately, the original interpretation of a Yq isochromosome has been used as the basis for conclusions regarding the location of the male determining factor.^{143,231} Devictor-Vuillet *et al.*¹²³ interpret the fragment reported by Greenblatt *et al.*¹⁶⁷ (case 20) as a Yq isochromosome. The fragment was described as closely resembling the F group chromosomes of either X or Y origin. It was found in a 25-year-old woman with gonadal dysgenesis, slight shield chest, and no evidence of masculinisation.

^b Jacobs⁹⁶ suggests that the presumed i(Yq-) could have been a pericentric inversion. If so, the original Y would have had to be a long variant, since the anomalous Y was about the size of the F group chromosomes (see p 167).

^c One of these cases was first reported by Court Brown *et al.*²⁵⁰ Both karyotypes were later confirmed by Robinson and Buckton.⁷⁵ (subjects I and II)
^d The i(Yp) in this case could very well be a metacentric Yq deletion (see asterisk, appendix 7). The authors suggest that the low amount of autoradiography grains over the anomalous Y compared to a normal Y indicates an i(Yp). However, since the densely labelled region of the Y is primarily confined to the distal Yq,¹⁹⁸ a metacentric Yq deletion would probably give the same pattern.

^e The authors suggest that this may be a dic(Yq) chromosome.

^f H-Y antigen determination reported by Moreira-Filho *et al.*⁸⁰

^g First reported by Kunkel *et al.*⁶⁹ (subject 1) and subsequently by Rary *et al.*⁷⁹ and Jones *et al.*¹⁹⁹ (case 17)

^h Although 40% of leucocyte metaphases were 45,X, the authors refer to the case as 46,X,i(Yp), as do Jones *et al.*¹⁹⁹ (patient 20) (table 1) Also, see pp 163, 170.

APPENDIX 3 *Reported cases of ring Y chromosomes*

Reference	Age	Height (cm)	External genitalia	Gonadal findings	Karyotype	Remarks
200(case 28)	11 yr	103	Female (enlarged clitoris?) ^a	Bilateral streaks with ovarian stroma	45,X/46,X,r(X or Y)	Short 4th metacarpal
231(case 1)	15 yr	153	Ambiguous (phallus resembling enlarged clitoris, hypospadias, rugose labia majora, dimple in place of vaginal orifice)	Ovary (right), testis (left)	46,XX/47,XX,r(Y)	47,XX,r(Y) cell line predominant in testis but not in ovary
23 ^b	33 yr		Normal male	Testes	45,X/46,X,r(Y)	Azoospermia, no intense Y fluorescence
106	12 yr	115	Normal female	Bilateral streaks with ovarian stroma, gonadoblastoma, and testicular remnants	45,X/46,X,r(Y)	Widely spaced nipples, shield chest, no intense Y fluorescence
24 ^c	49 yr	140	Normal male (short penis, 5 cm long)	Testes (small, but of normal consistency)	46,X,r(Y)	No intense Y fluorescence, mass of r(Y) no greater than that of normal Yp, loss of all or most of Yq and at least some of Yp
107	6 mth		'External genital abnormalities'	Mixed gonadal dysgenesis (testis and streak)	45,X/46,X,r(Y)	Male phenotype, intense Y fluorescence present
78 ^d	Newborn	45	Normal male		45,X/45,X,+ace (?Yp)/46,X,r(Y)	
25 ^e	22 yr	140	Normal male	Testes	45,X/46,X,r(Y)	No intense Y fluorescence, features of Turner's syndrome, mental retardation
108	8 yr	112	Male (4 cm phallus, hypospadias, empty bifid scrotum)	Testis (right), undifferentiated testis (left)	45,X/46,X,r(Y)	No intense Y fluorescence
26	30 yr	159	Normal male	Testes	45,X/46,X,r(Y)	Azoospermia, no intense Y fluorescence
27	53 yr	164	Male	Testes (small and soft)	46,X,r(Y)	Gynaecomastia, r(Y) no larger than normal Yp, no intense Y fluorescence
155	23 yr	152	Female (infantile)	Bilateral streaks with ovarian stroma, dysgenetic seminiferous tubules, Leydig cells, and epididymis-like tubules	46,X,r(Y)	No intense Y fluorescence, Turner's syndrome
71(case 11)			Male	Testes	46,X,r(Y)	H-Y +
71(case 12)			Male	Testis (right)	45,X/46,X,r(Y)	H-Y +
71(case 13)			Ambiguous		45,X/46,X,r(Y)	H-Y +
71(case 14)			Ambiguous	Testes (abdominal)	45,X/46,X,r(Y)	H-Y +
71(case 15)			Female		45,X/46,X,r(Y)	H-Y +, Turner's syndrome
71(case 16)			Female		45,X/46,X,r(Y)	H-Y +, Turner's syndrome
71(case 17)			Female		45,X/46,X,r(X or Y)	H-Y -, Turner's syndrome
109	Newborn	48	Ambiguous (short penis, hypospadias, urogenital sinus, vagina)	Testis (right)	45,X/46,X,r(Y)	Intense Y fluorescence present
110(observation 3)	12 yr	154	Male	Testes (ectopic, small)	45,X/46,X,r(Y)/47,X,r(Y),r(Y)	
28	31 yr	160	Normal male	Testes (seminiferous tubules without spermatogonia)	45,X/46,X,r(Y)/47,X,r(Y),r(Y)	Azoospermia, no intense Y fluorescence
201(case 3)	2 mth	Small	Ambiguous (bifid scrotum, small phallus without urethral orifice, urogenital sinus, left cryptorchidism)		45,X/46,X,r(Y)	No intense Y fluorescence

^a The authors indicate a normal clitoris in table 1 of their report, but an enlarged clitoris in table 5 and in the text (p 371). If it is indeed enlarged, this would suggest that the ring chromosome is derived from the Y.

