The human Y chromosome: the biological role of a “functional wasteland”

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“Functional wasteland,” “Nonrecombining desert,” and “Gene-poor chromosome” are only some examples of the different definitions given to the Y chromosome in the last decade. In comparison to the other chromosomes, the Y is poor in genes, being more than 50% of its sequence composed of repeated elements. Moreover, the Y genes are in continuous decay probably due to the lack of recombination of this chromosome. But the human Y chromosome, at the same time, plays a central role in human biology. The presence or absence of this chromosome determines gonadal sex. Thus, mammalian embryos with a Y chromosome develop testes, while those without it develop ovaries (Polani [1]). What is responsible for the male phenotype is the testis-determining SRY gene (Sinclair [2]) which remains the most distinguishing characteristic of this chromosome. In addition to SRY, the presence of other genes with important functions has been reported, including a region associated to Turner estigmata, a gene related to the development of gonadoblastoma and, most important, genes related to germ cell development and maintenance and then, related with male fertility (Lahn and Page [3]). This paper reviews the structure and the biological functions of this peculiar chromosome.

STRUCTURE OF THE Y CHROMOSOME

The Y is one of the smallest chromosomes in the human genome (~60 Mb) and represent around 2%–3% of a haploid genome. Cytogenetic observations based on chromosome-banding studies allowed different Y regions to be identified: the pseudoautosomal portion (divided into two regions: PAR1 and PAR2) and the euchromatic and heterochromatic regions (Figure 1).

The Pseudoautosomal regions (PAR): PAR1 is located at the terminal region of the short arm (Yp), and the PAR2 at the tip of the long arm (Yq). PAR1 and PAR2 cover approximately 2600 and 320 kb of DNA, respectively. The pseudoautosomal regions, and in particular PAR1, are where the Y chromosome pairs and exchanges genetic material with the pseudoautosomal region of the X chromosome during male meiosis. Consequently, genes located within the PAR are inherited in the same manner as autosomal genes. The euchromatic region is distal to the PAR1 and consists of the short arm paracentromeric region, the centromere and the long arm paracentromeric region. Finally, the heterochromatic region comprises distal Yq corresponding to Yq12. This region is assumed to be genetically inert, the euchromatic region has numerous highly repeated sequences but also contains some genes responsible for important biological functions that we will review here.

PHYSICAL AND MOLECULAR MAPPING

The physical mapping of the Y chromosome has mainly depended on naturally occurring deletions on this chromosome. The creation of a deletion map, and the resultant ordering of DNA loci along the chromosome, is very useful not only in locating genes but also in studying the structural diversity of the Y within and among human populations and primates. This allows information on the evolution of human species through paternal lineages to be obtained.

The first attempts at mapping the Y were based on cytogenetically detectable deletions on this chromosome and suffered then from the limited accuracy and resolution of chromosome banding patterns. However, these preliminary studies led, for the first time, to the hypothesis that a gene or genes located on Yq were related to spermatogenic failure (Tiepolo and Zuffardi [4]). Similar studies defined also a region associated with sex determination (Jacobs and Ross [5], Buhler [6]).

Vergnaud et al. [7] performed the first molecular map of the Y in 1986. By using different Y-specific probes on patients with microscopically detectable Y anomalies, they subdivided the Y chromosome into 7 intervals, corresponding with naturally occurring deletions of this chromosome. Later in 1992, Vollrath et al. [8] constructed a more precise deletion map of the Y chromosome based on the detection of about...
200 sequence-tagged sites (STS's). The presence or absence of these STS's on a large set of patients with a wide range of Y anomalies subdivided the euchromatic into 43 ordered intervals, all defined by naturally occurring chromosomal breakpoints. These 43 deletion intervals further refined the seven-interval map of Vergnaud et al. [7]. This collection of ordered STS's along the Y chromosome have been extensively used in order to define shortest deleted regions associated with particular phenotypes and then, in identifying Y chromosomal genes and exploring the origin of Y chromosome disorders. Moreover, the same group in Boston led by David Page prepared a library of yeast artificial clones (YAC) from a human XYYYY male. The clones were screened with the Y-specific STS's in order to identify those containing the corresponding sequences. Finally, an essentially complete physical map of the Y chromosome was generated with 196 overlapping DNA clones, which covered 98 percent of the euchromatic region (Foote et al. [9]). These Y physical maps have certainly accelerated the search for new genes and made it much easier to explore the biology of this chromosome.

