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Mapping the Human Y Chromosome

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Mapping the human Y chromosome

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This paper reviews past and present trends in mapping the human Y chromosome. So far, mapping has essentially used a combination of cytogenetic and molecular analyses of Y-chromosomal anomalies and sex reversal syndromes. This deletion mapping culminated recently in the isolation of the putative sex-determining locus *TDF*. With the availability of new separation and cloning techniques suited for large size fragments (over 100 kilobases), the next step will consist rather in the establishment of a physical map of fragments of known physical sizes. This may allow the definition of several variants of the human Y chromosome differing by the order or location of DNA sequences along the molecule.

1. Introduction

Sex chromosomes which first and foremost control sex determination can be observed when they are heteromorphic. This heteromorphism appears almost exclusively, though not necessarily, in species with male or female heterogamety. It reflects a difference in the constitution of the X and Y or Z and W chromosomes. But sex chromosomes may also differ from the autosomes. The X or Z is generally typical of autosomes and the Y or W is rather unusual and at least in part heterochromatic. This atypical aspect of the Y chromosome usually reflects its low genetic activity. The mammalian Y chromosome fits this general description. It is well established that the mammalian Y chromosome exerts a key function in sex determination through the testis-determining factor (TDF in man, Tdy in mouse) which triggers testis differentiation of undifferentiated gonads. However, other functions may be coded by loci on the mammalian Y chromosome, but so far have not been traced by classical genetics. With the advent of molecular cloning, isolation of functions known simply by their phenotype has become feasible in man by the procedures of reverse genetics (Orkin 1986). This approach has recently culminated in the cloning of DNA sequences probably representing the TDF locus (*TDF*) (Page *et al.* 1987*a*). Isolation of this gene opens a new way of analysing early development pathways in mammals. But molecular approaches have also provided a wealth of structural information on the human Y chromosome and evolution of mammalian sex chromosomes. Most of these conclusions are again derived from mapping studies using DNA probes. This paper briefly reviews some general aspects of mapping the human Y chromosome.

2. Mapping procedures using molecular probes

(*a*) *General remarks*

Although usual mapping procedures have been successfully applied to the human Y chromosome, some specific problems need to be overcome. (i) Very few genes have been mapped to the Y chromosome, confirming that it codes for a limited number of functions.

(ii) In addition, mutations in the most important of these functions may prevent their transmission to further generations. Unlike dominant or recessive X-linked genes, there is so far no definite evidence for a truly holandric transmission from fathers to sons. Even the case of hypertrychosis of the ear remains questionable. (iii) Because of its haploid state, most of the chromosome does not lend itself to recombination mapping.

(*b*) *Probe sources*

Single or low copy number Y-specific probes have been produced from two main sources: Y-only somatic-cell hybrid lines and chromosome preparations enriched by flow-sorting. An improvement in the use of somatic hybrids, allowing the isolation of more targetted probes, has been used by Pritchard & Goodfellow (1986). This procedure consists of a selection of fragments of the human Y chromosome, based on expression after chromosome-mediated gene transfer of a cell-surface antigen encoded by a Y-located gene (*MIC2*). A resistance marker had been integrated at a random location in the Y chromosome beforehand and could be used to preselect those cells that had incorporated Y-chromosomal fragments.

(*c*) *Mapping procedures*

(i) *Deletion mapping*

The present procedures combine cytogenetic and molecular methods. Mapping is essentially based on a fragmentation of the whole molecule. This breaking up can occur naturally and the resulting chromosomal deletions can be readily observed in routine karyotyping. These deletions are then probed by DNA analysis using Y-specific DNA fragments. Cytogenetic differences can be correlated with molecular differences, but the resolving power of molecular analysis allows discrimination even among cytogenetically undistinguishable anomalies. A combination of cytogenetics and molecular studies has led to the construction of the first deletion map of the human Y chromosome. This method has been extended even to cases of sex reversal in which the sex chromosomes showed no microscopic structural anomalies. It was first shown that the genome of males with an apparently 46,XX karyotype contained some Y-specific DNA (Guellaen *et al.* 1984). In such individuals (designated as Y(+) XX males) the presence of testicular tissue results from the effect of *TDF*, which is thus located in that part of the Y chromosome that they carry. The size of this chromosomal portion is variable among the different individuals analysed, but a map of overlapping fragments (nested series) could be derived and *TDF* was located in the region of shortest overlap. According to the established polarity of the map, *TDF* was in the distal interval of Yp (Vergnaud *et al.* 1986). This location was confirmed by analysis of XY women (pure gonadal dysgenesis) who lacked DNA from distal Yp (Disteche *et al.* 1986; Müller *et al.* 1986; Affara *et al.* 1987). Using this kind of approach Page *et al.* (1987*a*) were able to define an interval of 160 kilobases of Yp deleted in an XY female and present in an XX male. DNA sequences probably corresponding to exons of the TDF locus have been isolated within that interval. Using the same type of sex-reversal anomalies (Y(+) XX males and Yp- XY females), Simpson *et al.* (1987) were able to show that the H-Y locus defined by T-cell killing does not map to Yp and is thus, as in mouse, distinct from *TDF*.

