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Normal and abnormal interchanges between the human X and Y chromosomes

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Summary

A single obligatory recombination event takes place at male meiosis in the tips of the X- and Y-chromosome short arms (i.e. the pseudoautosomal region). The crossover point is at variable locations and thus allows recombination mapping of the pseudoautosomal loci along a gradient of sex linkage. Recombination at male meiosis in the terminal regions of the short arms of the X and Y chromosomes is 10- to 20-fold higher than between the same regions of the X chromosomes during female meiosis. The human pseudoautosomal region is rich in highly polymorphic loci associated with minisatellites. However, these minisatellites are unrelated to those resembling the bacterial Chi sequence and which possibly represent recombination hotspots. The high recombination activity of the pseudoautosomal region at male meiosis sometimes results in unequal crossover which can generate various sex-reversal syndromes.

Key words: pseudoautosomal region, testis determination, XX males, minisatellites, human.

Introduction

Occurrence of a normal crossover between the mammalian X and Y chromosomes was proposed as early as 1934 by Koller & Darlington, but direct genetic and molecular evidence was only produced some 50 years later (Keitges, Rivest, Siniscalco & Gartler, 1985; Cooke, Brown & Rappold, 1985; Simmler *et al.* 1985; Harbers, Soriano, Müller & Jaenisch, 1986). The features of the X–Y crossing over are unique among the human chromosomes. As a possible consequence of these peculiar features, abnormal X–Y crossing over can generate several types of anomalous sex chromosomes some of which may cause sex reversal. Abnormal crossover events may also partly influence the evolution of the mammalian sex chromosomes.

Recombination between the human X and Y chromosomes

The human X and Y chromosomes short arms share homologous DNA loci (Cooke, Brown & Rappold, 1985; Simmler *et al.* 1985; Buckle *et al.* 1985*a*; Rouyer *et al.* 1986*a*,*b*; Affara *et al.* 1986*a*). This homology extends up to the telomere (Cooke *et al.* 1985) but is restricted to the terminal part of the pairing region (Simmler *et al.* 1985; Vergnaud *et al.* 1986; see also Ashley, 1984) observed at male meiosis between the short arm of the Y chromosome and the distal short arm of the X chromosome (Chandley *et al.* 1984). DNA probes detecting restriction fragment length polymorphisms (RFLPs) at these loci have been isolated (Table 1). These RFLPs have been used in family studies to test for sex linkage. Most of the loci recombine with sexual phenotype (Cooke *et al.* 1985; Simmler *et al.* 1985; Rouyer *et al.* 1986*a*,*b*; Goodfellow, Darling, Thomas & Goodfellow, 1986) giving experimental support to the concept of pseudoautosomal loci proposed by Burgoyne (1982).

The segregation of four pseudoautosomal DNA loci has been followed through family analysis of about 100 male and female meioses (Rouyer *et al.* 1986*b*). Such a linkage analysis first showed that the different loci analysed recombine with sex at different frequencies (Table 2A) according to a gradient of sex linkage. This gradient can be represented on a map (Fig. 1), where the four loci are ordered with respect to their recombination distances with the X and Y sex-specific chromosomal blocks. The telomeric locus *DXYS14* recombines with the proposed

Table 1. *Pseudoautosomal probes detecting polymorphic unique DNA fragments*

HGM Locus	Probes	References
DXYS14	29C1	(Cooke *et al* 1985)
DXYS15	113B	(Simmler *et al* 1985)
	113D	(Simmler *et al* 1985)
	1131	(Simmler *et al* 1987)
DXYS17	601	(Rouyer *et al.* 1986*a*)
	602	(Simmler *et al* 1987)
*DXYS20**	pDP230	(Page *et al.* 1987)*
	362A	(Rouyer *et al* 1986*b*)
MIC2	pSG1	(Goodfellow *et al* 1986)
	p19B	(Goodfellow *et al.* 1986)
	68D2†	(Rouyer *et al.* unpublished)
	U7A‡	(Rouyer *et al.* in preparation)
	U7T‡	(Rouyer *et al.* in preparation)

* *DXYS20* and *DXYS14* are located a few kb apart and have not been separated by recombination mapping to date

† Probe 68D2 has not been distinguished from locus *DXYS15* in about 40 informative meioses.