^b Restudied by Robinson and Buckton.⁷⁵(subject VII) Also discussed by Chandley *et al.*^{46,202}

^c First reported by Simpson and German.²⁰³

^d Also reported by Wagenbichler and Golob.²⁰⁴

^e First reported by Zdansky *et al.*²⁰⁵

APPENDIX 4 Reported cases of Y;autosome translocations^a

Reference	Age	Height (cm)	External genitalia	Gonadal findings	Karyotype	Remarks
206 ^b	20 mth	73	Ambiguous (small penis, perineal hypospadias, bifid scrotum)	Testes (left, inguinal; right, abdominal)	46,XX,-D,-G,+t(Y;D),+t(Y;G) or 46,XX,-D,-G,+t(D;G),+t(Y;G) 21pss (presumptive t(Y;21))	Klinefelter's syndrome
207/208 ^c			Hypogonadic hypospadias			
111/112	47 yr	160	Male (hypogonadism)	Testes	46,X,-2,+t(Y;2) (2pter→2p1::Yp11→Yqter)	Some spermatogenesis
141	23 yr	146	Ambiguous (enlarged non-patent phallus, bifid scrotum)	Streak with ovarian stroma (right), testis (left)	45,X/45,X,-D,+t(Y;D) ^d	Lack of breast development, primary amenorrhoea
209	15 mth	50th centile	Male (small penis)	Small testis (right), no palpable testis on the left	47,XY,+t(YqGq)	
210	27 yr		Female	Ovaries (small)	46,XX/46,XX,-D,+t(Y;D)	Eunuchoidism, primary amenorrhoea
211	33 yr		Normal male	Testes	46,XYq,17ps ^e	Phenotypically normal father with same satellited Y
49 ^f	13 yr	156	Male	Testis	46,XY,-15,+t(Y;15)(Yqter→Yq1::15p1→15qter)	Arrest of spermatogenesis at pachytene; phenotypically normal mother and 2 sisters with same translocation
212(case 20)	18 dy	≤ 3rd centile	Male	Testes (inguinal)	47,X,-6,+t(Y;6) (6pter→6q1::Yq11→Yqter; Ypter→Yq11::6q1→6qter),+21 (Ypter→Yq1::2p2→2pter)/47,XY	Down's syndrome
213(case 4)	21 yr	160	Normal male	Testes	45,X/46,X,t(Y;2) (Ypter→Yq1::2p2→2pter)/47,XY	Some congenital anomalies
214/215			Female		46,X,t(Y; autosome)	Multiple malformations, translocated chromosome includes brightly fluorescent Yq segment
216	52 yr	160	Normal male		46,XY,-15,+t(Y;15)(Yqter→Yq1::15p1→15qter)	Subject found from prison screening, father of 12 children
184(case 5)		155	Female	Bilateral streaks	45,X,-B,+t(Y;B) (Bpter→Bq3::Yq1→Yqter)	Primary amenorrhoea, lack of breast development
217/218	Aborted fetus		Normal male	Testes	45,X,-13,+t(Y;13)(Yqter→Yq1::13p1→13qter)/46,XY	Therapeutic abortion
113	Newborn		Male	Testes (immature)	46,X,-14,+t(Y;14) (Yqter→Yp11::14q2→14qter; 14pter→14q2::)	Died at 6 days of age because of prematurity and anoxia
219/220/221 ^g			32 males		46,XYq ^g	Satellited Y traced back 300 years in 2 families of presumed common French origin (1 male with trisomy 21); silver stain reveals satellite to be NOR
222		> 183	Male		46,XY,-22,+t(Y;22) (Yqter→Yq12::22p11 or 12→22qter)	
47	14 yr		Male (small genitalia)		46,XY,-22,+t(Y;22)(Yqter→Yq1::22p1→22qter)	Phenotypically normal father and paternal grandmother with same translocation

APPENDIX 4—continued

Reference	Age	Height (cm)	External genitalia	Gonadal findings	Karyotype	Remarks
48 ^f	29 yr	183	Male (small penis)	Testes (small and soft)	47,XXY,-15,+t(Y;15)(Yqter→Yq11:15p1→15qter)	Klinefelter's syndrome; phenotypically normal mother, sister, and maternal aunt with same translocation
223	8 yr		Male (hypoplastic scrotum)	Testes which had been recorded earlier were not palpable	46,X,-15,+t(Y;15)(Yqter→Yq11:15p1→15qter; Ypter→Yq11:)	Hypogonadism suggested by endocrinological studies
44/45	29 yr		Normal female		46,XX,-15,+t(Y;15)(Yqter→Yq11:15p1→15qter)	Phenotypically normal mother, sister, son, and niece with same translocation; one other niece with same translocation and trisomy 21
224	9 mth	68	Normal male	Testes	46,X,-7,+t(Y;7)(7pter→7q3:1Yq1→Yqter; Ypter→Yq1:)	Multiple congenital anomalies
225	1 yr	80	Normal male	Testes	46,XXY,-13,+t(Y;13)(13pter→13q2 or 3:1Yq1→Yqter)	Mentally retarded, features of 13q-syndrome
226					t(Y;22)(Yqter→Yq1:22p1→22qter)	
227					t(Y;13)	
118	Newborn	37	Normal female	Gonads with persistent sex cords and one generative follicle	45,X,-21,+t(Y;21)(Yqter→Yq12:1:21p12→21qter)	Turner's syndrome, several congenital defects, died at 4½ hours of age from cardiac rupture
29	16 mth		Male		45,X,-15,+t(Y;15)(Yq11→Yp11:15q11→15qter) ¹	Phenotypically normal father, paternal grandfather and great grandfather with same translocation
228	15 yr	142	Normal female	Dysgerminoma and Sertoli cell tumour (left), streak with ovarian tissue and gonadoblastoma (right)	45,X,-16,+t(Y;16)(16pter→16q1 or 2:1Yq11→Yqter)/46,X,-16,+t(Y;16)(16pter→16q1 or 2:1Yq11→Yqter; Ypter→Yq11:)	Menarche at age 11
229			10 cases ^f		t(Y;D or G)(Yqter→Yq1:1D or Gp1→D or Gqter)	
230					t(Y;13)	
130	30 yr	175	Normal male	Testes (moderate hypotrophy)	46,X,-5,+t(Y;5)(Ypter→Yq11:5p15.3→5pter; Yqter→Yq11:5p15.3→5qter)	Azoospermia
128			Male		45,X,-21,+t(Y;21)	Oligospermia (<10 million/ml)
46(patient JS)/51/63	34 yr	165	Normal male	Testes	46,XY,22p+	(-)DA-DAPI staining [→enlarged satellite, not t(Y;22)(Yqter→Yq12:22p13→22qter) as previously reported], only one interphase Y body seen, 22p+ present in many other normal (male and female) relatives
85/86	46 yr	178	Normal male	Testes (small and hard)	46,XX/46,XX,17p+/47,XXY (presumptive t(Y;17)(Ypter→Yp1:17p13→17qter))	Gynaecomastia, azoospermia, H-Y+