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(ii) *Recombination mapping*

A region of strict homology shared by the tips of the short arms of the X and Y chromosomes (Cooke *et al.* 1985; Simmler *et al.* 1985; Buckle *et al.* 1985) has only recently been found, some fifty years after its prediction by Koller & Darlington (1934). It corresponds to the telomeric part of the X–Y pairing region observed at male meiosis (Pearson & Bobrow 1970; Chen & Falek 1971). Exchange of polymorphic loci from that region through meiotic crossing-over in male gametogenesis has been observed between the two sex chromosomes (Cooke *et al.* 1985; Simmler *et al.* 1985). Genetic segregation of such loci is thus reminiscent of autosomal behaviour and was therefore termed pseudoautosomal (Burgoyne 1982). Existence of this pairing region has split the human sex chromosomes into two distinct parts: the pseudoautosomal region located at the tip of the short arm and the much larger sex-specific part which does not recombine at male meiosis.

X–Y crossing-over appears as a single, obligatory but not uniquely localized event at male meiosis (Rouyer *et al.* 1986*a*,*b*; Goodfellow *et al.* 1986; Page *et al.* 1987*b*). Loci from the pseudoautosomal region can therefore be readily mapped by family studies. The obligatory character of this X–Y crossing over facilitates accurate mapping. In addition, pseudoautosomal recombination distances measured in male meiosis appear to be 10- to 20-fold higher than in female meiosis (Rouyer *et al.* 1986*a*,*b*; Goodfellow *et al.* 1986; Page *et al.* 1987*b*), making recombination mapping in this region far more accurate than elsewhere in the genome. Mapping of the pseudoautosomal loci relative to each other can also be achieved by measuring linkage to *TDF*. Loci will be ordered from the most distal telomeric to the most proximal according to an increasing gradient of sex linkage (table 1).

Table 1. Sex linkage of pseudoautosomal loci

(Compilation of data collected from Rouyer *et al.* (1986*b*); Goodfellow *et al.* (1986); Page *et al.* (1987*b*); M. C. Simmler, F. Rouyer & J. Weissenbach, unpublished results. Locus *DXYS60* is located distal to *DXYS28* on the basis of a recombination between those two loci (Rouyer *et al.* 1987). Other loci show the same order on recombination and physical maps (Petit *et al.* 1988).)

loci	meioses	recombinations	θ (%)	sex-linkage, 1–θ (%)
DXYS14/DXYS20	363	172	47.4	52.6
DXYS60	37	13	35.1	64.9
DXYS28	179	68	38.0	62.0
DXYS59	38	14	36.8	63.2
DXYS15	85	28	32.9	67.1
DXYS17	145	18	12.4	87.6
MIC2	99	2	2.0	98.0

So far, no male meiosis with a double recombination event in the human pseudoautosomal region has been observed. As a consequence of this complete interference, genetic distances between loci, when measured directly, are practically identical to the recombination intervals deduced from sex-linkage values. Contrary to human, it has been shown recently that double recombination events are not infrequent in the mouse pseudoautosomal region (Keitges *et al.* 1987; Soriano *et al.* 1987). The occurrence of double events in the mouse would imply that telomeric loci recombine at a rate below 50% in this species.

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(*d*) *Genes located on the Y chromosome*

So far, three clearly defined genes have been mapped to the human Y chromosome, namely *TDF* (Page *et al.* 1987*a*) and the surface antigens 12E7, specified by gene *MIC2* (Buckle *et al.* 1985), and H-Y (Simpson *et al.* 1987). These localizations are more accurate than the best resolved cytogenetic maps. *MIC2* is pseudoautosomal (Goodfellow *et al.* 1986). Another pseudoautosomal gene, the *XGR* locus, has been proposed by Goodfellow *et al.* 1987) on genetic grounds. The *XGR* locus controls in cis, expression of the *MIC2* and *XG* loci on red blood cells. On the Y chromosome, this locus was previously termed *YG* and was shown to control 12E7 red-cell quantitative polymorphism (Goodfellow & Tippett 1981; Tippett *et al.* 1986). Similarly, *XGR* is polymorphic with two alleles. In cis the same allele induces XGa antigen expression from the *XG* locus and high level 12E7 antigen expression from the *MIC2* locus. However, a recombination between *TDF* and *XGR* (*YG*) suggested that this latter is pseudoautosomal (Goodfellow *et al.* 1987). It has also been proposed that the Y chromosome carries some other functions controlling growth (Alvesalo & de la Chapelle 1981) and fertility (Tiepolo & Zuffardi 1976).