‡ Probes U7A and U7T detect a locus mapping between *DXYS14* and *DXYS15*

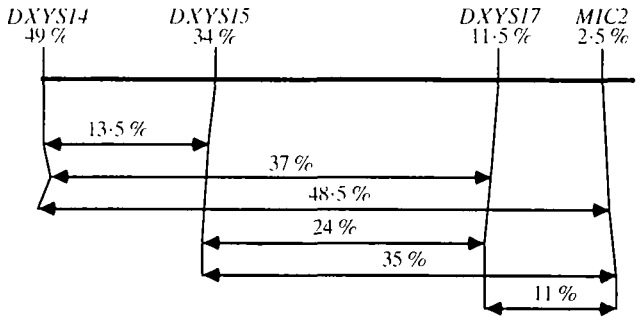

Fig. 1. Map of the human pseudoautosomal region. The upper line represents loci *DXYS14*, *DXYS15*, *DXYS17* and *MIC2* with their recombination values with *TDF* on a linear map representing the sex-linkage gradient. The lower arrowed lines represent the recombination distances between two pseudoautosomal loci measured in male meiosis and show the superimposability of the different recombination intervals.

testis-determining factor (*TDF*) at a frequency of almost 50 % and is thus not sex linked, whereas all other pseudoautosomal loci analysed display partial sex linkage.

Three-point analyses of these different loci have also shown that loci recombining less frequently never segregate independently from loci recombining more frequently (Rouyer *et al.* 1986*a*,*b*). This indicates that X–Y interchange of pseudoautosomal loci results from a crossing over and not from other genetic exchange events, such as gene conversion, through which the different loci would segregate at random. These results also strongly suggest that a

Table 2. *Recombination between TDF and pseudoautosomal loci*

Locus	Meioses	Recombinations	Recombination fraction
(A)			
DXYS14	114	56	0·49
DXYS15	82	28	0·34
DXYS17	86	10	0·115
MIC2	37	1	0·025
(B)			
DXYS14	148	70	0·475
DXYS15	89	31	0·35
DXYS17	124	17	0·135
MIC2	83	2	0·025

Panel A: our results

Panel B: collection of published data including results from Goodfellow *et al* (1986) and from panel A.

single crossover event occurs between the X and Y chromosomes and no examples of double recombination have been found to date. In addition, since different pseudoautosomal loci do not recombine at the same frequency, the crossover points are scattered throughout the pseudoautosomal region.

These features have been confirmed by measurements of recombination frequencies between different pseudoautosomal loci. In all instances, it appears that the sum of the recombination frequencies of two or more adjacent intervals equals the frequency measured directly between the outermost loci (Fig. 1) (Table 3A). When measured between the telomere (locus *DXYS14*) and the sex-specific part of the chromosomes, the recombination distance of the entire pseudoautosomal region stretches over 50 cM which is practically identical to the *DXYS14–MIC2* interval. Since the pseudoautosomal telomeres recombine with a frequency of 50 %, it appears that the human sex chromosomes undergo a crossing over at each male meiosis. Combining the data of Goodfellow, Darling, Thomas & Goodfellow (1986) with those of Rouyer *et al.* (1986*b*) gives slightly modified values but does not alter the present conclusions (Tables 2B, 3B). Recombination frequencies between pseudoautosomal loci are dramatically decreased in female meiosis (Table 3A). A total of three recombination events has been detected out of 100 female meioses, whereas 50 % of male gametes are recombined in the pseudoautosomal region. This striking difference reflects the obligatory character of the human X–Y crossover. If, as proposed by Koller & Darlington (1934), one chiasma at least takes place in each bivalent to ensure proper segregation during the first meiotic division, then the 10- to 20-fold increase in male recombination frequency is a direct