Localisation of male determining factors in man

APPENDIX 4—continued

Reference	Age	Height (cm)	External genitalia	Gonadal findings	Karyotype	Remarks
135(observa- tion 21)					46,X,t(Y;16) (Ypter→Yq12: : 16q11→16qter)	Sterility
50(case 1)	1½ yr		Normal male	Testes	46,XY,-15,+t (Y;15)(Yqter→ Yq12: :15p13→ 15qter)	Phenotypically normal mother, maternal grandfather, 2 cousins (1 female), and 4 great-aunts with same trans- location
50(case 2)	3 yr		Normal female		46,XX,-15,+t (Y;15)(Yqter→ Yq12: :15p13→ 15qter)	Phenotypically normal mother, brother, and maternal grand- mother with same translocation
50(case 3)	10 mth ^f	83	Normal female		46,XX,-22,+t (Y;22)(Yqter→ Yq12: :22p13→ 22qter)	Phenotypically normal mother, brother, 2 maternal uncles, and a cousin (female) with same translocation
50(case 4)			Normal female		46,XX,-15,+t (Y;15)(Yqter→ Yq12: :15p13→ 15qter)	Phenotypically normal sister, father, paternal grandmother, cousin (case 5), and cousin's father and paternal grand- mother with same translocation
50(case 5)	2 yr		Normal male	Testes	46,XY,-15,+t (Y;15)(Yqter→ Yq12: :15p13→ 15qter)	Phenotypically normal relatives (see case 4) with same translocation
50(case 6)	10 mth ^f	73	Normal male	Testes	46,XY,-15,+t (Y;15)(Yqter→ Yq12: :15p13→ 15qter)	Phenotypically normal father, paternal aunt and grandmother with same trans- location (father is mosaic with normal chromosome 15 in some cells)
233	Newborn	41	Male (small penis, cryptorchidism)		47,XY,-22,+t (Y;22)(Yqter→ Yq12: :22p1→ 22qter),+E	Multiple congenital anomalies, E trisomy phenotype, died at 26 days of age; father with same translocation
234/235	26 yr	156	Male		47,X,Yqs,+21,inv (9)(p13q12) ^e	Down's syndrome, brother with same satellited Y; silver stain reveals satellite to be NOR
133	15 yr	166	Male (small penis)	Testes (small)	46,X,-16,+t(Y;16) (16pter→16q12: : Yq12→Yqter; Ypter→Yq12:)	
236			Male		46,XY,-9,+t(Y;9) (Yqter→Yq1: : 9p1 or 2→9qh+→ 9qter)	Wife had 4 spontan- eous abortions
131	30 yr		Normal male	Testes (slight hypotrophy of the right testis)	46,X,-14,+t(Y;14) (Yqter→Yq11: : 14p11→14qter; Ypter→Yq11:)	Azoospermia
132	30 yr		Male	Testes (slight hypotrophy)	46,X,-7,+t(Y;7) (Ypter→Yq12.2: : 7q11.1→7qter; 7pter→7q11.1: : Yq12.2→Yqter)	Azoospermia
71(case 7) ^k 69(subject 8)		Short	Male	Testes (small)	45,X/45,X,-22,+t (Y;22)(22pter→ 22q13: :Ypter→ Yp1)	H-Y ⁺ , mental retardation

APPENDIX 4—continued

Reference	Age	Height (cm)	External genitalia	Gonadal findings	Karyotype	Remarks
30	4 yr	91	Normal male	Testes	45,X,del(5)(p14)/45,X,-5,+tdic(Y;5)(Ypter→Yq11: :5p14→5qter)	Cri du chat syndrome and gross malformation of distal left arm
119	Child		Female	Bilateral streaks with remnants of Wolffian ducts	46,X,t(Y;8)(8pter→8q1 or 2: :Yq11→Yqter)	Some features of trisomy 8
237	26 yr	185	Normal male	Testes	46,XY,-13,+t(Y;13)(Yqter→Yq12: :13p11→13qter)	Oligospermia (3–9 million/ml) with reduced sperm motility
238	3.5 yr	92	Normal male	Testes	46,X,-6,+t(Y;6)(6pter→6q27: :Yq12→Yqter; Ypter→Yq12: :)/47,X,del(Y)(q12),-6,+t(Y;6)(6pter→6q27: :Yq12→Yqter; Ypter→Yq12: :)	Moderate retardation, multiple congenital anomalies
239 240/110(observation 10)	7 yr	115	Male Male	Testis (right), undescended testis (left)	Satellited and small Y ^e 46,XY,-2,-5,-13,+t(2;13)(2pter→2q32: :13q13→13qter;13pter→13q13: :2q32→2qter),+t(Y;5)(Yqter→Yq11: :5p13→5qter)	Cri du chat syndrome and various other anomalies
51/63			Normal female		46,XX,-15,+t(Y;15)(Yqter→Yq11: :15p12→15qter)	Presence of male specific 3.5 kilobase DNA fragment, (+) DA-DAPI staining (→ not enlarged satellite); same translocation in male members of family (with extra Y body)
64(case 7)	1 yr		Male		46,XY,-13,+t(Y;13)(Yqter→Yq1: :13p1→13qter)	Encephalocele; presence of Y specific BSu restriction DNA fragment (150% of amount in 46,XY males)
241	4 mth	60	Normal male	Testes	46,X,-1,+t(Y;1)(Ypter→Yq11: :1q21→1qter; 1pter→1q12: :Yq11→Yqter)	Psychomotor retardation, infantile spasms, hypotonia
242	Newborn	50	Normal male	Testes	46,X,-22,+t(Y;22)H-Y ⁺ , karyotype (Yqter→Yq11: :22p1→22qter; Ypter→Yq11: :)	determined prenatally, mother with previous birth of girl with trisomy 13
243	9.5 yr		Ambiguous (small penis, penile urethra, small meatus, non-rugated and hypoplastic scrotum, rudimentary labia majora)	Testes (small and soft)	46,X,-15,+t(Y;15)(Yqter→Yq12: :15p13→15qter; Ypter→Yq12: :)	Phenotypically normal father with same karyotype
52	35 yr		Normal female		46,XX,-22,+t(Y;22)(Yqter→Yq1: :22p1→22qter)	Sister, brother (42 years old, 186 cm tall), 2 nieces, and a nephew with same translocation
245	5.5 mth	57	Male (small penis)	Testes	Yqs ^e	Mental retardation, facial dysmorphism, congenital heart disease, amaurosis; silver stain reveals satellite to be NOR
63			Male and female members of 3 families (including reference 51 above)		46,XX or XY,-15,+t(Y;15)(Yqter→Yq1: :15p12→15qter)	(+) DA-DAPI staining (→ not enlarged satellite), extra Y body in males