(*e*) *Limitations*

Recombination and deletion mapping have provided reliable structural data allowing ordering of numerous anonymous DNA loci and location of a few genes. But these methods are subject to several limitations. (i) They do not provide physical distances. (ii) Is the order deduced from chromosomal anomalies identical to that of a 'normal' Y chromosome? Some deletions that appear to result from single breaks on cytogenetic criteria have actually occurred through complex rearrangements and give rise to chromosomal blocks irrelevant to any single contiguous part of the original chromosome. Such rearrangements are often associated with duplications due to fusions consequent upon a primary break (Magenis *et al.* 1985). In other instances an inversion may occur before the break. (iii) Is there a 'normal' or typical Y chromosome? The order of loci is practically immutable within an autosome of a given species and its disruption suppresses recombination as illustrated by the T-locus inversions in the mouse (Artzt *et al.* 1982). Such disruption may therefore lead to progressive genetic isolation, and may have caused divergence of mammalian sex chromosomes simultaneously with crossover suppression (Muller 1964). As long as new rearrangements of the Y-chromosome-specific part do not impair its essential functions (sex determination and fertility), they can be regarded as neutral mutations. Thus it is theoretically possible to observe several orders of the different loci, though the initial mapping by molecular analysis was based on existence of a single map. The first mapping results were consistent with a unique order but soon several discrepancies were reported. In some Y(+) XX males presence of proximal Yp is found in the absence of distal Yp sequences (Affara *et al.* 1986, 1987; G. Vergnaud & J. Weissenbach, unpublished data). Similar reciprocal results have been observed in a 46,XYp- female (Disteche *et al.* 1986; Page 1986). It was proposed to ascribe such variants to inversion polymorphisms, but this still needs further confirmation by physical mapping of Y chromosomes from normal males (see below).

3. Estimating physical distances

The advent of pulsed-field electrophoretic procedures (Schwartz & Cantor 1984; Carle & Olson 1984; Carle *et al.* 1986; Chu *et al.* 1986) resolving fragments up to several megabases opens the possibility of establishing maps of large chromosomal segments and evaluating

physical distances. This may make it possible to map directly Y chromosomes without anomalies and to confirm the existence of several variants of the Y chromosome differing by gross rearrangements.

The first tentative estimations of physical distances of defined areas of the Y chromosome with pulsed-field gel electrophoresis have been focused on the centromeric alphoid repetitive sequence *DYZ3* (Wolfe *et al.* 1985) and on the boundary of the pseudoautosomal region (Pritchard *et al.* 1987). All *DYZ3* repeats are clustered within a single block of variable size of approximately 500 kilobases (Tyler-Smith & Brown 1987). A long-range restriction map covering approximately 1.1 megabases of DNA including this *DYZ3* cluster has been proposed (Tyler-Smith & Brown 1987). Another map frames the proximal boundary of the pseudoautosomal region between two *HTF* islands. The most distal island corresponds to the 5′ end of gene *MIC2*. On its 3′ end this gene is linked to Y-specific DNA up to a second *HTF* island adjacent to the *TDF* locus (Pritchard *et al.* 1987; Page *et al.* 1987*a*).

This second embryonic map can now be extended to the entire pseudoautosomal region (Brown 1988; Petit *et al.* 1988; Rappold & Lehrach 1988). The pseudoautosomal region spans a chromosomal segment of almost 3 Mb which fits well with a 15- to 20-fold higher recombination frequency in male than in female meiosis. In male meiosis 1 cM† would thus represent about 60 kilobases of pseudoautosomal DNA. The region is characterized in its terminal part by a very high density of CpG doublets. Several other more classical *HTF* islands are scattered throughout the region. At the present level of resolution there is no obvious distortion between the physical and recombination maps, suggesting that recombination occurs either at random or in very many preferential points.

4. Future challenges in mapping the human Y chromosome

Some important genes of the mammalian Y chromosome remain to be isolated. The H-Y antigen will be mapped with increased accuracy and possibly cloned in the forthcoming years. This may shed some new light on the possible involvement of H-Y in spermatogenesis (Burgoyne *et al.* 1986). Restriction maps of large chromosomal segments should enable variants to be distinguished among apparently identical chromosomes and hence gross rearrangements to be detected by comparison with other primates. This may help to establish a patriarchal phylogeny of the human Y chromosome with some relevance to population genetics. Similarly, the evolution of mammalian sex chromosomes could be approached through detailed structural analysis of some specific sites, such as the pseudoautosomal boundary, with respect to their stability or variation in human populations and those of closely related species.

The dearth of genetic functions has not seriously hampered the first attempts at mapping. Paradoxically, the chromosome bearing the fewest genes has the relatively most extended physical map at present!

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† The morgan is the unit of relative distance between genes on a chromosome. One centimorgan represents a crossover value of 1%.

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