Table 3. *Recombination between pseudoautosomal loci in male and female meiosis*

	Male meiosis		Female meiosis	
Interval	(R/M)	Recombination fraction	(R/M)	Recombination fraction
A				
DXYS14-DXYS15	(11/82)	0·135	(0/70)	0
DXYS14-DXYS17	(32/86)	0·37	(2/88)	0·025
DXYS14-MIC2	(18/37)	0·485	(1/50)	0·02
DXYS15-DXYS17	(13/54)	0·24	(2/62)	0·032
DXYS15-MIC2	(13/37)	0·35	(1/31)	0·032
DXYS17-MIC2	(2/18)	0·11	(0/29)	0
B				
DXYS14-DXYS15	(11/89)	0·125		
DXYS14-DXYS17	(40/117)	0·34		
DXYS14-MIC2	(30/70)	0·43		
DXYS15-DXYS17	(15/58)	0·26		
DXYS15-MIC2	(14/40)	0·35		
DXYS17-MIC2	(8/52)	0·155		

(R/M): number of recombinations/number of informative meioses.
Panel A: our results.
Panel B: collection of published data including results from Goodfellow *et al.* (1986) and from panel A

consequence of a chiasma having to be formed in a chromosomal segment as limited as the pseudoautosomal region.

Hypervariability in the pseudoautosomal region

The restriction fragment length polymorphisms of many pseudoautosomal loci e.g. *DXYS14*, *DXYS15*, *DXYS17*, and *DXYS20* (Table 1) are characterized by numerous allelic variations. This important variability is caused by copy number variations of small repeated nucleotide sequences or minisatellites. It has been suggested that the extreme variability of minisatellites from the myoglobin family is related to a high frequency of recombination in these sequences (Jeffreys, Wilson & Thein, 1985). Recently, a similar role was attributed to a minisatellite from the mouse major histocompatibility complex (Steinmetz, Stephan & Fisher-Lindahl, 1986; Uematsu *et al.* 1986; Kobori, Strauss, Minard & Hood, 1986). Since the human pseudoautosomal region is characterized by an extremely high recombination activity in male meiosis, it was of interest to determine if the hypervariability of pseudoautosomal loci also resulted from the presence of minisatellites. If so, these latter could be related to other hypervariable regions (HVRs) reported earlier, especially those with a putative role in recombination. Therefore, the HVRs of loci *DXYS15*, *DXYS17* and *DXYS20* have been isolated, sequenced and used as probes in the search for other related minisatellite sequences (Simmler *et al.* 1987).

In the three cases analysed (Table 4), the variations result from DNA rearrangements occurring in minisatellites of 21–29 nucleotides for *DXYS15*, 28–33 nucleotides for *DXYS17* (Simmler *et al.* 1987) and 61 nucleotides for *DXYS20* (Vergnaud *et al.* unpublished data). At reduced stringency, the *DXYS15* minisatellite detects other hypervariable sequences located in other parts of the genome and hence represents a new

Table 4. *Consensus DNA sequences of three pseudoautosomal minisatellites*

DXYS15 minisatellite
GATATATATTACAGATATATA(GATATATA)

DXYS17 minisatellite
GAAATAGACTAGAAATA(GCCTA)GTCTGTTCTAC

DXYS20 minisatellite
TGCTCTCTATCTGTCCTCAATGAGACCTAGGCCCAATGCAGACTCTAAAGGTTGCACACTC

In addition to copy number variations, several point mutations of *DXYS20* minisatellite result in restriction sites polymorphisms for *Taq*I, *Hin*dIII, *Xba*I etc.

family of minisatellites (Simmler *et al.* 1987). In contrast to most other known hypervariable families, the *DXYS15* HVR displays a very high AT content.

In line with the function that myoglobin-like minisatellites may play in recombination, it is tempting to relate the high recombinational activity of the pseudoautosomal region to the important variability of many known pseudoautosomal DNA loci. However, the minisatellite sequences presented above are totally unrelated to the myoglobin core sequence (Jeffreys *et al.* 1985) and do not share any features in common with the bacterial Chi sequence or with other reported minisatellites. The hypothesis of characteristics specific to the pseudoautosomal region can also be rejected in view of the numerous autosomal RFLPs related to the *DXYS15* minisatellite. Recently it has been shown that some limited autosomal regions recombine more frequently in male meiosis (White *et al.* 1985). If minisatellite structures are indeed more recombinogenic than others it would be of interest to examine if the *DXYS15*-like HVRs map to regions recombining more frequently at male meiosis.