Localisation of male determining factors in man

APPENDIX 4—continued

Reference	Age	Height (cm)	External genitalia	Gonadal findings	Karyotype	Remarks
54	10 yr		Female		46,XX,—5,—22,+t(1;5)(5qter→5p15::1q44→1qter),+t(Y;22)(Yqter→Yq12::22p13→22qter)	Mental deficiency; same t(Y;22) in normal brother, 3 sisters, mother, maternal uncle, and uncle's son
247(case 4)	11 mth	77.5	Normal male	Testes	46,XY,—D,+t(Y;D) ¹	Father with same translocation
121	18 yr		Female	Streak gonads and gonadoblastoma	46,X,—17,+t(Y;17)(Ypter→Yq11::17p13→17pter; Yqter→Yq11::17p13→17qter)	Amenorrhoea
248	5 yr	99	Normal female	Bilateral streaks and gonadoblastomas	45,X/45,X,—18,+t(Y;18)(Yqter→Yq11::18p11→18qter)	
55 ^f	4 ped'grees				46,XX or XY,—13 or 15,+t(Y;13 or 15)(Yqter→Yq11::13 or 15p1→13 or 15qter)	Both males and females with translocation in each pedigree
115	28 mth	85	Male (hypoplastic scrotum, cryptorchidism)		46,X,+t(Y;10)(10pter→10p12::Yp1→Yqter)	Mental retardation, multiple congenital anomalies (trisomy 10p stigmata)
134	29 yr	165	Normal male (except for varicocele)	Testes (hypotrophic, spermatogenic arrest)	46,X,—10,+t(Y;10)(Ypter→Yq12::10p13→10pter; Yqter→Yq12::10p13→10qter)	Azoospermia
53	71 yr		Normal male	Testes	46,XY,—15,+t(Y;15)(Yqter→Yq1::15p1→15qter)	Myeloid metaplasia; son, daughter, grandson, and 2 granddaughters with same translocation
56	Newborn		Normal female		46,XX,—14,+t(Y;14)(Yqter→Yq12::14p12→14qter)	(+) DA-DAPI staining (→ not enlarged satellite); karyotype determined prenatally; mother with same karyotype

* The karyotypes in this appendix are according to the system of nomenclature devised at the Paris Conference,¹⁸⁰ although previous systems were often used in the studies cited. The long form is presented so as to afford maximum information concerning the rearranged chromosomes. Even when this system was used by the authors, some minor changes have been made here for the sake of consistency and in cases when minor deviations from the rules of the Paris Conference occurred. For instance, the description of the composition of a structurally rearranged chromosome begins at the end of the short arm of the chromosome and proceeds through to the end of the long arm. If, however, no short arm segment is present at the end of either arm, the description begins at the end of the long arm segment with the lowest chromosome number.¹⁸⁰ (p 26) If a sex chromosome is involved, it receives priority as the lowest chromosome number, assuming the use of the same convention in designating the order of the two altered chromosomes¹⁸⁰ (p 22). Thus, the rearranged chromosome described by Hahnemann *et al.*⁴⁵ as (15qter→15p1::Yq11→Yqter) is described here as (Yqter→Yq11::15p1→15qter). This change will undoubtedly seem trivial to some, but it was with such meticulousness that the Paris Conference system was designed.

The Dp+ chromosomes described by Käosaar²⁵² and Stoll *et al.*²⁵⁴ are assumed to represent Y;15 translocations by Nielsen and Rasmussen,⁵⁰ although the original authors did not suggest this possibility.

^a First reported by Turpin and Lejeune.²⁵⁶

^d See text, p 166.

^b First reported by Lamy *et al.*²⁵⁵

^e These satellited Y chromosomes are presumptive t(Y;D or G)(Ypter→Yq12::D or Gp11→D or Gpter).
^f Apparently, there is a good deal of overlap of probands in these cases^{48–50,55,229} and one other case.²⁵⁷ Since some of these papers failed to identify the probands clearly and/or failed to state where the cases had been published previously, the degree of overlap is at times impossible to determine. The following is the information available. Nielsen *et al.*²²⁹ reported 10 presumptive cases of (Y;D or G) translocations. They indicate that these included the case reported by Noel *et al.*⁴⁹ the 2 cases of Friedrich and Nielsen,²⁵⁷ and the case of Hreidarsson *et al.*⁴⁸ Nielsen and Rasmussen⁵⁰ reported one case of t(Y;22) and 5 cases of t(Y;15). Two of these (cases 3 and 6) are obviously the same as those reported earlier by Friedrich and Nielsen.²⁵⁷ Nielsen and Rasmussen⁵⁰ also indicate in their table 2 that 5 cases of t(Y;15) reported by Nielsen *et al.*²²⁹ were found by Noel *et al.*⁴⁹ Cooke and Noel⁵⁵ report 4 pedigrees of t(Y;13 or 15), one of which is the same as that of Noel *et al.*⁴⁹

^g Preliminary and other reports by Genest *et al.*^{258–261} Dumars *et al.*^{262,263} also reported a satellited Y in 6 males (one with 47,XXYq,t(Xq+;9p–)) of a family presumed to be related to the family described by Genest *et al.* ^h This karyotype was incorrectly reported as 46,X...

ⁱ This karyotype was incorrectly reported as... t(Y;15)(Yqter→Yp11::15q11→15qter), as the authors emphasised and diagrammed the loss of the positive Q and C bands of the heterochromatic portion of the Y chromosome.

^j Redescribed by Kunkel *et al.*⁶⁹(subject 5) after further study as 45,X,—17,+t(Y;17)(Yqter→Yq11::17p13→17qter)/46,X,—17,+t(Y;17)(17pter→17p13::Yq11→Ypter;Yqter→Yq11::17p13→17qter). Also reported by Manuel *et al.*²⁶⁴

^k This case was also studied by Fineman *et al.*²⁶⁵ See discussion on p 163. Cases 2 to 4 of Koo *et al.*⁷¹ are also assumed to be Y translocations, but solely on the basis of non-fluorescence of a Y chromosome "of average size and typical morphology" (in addition to a 45,X cell line). However, many other cases of non-fluorescent Y chromosomes in 45,X/46,XY mosaicism have been reported with alternative hypotheses offered (see footnote a, appendix 7).