Crossing over anomalies between the human X and Y chromosomes

The physical size of the human pseudoautosomal region is still unknown, but probably does not exceed 2 to 3 Mb. At each male meiosis, a crossover takes place in this very limited region. If all recombination processes are affected by a constant rate of unequal exchange events, the terminal short arms of the human sex chromosomes are exceptionally prone to abnormal crossover. Similarly, unequal exchanges between the mouse X and Y chromosomes seem to occur with a very high incidence (Harbers, Soriano, Müller & Jaenisch, 1986). As shown in Fig. 2, different types of sex chromosome anomalies can be generated by single accidental events. An abnormal terminal X–Y interchange has been proposed by Ferguson-Smith (1966) to account for XX maleness. In this model, a single but unequal crossover is initiated in a region proximal to the *TDF* locus on the Y chromosome involving the distal part of the Y chromosome up to the telomere (Fig. 2B,C).

DNA analysis has shown the presence of Yp-specific DNA in a majority of XX males (Y(+) XX males) (Vergnaud *et al.* 1986; Affara *et al.* 1986*a*,*b*; Müller *et al.* 1986) and the inheritance of the paternal X chromosome in these patients (Page & de la Chapelle, 1984). These observations are compatible with Ferguson-Smith's hypothesis. Other results provide even more direct support for the interchange model. In many families, the XX male proband does not express his father's *XG* allele (reviewed by de la Chapelle, 1981). In one case (de la Chapelle, Tippett, Wetterstrand & Page, 1984), this loss of paternal *XG* expression was associated with the acquisition of the Y-linked allele for *MIC2*, a pseudoautosomal gene. Using chromosomal *in situ* hybridization, Y-specific DNA was detected at the short-arm telomere of one of the X chromosomes of several patients (Buckle *et al.* 1985*b*; Casanova *et al.* 1985; Magenis *et al.* 1985; Andersson, Page & de la Chapelle, 1986). However, these results do not show if the paternal X chromosome of Y(+) XX males actually results from an interchange involving the terminal part of both paternal sex chromosomes.

Using pseudoautosomal probes, inheritance of the paternal pseudoautosomal region has been studied in nine Y(+) XX males by segregating the paternal X chromosome in somatic hybrids (Petit *et al.* 1987, and unpublished data) or by family analysis (Page, Brown & de la Chapelle, 1987). All these patients have inherited the entire pseudoautosomal region from the Y chromosome and lost the pseudoautosomal region from the paternal X chromosome (Table 5). In addition, the deletion of locus *X-68*, a DNA locus tightly linked to the pseudoautosomal region has been observed on the paternal X chromosome from several patients of our study (Table 5). These results show that Y(+) XX maleness is initiated by an abnormal terminal X–Y interchange, which apparently happens instead of the normal pseudoautosomal crossover. In several cases, the X-chromosomal breakpoint occurs also proximal to the pseudoautosomal region and could also involve the paternal *XG* locus, thus directly accounting for the loss of expression of the paternal *XG* allele (Fig. 2B). The extent of such Xp-specific deletions is unknown. If it is limited to the non- or partially inactivated region there may be little or no phenotypic effect even on clones having the maternal X inactivated.

In the seven cases of our study mentioned above, there is no apparent remnant of pseudoautosomal material from the paternal X chromosome. However, the presence of three copies of several pseudoautosomal loci has already been observed in one patient (Rouyer *et al.* 1986*b*; Rouyer, Simmler, Page & Weissenbach, 1987) and strongly suggests that the breakpoint on the paternal X chromosome can sometimes take place within the pseudoautosomal region (Fig. 2C). In another study, it has been shown that in an XY female with Turner stigmata there is a deletion of both the distal Yp-specific loci and proximal pseudoautosomal loci from paternal origin (J. Levilliers *et al.* unpublished data). Moreover, the proband inherited distal pseudoautosomal loci from the paternal X chromosome. These pseudoautosomal DNA loci have been localized to the short-arm tip of the deleted Y chromosome by *in situ* hybridization. This suggests that the deletion could be generated by