^l The translocation is referred to both as 't(Dp;Yq)' and 't(Dq;Yq)', and is described as "a submetacentric chromosome with an intensely fluorescent short arm".

APPENDIX 5 *Reported cases of Y;X translocations^a*

Reference	Age	Height (cm)	External genitalia	Gonadal findings	Karyotype	Remarks
57/58	31 yr	137	Normal female	Cystic ovaries	46,X,t(X;Y) (Xqter→Xp22:: Yq11→Yqter)	One normal child, subsequent reproductive failure; complete Yq translocated, X _t inactivated in 12 informative cells
60/69(subject 6)/71(case 8)/199(patient 18)	17 yr	142	Normal female	Bilateral streaks	46,X,t(X;Y) (Xpter→Xq11:: Yq11→Yqter)	Turner stigmata, H-Y ⁺ , X _t inactivated, amenorrhoea, poor breast development, scanty pubic hair
82/83			Male	Testes (small)	46,XXp+ (presumptive t(X;Y) (Ypter→Yp11:: Xp22→Xqter))	Infertility; additional Xp material equivalent in size to Yp
84(case 1)	24 yr		Normal male	Testes (small)	46,XXp+ (presumptive t(X;Y) (Ypter→Yp11:: Xp22→Xqter))	No spermatogenesis, H-Y ⁺ ; additional Xp material "no larger than the short arm of the Y"
61(case 1)/266	14 yr	145	Normal female	Ovaries	46,X,t(X;Y) (Xqter→Xp1or2:: Yq11→Yqter)	Some Turner stigmata, menarche at age 14; X _t inactivated in 19 of 36 cells
61(case 2)/266	22 yr	179	Male	Testes (small)	46,X,t(X;Y) (Xqter→Xp1or2:: Yq1→Yqter)/ 47,XXY	No spermatogenesis, features of Klinefelter's syndrome; X _t inactivated in 32 of 38 cells
61(case 3)/266	Newborn	47	Normal male	Testes	46,Y,t(X;Y) (Xqter→Xp1or2:: Yq1→Yqter)	Slight craniofacial dysmorphism
61(case 4)/266	27 yr	149	Normal female		46,X,t(X;Y) (Xqter→Xp1or2:: Yq1→Yqter)	Mother of case 3; X _t inactivated in all 12 cells examined
61(case 5)/266	2 yr	3rd centile	Normal female		46,X,t(X;Y) (Xqter→Xp1or2:: Yq1→Yqter)	Sister of case 3; X _t inactivated in 12 of 13 cells
267			Male		46,XX (possible t(X;Y)) ^b	Aberrant inheritance of the X linked Xg blood group
62/64(case 3)	4 mth	Normal	Male (small penis, empty, hypoplastic scrotum)		46,Y,t(X;Y) (Xqter→Xp22.2:: Yq11→Yqter) ^c	Normal mother ^d (case 4) with same translocation, Y specific BSu restriction DNA fragment present in each
120	5 yr	95	Normal male	Testes (both small; soft left testis)	46,X,t(X;Y) (Xqter→Xp22:: Yq11→Yqter)	Mental retardation, skeletal deformities, preferential inactivation of normal X, aberrant inheritance of Xg blood group
88(case 1) ^d	34 yr	182	Normal male	Testes (small)	46,X,t(X;Y) (Ypter→Yp1:: Xp22→Xqter)	Azoospermia
88(case 2)	22 yr	160	Normal male	Testes (small)	Same as case 1	Azoospermia, sparse facial hair
88(case 6)	6 yr		Normal male	Testes (small)	Same as case 1	
88(case 7)	19 yr	165	Normal male	Testes (small)	Same as case 1	No facial hair, gynaecomastia
88(case 8)	25 yr	168	Normal male	Testes (small)	Same as case 1	Sparse axillary and facial hair, gynaecomastia
88(case 10)	71 yr	158	Normal male	Testes (small)	Same as case 1	Sparse axillary hair
88(case 11)	5 yr		Male (normal penis, poorly developed scrotum)	Testes (small, abdominal)	Same as case 1	
88(case 12)	5 yr		Male (normal penis, hypoplastic scrotum)	Testes (small, abdominal)	Same as case 1	
88(addendum)			Male		Same as case 1	

^a Reitalu *et al*²⁶⁸ postulated structural exchange between the X and Y chromosomes as the cause of hypogonadism on mostly theoretical grounds.^b The authors cite X chromosome polymorphism as "direct cytogenetic evidence" for an X;Y translocation. However, since the proband's mother as well as her 46,XX son had the same polymorphism, this evidence is questionable.^c The X_t was inactivated in 31 of 35 cells according to Tiepolo *et al*,⁶² in 27 of 31 cells according to Kinross *et al*.⁶⁴^d See p 163.

APPENDIX 6 *Reported cases of Y;Y translocations^a*

Reference	Age	Height (cm)	External genitalia	Gonadal findings	Karyotype	Remarks
114	67 yr	140	Male	Testes (small and soft)	45,X/46,X,t(Y;Y) (qter→p11: :q11→qter)	Skeletal deformities
269 ^b	2 yr	82	Normal male	Testes	45,X/46,XY/46,X,del(Y)(q11)/46,X,t(Y;Y)(qter→p11: :q11→qter)/47,XXYY/47,XY,t(Y;Y)/47,X,t(Y;Y),t(Y;Y)	Craniosynostosis

^a These Y;Y translocations may be similar in appearance to the original appearance of the dicentric Yq chromosome studied by Buchanan.¹⁸⁹ One of its centromeres was initially not visible (see appendix 1, footnote 1), the chromosome thus appearing submetacentric (monocentric) with brightly fluorescing Yq material at the distal region of each end.

^b Cited earlier by van den Berghe.²⁷⁰

APPENDIX 7 *Reported cases of Y chromosome deletions^a*

Reference	Age	Height (cm)	External genitalia	Gonadal findings	Karyotype	Remarks
271	4½ yr	86	Ambiguous (enlarged phallus, 2 cm long; partially fused labia)	Dysplastic gonads	46,X,del(Y)	Del(Y) = ½ the length of chromosome 22, no visible centromere
272	13 yr	147	Ambiguous (small vagina, rugose labia majora, enlarged clitoris)	Testis (left), hypoplastic ovary (right)	45,X/46,X,del(Y)	Amenorrhoea, no breast development; del(Y) = ½ the length of chromosomes 21–22
273/274	43 yr		Male (hypospadias)		46,X,del(Y)	Muscular dystrophy, del(Y) = loss of ½–¾ of Yq; brother with muscular dystrophy and same del(Y), 2 sons with same del(Y) and hypospadias
124	45 yr		Normal male	Testes (slightly soft)	46,X,del(Y)	Oligospermia (3–4 million/ml)
139(case 2)	13½ yr	135	Infantile female	Bilateral streaks with ovarian stroma	45,X/46,X,del(Y)	Lack of breast development; primary amenorrhoea, hirsutism, masculine muscular development; del(Y) = ½ the length of chromosome 22
275/276	61 yr	150	Ambiguous (short, narrow vagina, considerable hypertrophy of the clitoris)	Primitive ovotestis (left, inguinal)	45,X/46,X,del(Y)* 48,XXX,del(Y)	Primary amenorrhoea, little breast development
277				Atrophic testis and atrophic undifferentiated gonad	45,X/46,X,del(Y)	
277	Adult		Normal male	Testes	46,X,del(Y)	Observed by H Klinger
200(case 29)	13 yr	119	Ambiguous (enlarged clitoris, slight labial fusion)	Rudimentary testis and streak (right), rudimentary testis (left)	46,X,del(Y)	Features of Turner's syndrome; del(Y) is metacentric
125/126	33 yr	172	Male (hypospadias)	Testes (undescended, small, soft right testis)	46,X,del(Y)	Oligospermia (2–17 million/ml); childless paternal uncle with same del(Y)
278	24 yr	Normal	Ambiguous (3–4 cm phallus, no scrotum, no vagina)	None found on laparotomy	46,X,del(Y)	
279				Asymmetrical gonadal dysgenesis	45,X/46,X,del(Y)	
280	17 yr	145	Normal male	Testes (small)	45,X/46,X,del(Y) (q1)	Webbed neck, increased carrying angle; del(Y) is metacentric
281	16 yr	Tall	Male (infantile penis)	Testes (small, inguinal)	46,X,del(Y)(q1)	Gynaecomastia, brother with same del(Y)

APPENDIX 7—continued

Reference	Age	Height (cm)	External genitalia	Gonadal findings	Karyotype	Remarks
282	28 yr	150	Ambiguous (8 cm phallus, hypospadias, narrow vagina 11 cm deep, labia majora)		45,X/46,X,del(Y)(q1)	High arched palate; del(Y) = $\frac{1}{4}$ the length of chromosome 22
65	29 mth	80.5	Normal male	Testes	45,X/46,X,del(Y)	Mental retardation, generalised muscular hypotonia; del(Y) = the length of the short arm of a G group chromosome, centromere observable in some cells
283(case 4)	13 yr		Ambiguous (enlarged clitoris, no labia minora, vagina, posterior fusion of labio-scrotal folds)	Testes (abdominal)	45,X/46,X,del(Y)	Lack of breast development
284	14 mth		Ambiguous (moderate sized phallus, hypospadias, bifid scrotum)	Immature ovary (right), testis (left)	45,X/47,XX,del(Y)	Vagina without external orifice; del(Y) is small and metacentric
285	25 yr		Male		46,X,del(Y)	Schizophrenia, del(Y) = $\frac{2}{3}$ the size of a normal Y
13(patient US)	4 yr	98	Ambiguous (enlarged phallus, large and swollen labia majora, perineal urinary meatus, vagina)	Testis (left), streak (right)	45,X/46,X,del(Y)(q1)	Dermatoglyphic features of Turner's syndrome
13(patient KT)	33 yr	174	Normal female	Streak (right), small undifferentiated gonad (left)	46,X,del(Y)	Primary amenorrhoea, infantile breasts, small uterus and tubes
286	12 yr	128	Ambiguous (hypospadias)	Testis (right), undifferentiated gonad with ovarian stroma (left)	45,X/46,X,del(Y)*	
287	18 yr	145	Infantile female but slightly hypertrophic clitoris	Bilateral streaks	45,X/46,XY/46,X,del(Y)(q1)	Turner's syndrome
193	9 yr	118	Ambiguous (enlarged phallus, rugose labia majora)	Testis (left, inguinal), streak (right)	45,X/46,X,del(Y)	Features of Turner's syndrome
167(case 7)	17 yr	137	Female (infantile)	Bilateral streaks	46,X,del(X or Y)	High palate, primary amenorrhoea
167(case 19)/288	21 yr	163	Female (infantile)	Bilateral streaks and gonadoblastoma (right)	45,X/46,X,del(Y) ^b	Primary amenorrhoea, poor breast development
59	34 yr	181	Male	Testes (small)	47,XX,del(Y)(q1)	Mental retardation, Klinefelter's syndrome (gynaecomastia, female habitus, hypogonadism)
289	20 yr	139	Infantile female but moderately hypertrophic clitoris	Bilateral streaks	45,X/46,X,del(Y)(q1)	Lack of breast development, male habitus, hair distribution, and subcutaneous fat tissue distribution; del(Y) = $\frac{1}{2}$ the length of chromosome 22
116(case 1)	17 yr	Normal	Female (absent vaginal cavity)	Dysgenetic gonads	46,X,del(Y)(q1)	Primary amenorrhoea, lack of breast development, absent uterus > $\frac{1}{2}$ of Yq deleted
122(case BJ)	6 dy	46	Male (small penis, complete hypospadias)	Testes	45,X/46,X,del(Y)(q1)	
122(case PP)	12 yr	128	Male (2 cm penis)	Testes (small)	45,X,1q+,2q+/46,X,del(Y),1q+,2q+	Features of Turner's syndrome, del(Y) is very small centromeric fragment
122(case NH)	> 20 yr	178	Male	Testes (small)	45,X/46,X,del(Y)(q1)	Gynaecomastia, azoospermia
122(case RJL)	6 dy	46	Normal male	Testes	46,X,del(Y)(q1),del(5)(p1)	Atypical cri du chat syndrome, father with same del(Y), $\frac{1}{2}$ of Yq ₁ deleted