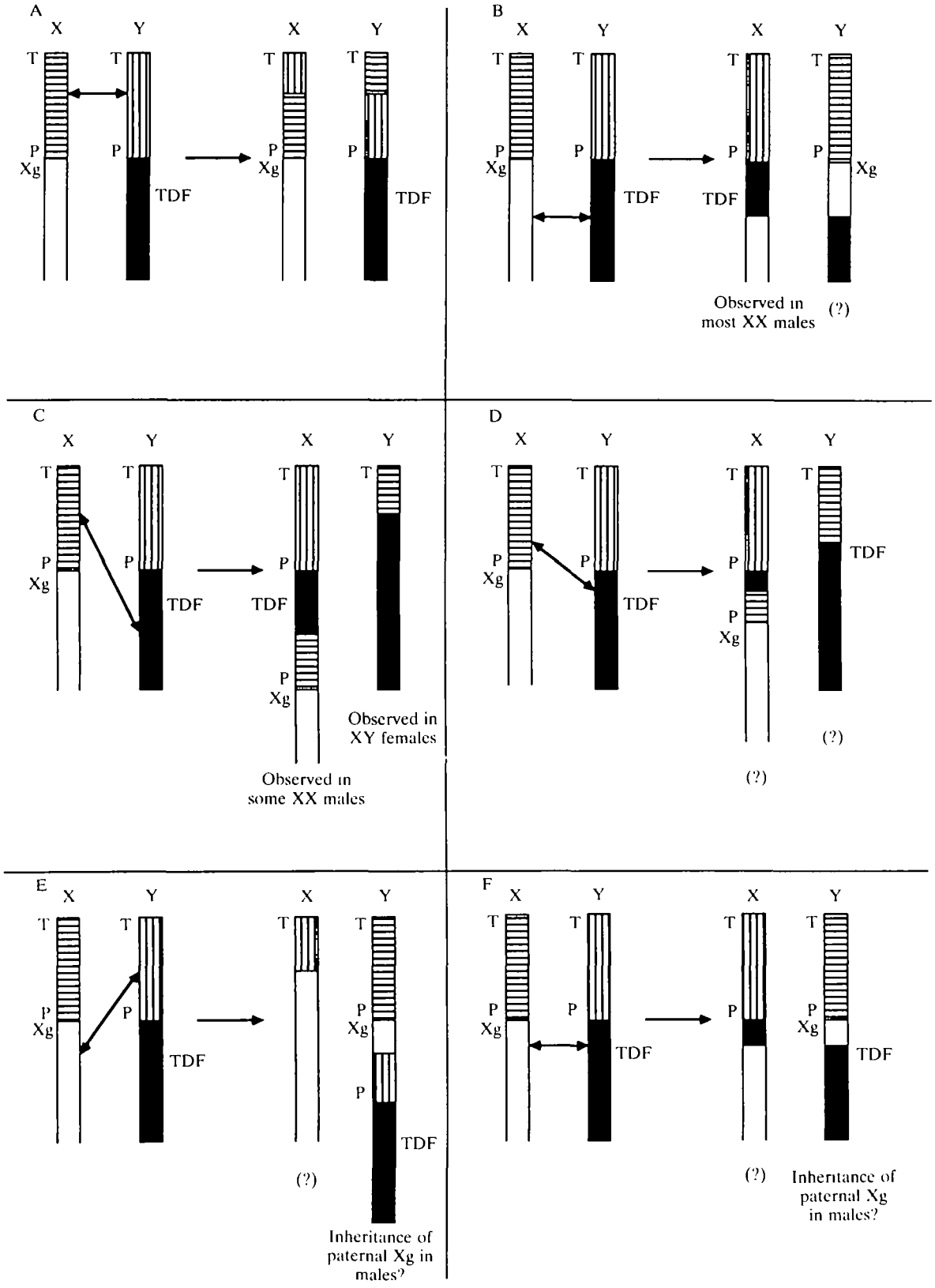

Fig. 2. Normal and possible abnormal sex chromosomes resulting from a single X–Y crossover. The double arrows indicate the respective crossover breakpoints on each sex chromosome during a meiosis. The chromosomal products from a single meiosis are represented in the right part of each panel. Pseudoautosomal regions are represented by vertical and horizontal hatched lines; black parts, Yp-specific material; white parts, Xp-specific material. (A) Normal crossing over. (B–F) Represent some possible unequal crossing over.