Localisation of male determining factors in man

APPENDIX 7—continued

Reference	Age	Height (cm)	External genitalia	Gonadal findings	Karyotype	Remarks
290/183		Normal	10 fertile males		46,X,del(Y)(q12) ^c	Same del(Y) in 10 male members of an Old Order Amish family who are a maximum of 11 generations removed
291(observation 8)	10 yr	123	Male	Testis (right), gonadoblastoma (left)	45,X/46,X,del(Y)(q1)	Features of Turner's syndrome, vagina revealed by urethrography
292	27 yr	140	Infantile female	Hypoplastic testis (left), streak (right)	45,X/46,X,del(Y)(q1)	Primary amenorrhoea, lack of breast development, features of Turner's syndrome; del(Y) = 38% of the length of the father's long Y
293/294			20 males		46,X,del(Y)(q1)	Same del(Y) in 20 males with a common French ancestor, transmitted through at least 11 generations
66	9 mth	61	Male (empty, hypoplastic scrotum)		46,X,del(Y)(q1)*	Mental retardation, other congenital anomalies; died at 9½ months of age; del(Y) = the size of a normal Gp
213	26 yr		Male		46,X,del(Y)(q11)	Healthy male whose wife had one early and 2 late spontaneous abortions
295/296	18 yr	165	Normal male	Testes (soft)	47,X,del(X)(p11→q13): : q21→q24), del(Y)(q11)*	Hirsutism of face and neck, amenorrhoea; small, metacentric fragment
297	25 yr	163	Female (enlarged clitoris, hypoplastic labia minora and vagina)	Streak (right) and gonadoblastoma (left)	45,X/46,X,?Y/46,X,del(Y)	Reduced fertility; phenotypically normal father with same karyotype
298	22 yr	175	Normal male	Testes	47,XY,del(Y)(q1)*	Oligospermia
127	Adult		Male		46,X,?del(Y)(q11) ^d	Absence of spermatogenesis, kyphoscoliosis
123(case MG)	51 yr	163	Normal male	Testes (hypotrophic)	46,XY/46,X,del(Y)(q1)*	Azoospermia, ?gynaecomastia
123(case AF)	28 yr	173	Normal male	Testes	46,X,del(Y)(q1)	Mental retardation; del(Y) < ½ the length of the G group chromosomes, same del(Y) in phenotypically normal and fertile 43-year-old brother (height = 179 cm) and presumably their father
32	36 yr	179	Normal male	Testes	46,X,del(Y)(q11)*	Dermatoglyphic features of Turner's syndrome, achieved ejaculation (see p 165)
33	22 yr	156	Normal male	Testes	45,X/45,X,+ace(?Yp)	Dyschondrosteosis; only ¼ of non-fluorescent segment of Yq is present
43(case 'Short Y-e')		Short	Normal male	Testes	46,X,del(Y)(q11)	Eosinophilic leukaemia with fibrosing endocarditis
299 ^e	57 yr		Male		46,X,del(Y)(q11)	Aspermia, diabetes
34	20 yr	174	Normal male	Testes	46,X,del(Y)(q11)	

APPENDIX 7—continued

Reference	Age	Height (cm)	External genitalia	Gonadal findings	Karyotype	Remarks
300 ^e	76 yr		Male	Testes	46,X,del(Y)(q11)/47,X,del(Y)(q11),+1	Right orchiectomy for testicular abscess at age 65, erythraemic myelosis; del(Y) arose in bone marrow cells
301(case 1)	13 yr	132	Male (small penis)	Testes (small)	45,X/46,X,del(Y)(q11)	Moderate breast development
301(case 2)	19 yr	133	Ambiguous (enlarged clitoris, partial labial fusion, small vagina)	Streak (left), atrophic testis (right)	45,X/46,X,del(Y)(q11)	Primary amenorrhoea, lack of breast development, features of Turner's syndrome
35	5 yr	3rd centile	Normal male	Testes	46,X,del(Y)(q11)*	Del(Y) = $\frac{1}{2}$ the length of the G group chromosomes
129(case 8)			Male (hypoplastic penis)	Testes (hypoplastic)	46,X,del(Y)(q1)	Oligospermia (4 million/ml)
31(case 7)	32 yr		Normal male	Testes	46,X,del(Y)(q1)	Son with congenital anomalies; del(Y) is non-fluorescent but small telomeric portion of the Yq shows a dark C band
36	23 yr	152	Normal male	Testes	46,X,del(Y)(q11)	Del(Y) = the length of the short arm of the G group chromosomes
37	Fetus		Normal male	Testes	46,X,del(Y)(q11)	Phenotypically normal father with same del(Y)
302(twin 1)	5.5 yr	101	Ambiguous (enlarged clitoris, labial fusion, common vaginal and urethral orifice)	Immature testes	45,X/46,X,del(Y)(q11)	Monozygotic twin with same characteristics, except for presence of only 1 testis
38	9 mth	77	Normal male	Testes	46,X,del(Y)(q11), 22ps+	Father, brother, and sister with same 22ps+
303					47,X,del(Y)(q1), +21/?	Down's syndrome
39	26 yr	183	Normal male	Testes	46,X,del(Y)(q1)	Del(Y) is non-fluorescent but small telomeric portion of the Yq shows a dark C band
264				Asymmetrical gonadal differentiation	45,X/46,X,del(Y)(q1)	
305	Fetus				45,X/46,X,Yp—	Medically induced aborted fetus
40(case 1) ^f	37 yr	167	Normal male	Testes (hypoplastic)	45,X/46,X,del(Y)(q11)	Azoospermia; del(Y) < $\frac{1}{2}$ the length of the G group chromosomes, and is submetacentric, ruling out an i(Yp)
40(case 2)	32 yr	158	Normal male	Testes (hypoplastic)	46,X,del(Y)(q11)	Same as case 1
40(case 3)	35 yr	172	Normal male	Testes (hypoplastic)	46,X,del(Y)(q11)	Same as case 1
40(case 4)	Adult	170	Normal male	Testes (hypoplastic)	46,X,del(Y)(q11)	Same as case 1
40(case 5)	35 yr	170	Normal male	Testes (hypoplastic)	46,X,del(Y)(q11)	Same as case 1
40(case 6)	Adult	160	Normal male	Testes	46,X,del(Y)(q11)	Same as case 1
41	36 yr	146	Normal male	Testes	46,X,del(Y)(q11)	Aspermia; pericentromeric C band seen in some cells, ruling out an i(Yp)
306	4 yr	Normal	Ambiguous (short penis, bifid scrotum, scrotal hypospadias)	Streak (left), testis (right)	45,X/46,X,del(Y)(q11)	Vagina revealed by urethrocytography
71(case 9)			Male (4th degree hypospadias)	Testes	45,X/46,X,del(Y)(q11)	H-Y ⁺ , del(Y) is metacentric
71(case 10)			Female		45,X/46,X,del(Y)(q11)	Turner's syndrome, H-Y ⁺ ; del(Y) is metacentric

APPENDIX 7—continued

Reference	Age	Height (cm)	External genitalia	Gonadal findings	Karyotype	Remarks
307			Normal male	Testes	del(Y)	Only tiny pericentric region of Y present in 3 generations of perfectly fertile men (see p 163)
308	47 yr	159	Male (small penis)	Testes (no germ cells)	45,X/46,X,del(Y)(q11)	Gynaecomastia
42	16 yr	Short	Male	Testes	46,X,del(Y)(q11)	Some features of Noonan's syndrome, H-Y +
309	20 yr	165	Normal female	Testes (abdominal)	46,X,del(Y)(q11)	Testicular feminisation; father with same del(Y)
51					46,X,del(Y)(q11)	
199(patient 19)	30 yr	Normal	Normal male	Testes	46,X,del(Y)(q11)	H-Y +
110(observation 1)	9 yr	25th centile	Normal female	Undifferentiated gonads	46,X,del(Y)(q11)	Severe oligospermia
76		180	Male (small penis)	Undifferentiated gonads	46,X,del(Y)(p1)	Turner stigmata, H-Y - (see p 163)
310(patient 2)	34 yr		Male (small penis)	Testes (small, soft)	45,X/46,XY/46,X,del(Y)(q11)	H-Y +, azoospermia, normal Y is non-fluorescent (see footnote a)
251	6 mth	65	Normal male	Testes	46,X,del(Y)(q11)	Multiple congenital malformations; del(Y) indicated by authors as del(Y)(p11,q11)
311	42 yr	150	Ambiguous (3rd degree hypospadias, bifid scrotum without palpable gonads, 4 cm phallus)	Undifferentiated testes (abdominal)	45,X/46,X,del(Y)(q11)	H-Y +; vagina, infantile uterus, bilateral fallopian tubes, some Turner stigmata
210(case 2)	7 mth	Small	Ambiguous (urogenital sinus, enlarged clitoris, vagina)	Immature testicular tissue	45,X/46,X,del(Y)(q11)	

*The authors suggest that the del(Y) chromosome may actually be a Yp isochromosome. These are difficult to distinguish from one another when a Yq deletion gives rise to a metacentric chromosome. The presence of the pericentromeric Yq C band⁸¹ would rule out a Yp isochromosome.⁴¹ Its absence, though, would not confirm an i(Yp) since this band is only seen in high quality preparations. Rary *et al*⁷⁹ favour an i(Yp) in their case because of a 'double positive' H-Y antigen level.

^a Deletions of the Y chromosome are often difficult to distinguish from 'normal' short variants of the Y. Since most of the polymorphism of the Y is the result of variation in the length of the heterochromatic portion,³¹² decreases in the length of this region (band q12) are not considered as deletions here. Without banding techniques, this determination is quite subjective, and thus most earlier reports are included. Cases of Y deletions reported in population studies³¹³⁻³¹⁵ are generally not presented here because of the paucity of information given.

The familial metacentric Y reported by Berger *et al*³¹⁶ is described as slightly less than the length of an F group chromosome. Thus, it is probably not a deleted Y, as described by Borgaonkar,²¹²² but more likely a pericentric inversion.

The centric fragment described by Hart *et al*³¹⁷ is probably not derived from the Y since there is no evidence of masculinisation and the male determining factor is pericentromeric (see text).

At least 28 examples of non-fluorescent Y chromosomes have been reported in the following karyotypes:

45,X/46,XY	References 69(subject 10), 71(cases 2-4)(see footnote k, appendix 4), 310(patient 1), 213(case 7), 318-320, 321(patient 6), 322-325, 326/327(3 cases), 328, 332
45,X/46,XY/47,XXY	References 64(case 2), 213(cases 2, 3), 310(patient 3), 201(case 1)
45,X/46,XY/46,XX	Reference 329
45,X/46,XY/46,X,del(Y)(q11)	Reference 310(patient 2)
46,XY gonadal dysgenesis	References 330 (case 2), 331

These cases have shown no evidence of translocation and cannot be explained by a simple deletion. This is because of the fact that either the Y is of normal length or that the weakly fluorescent part of the father's (or brother's) Y is considerably smaller than the patient's whole non-fluorescent Y. The mechanism of this occurrence is unknown but may be the result of a molecular alteration in the heterochromatic DNA which decreases its quinacrine and Giemsa binding capacity. Patient 4 (and father) of Wilson *et al*³²¹ probably also falls into this category, since the Y chromosome showed no bright fluorescence and was "of comparable size to a G chromosome". Wilson *et al* state that lack of fluorescence is expected based on the size of the Y. However, since the Y chromosome is only slightly longer than the G group chromosomes, loss of the entire brightly fluorescent segment would probably result in a Y chromosome considerably shorter than chromosomes 21-22. One last study which may be included here is the non-fluorescent Y reported by Winters *et al*³³³ in a 45,X/46,XY/247,XXY subject. Since no information on the length of the Y is given, it is possible that it represents a Yq deletion.

Other cases of Y deletions in which another anomaly of the Y was found are present in appendices 1-4, 6.

Dutrillaux²³² reported azoospermia in a case of '47,XYq-?' and oligospermia in 3 cases of 46,XYq-?, in one case of 46,XYq-?, 16qh+, and in one of 46,XYq-?, 22p+.

^b The finding of a gonadoblastoma favours the possibility that the fragment is derived from the Y, since gonadoblastomas are almost always associated with the presence of the Y.^{334 335}

^c O J Miller (New York City) was able to demonstrate persistence of a small part of the fluorescent segment "by particularly sensitive methods".³³⁶

^d The authors suggest that this non-fluorescent Y chromosome (submetacentric) is a pericentric inversion or a Yq deletion. This case may be the same as the one reported by Van Zyl *et al*¹²⁸ of an azoospermic male with 46,XYq-.

^e These Y deletions were originally diagnosed as Philadelphia (Ph¹) chromosomes, since they are difficult to distinguish from one another without current banding techniques. Another such chromosome was originally diagnosed as a Ph¹ chromosome,³³⁷ but was later found to be a small Y.³³⁸ However, it may be within the normal range of variation and not a del(Y)(q11). The same may be true for the small Y reported by Padre-Mendoza *et al*,³³⁹ which was also mistaken for a Ph¹ chromosome.

^f Reported earlier by Fraccaro *et al*.³⁰⁴ Case 2 of Tiepolo and Zuffardi⁴⁰ may be the same as case 8 of Kinross *et al*.⁶⁴

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