Table 5. *Chromosomal origin of the paternal pseudoautosomal region in some sex reversals*

Sex reversal	Number of probands	Paternal pseudoautosomal loci: Copy number per proband	Paternal pseudoautosomal loci: Chromosomal origin	Loss of locus X-68 (a/i)*
Y(+) XX males	7	1	Y	3/3
Yp(−) XY females	1	1 or 0	X	0/1

* a, number of probands who lost distal Xp-specific locus X-68; i, number of informative probands.

an unequal crossing over. This anomaly may thus be regarded as the countertype of XX males with three copies of proximal pseudoautosomal loci (Fig. 2C). Curiously Yp(−) XY females with an entire pseudoautosomal region have not been described to date though they are the theoretical countertype of the majority of Y(+) XX males (Fig. 2B). Yp deletions have been reported in two other XY females (Disteche *et al.* 1986). These two cases also display Turner stigmata suggesting that the deletions extend to loci of the pseudoautosomal region. They may thus have the same origin as the case described above.

Recent evolution of the human sex chromosomes

Obviously the incidence of unequal X–Y interchanges cannot be neglected. One critical issue of such unequal events stems from the exact location of *TDF*. If *TDF* is not immediately adjacent to the pseudoautosomal region, the Y breakpoint could occasionally take place between *TDF* and the proximal end of the pseudoautosomal region (Fig. 2D,F).

Such events would result both in loss of Y-specific material and acquisition of this material by an X chromosome. Are these chromosomal anomalies viable and genetically transmittable? Would they give rise to abnormal phenotypes? The mammalian Y chromosome is supposed to code for very few functions apart from that determining the male sex. These functions have been tentatively mapped to the long arm of the human Y chromosome (see Goodfellow, Darling & Wolfe, 1985). With the exception of the hypothetical *Yg* locus (Goodfellow, 1983; Tippett, Shaw, Green & Daniels, 1986) it is likely that there is no Y-specific gene distal to *TDF*. Thus, transfer of Y-specific material distal to *TDF* onto the human X chromosome may occur without any phenotypic effect. Hence a heterogeneity may exist on the distal X-chromosome short arm, either within or just proximal to the human pseudoautosomal region. However, unless *YG* is proximal to *TDF*, this heterogeneity is not consistent with the absolute linkage observed on X chromosomes between the *XG* silent allele and 12E7 low expression (Goodfellow & Tippett, 1981). Alternatively, the different X-chromosome variants may have already undergone a progressive homogenization until all Yp-specific material distal to TDF and proximal to the pseudoautosomal region has become pseudoautosomal (shared by the human Y and all X chromosomes) or lost. It is therefore conceivable that evolution of the human X and Y chromosomes has reached a point where *TDF* is immediately adjacent to the proximal end of the pseudoautosomal region or even partially pseudoautosomal. A similar possibility has been outlined by Bengtsson & Goodfellow (1987). Otherwise, acquisition of Yp-specific loci distal to *TDF* should be deleterious in females in the absence of *TDF*.

Symmetrically, there may be abnormal X–Y crossover breakpoints proximal to the X pseudoautosomal region. Such events may result in deletions in distal Xp (Fig. 2E,F), possibly counterselected, and transfer of X-specific loci on the Y chromosome. As already suggested, such a mechanism for instance could account for the unusual inheritance of the *XG* blood group observed in two families where all sons have a normal 46,XY karyotype and apparently inherited the paternal XG^a allele (Sanger *et al.* 1964). Family analyses for locus *X-68* could provide a better insight into this unusual mode of inheritance of *XG*.

More generally, the availability of new probes from the distal parts of the X and Y short arms and analysis of these critical regions on a broader range by *in situ* hybridization and pulsed-field gel electrophoresis will shed some new light on possible but yet undetected unequal X–Y crossovers.

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