**GENES ON THE Y CHROMOSOME**

Compared to the other human chromosomes, the Y chromosome has a limited number of genes. The Y gene poverty may have been the result of the known tendency of Y chromosome's genes to degenerate during evolution, being nowadays the relic of an ancient common ancestry with the X chromosome (Graves [10]). Both mammalian X and Y chromosomes evolved from ancestral autosomes. The most ancestral gene functions were retained on the nascent X chromosome but deteriorated on NRY portion of the emerging Y (Bull [11]) giving females with two copies but males with only one copy of many genes. The gene dosage problem has been solved through inactivation of one X chromosome in females.

In spite of the limited make-up of genes, different transcription units or families of closely related transcription units have been identified in the NRY region during the past decade (see [12–14, 2, 15–18]). Recently, Lahn and Page [3] identified 12 novel genes or gene families and assessed their expression in diverse human tissues. The different genes identified so far throughout both the NRY region and the two pseudoautosomal regions are summarised in Table 1, together with some information on their location and possible pathological implications. According to the same authors, all NRY genes can be divided into two different categories. The first comprises those genes which are ubiquitously expressed, have X homologues, appear in a single copy on the NRY and exhibit housekeeping cell functions. The second category include genes expressed specifically in the testes, exist in multiple copies (with the exception of SRY) on the NRY and encode proteins which more specialised functions. It is worth mentioning the finding of X-homologous NRY genes, which suggest an alternative solution for the gene dosage compensation. It has been proposed that these genes should escape X-inactivation and encoded proteins functionally interchangeable (Lahn and Page [3]).
| Gene symbol | Location | Gene name | Associate pathology/function | X-homologs | Reference |
|-------------|----------|-----------|-----------------------------|------------|-----------|
| CSFR2R      | α        | GM-CSF receptor α subunit | unknown | +            | Disteche et al. 1992 [19] |
| IL3RA       | α        | Interleukin-3 receptor α subunit | unknown | +            | Ellison et al. 1996 [21] |
| ANT3        |          | Adenine nucleotide translocase | unknown | +            | Shiriebel et al. 1993 [22] |
| ASMTL       |          | Acetylspermine methyltransferase-like | unknown | +            | Reed et al. 1998 [23] |
| ASMT        |          | Acetylspermine methyltransferase | unknown | +            | Ried et al. 1998 [25] |
| XE7         |          | X-escape | unknown | +            | Ellison et al. 1996 [21] |
| PGPI        |          | Pseudouniosomal GTP-binding protein-like | unknown | +            | Gianfrancesco et al. 1998 [26] |
| MCI2        |          | unknown | +            |             | Goodfellow et al. 1988 [26] |
| SRY*        | Yp: 1A1A | Sex reversal Y | Sex reversal | −            | Siminovitch et al. 1990 [1] |
| EIF3Y       | Yp: 1A1R | Ribosomal protein S4,Y | Turner syndrome? | +            | Fisher et al. 1990 [14] |
| ZFY         | Yp: 1A2  | Zinc-finger Y | Turner syndrome? | +            | Page et al. 1987 [13] |
| PRKX        | Yp: 3C-4A | protein kinase, Y | unknown | +            | Shiriebel et al. 1997 [27] |
| TTY1*       | Yp: 4A   | testis transcript, Y1 | unknown | −            | Reijo et al. 1995 [17] |
| TSPY*       | Yp: 3C+5 | testis-specific protein, Y | gonadoblastoma? | −            | Astermann et al. 1987 [12] |
| AMELY       | Yp: 4A   | Anoegenin,Y | unknown | +            | Nakahori et al. 1994 [28] |
| PRY*        | Y: 4A,6E | putative tyrosine phosphatase protein-related Y | infertility? | −            | Reijo et al. 1995 [17] |
| TTY2*       | Y: 4A,6C | testis transcript, Y2 | unknown | −            | Reijo et al. 1995 [17] |
| USP9Y (or DFFRY) | Yq: 3C | ubiquitin-specific protease (or Drosophila fat-facets related, Y) | azoospermia? | +            | Lahn and Page 1997 [3] |
| DRY         | Yq: 3C   | SKA6 box, Y | infertility? | +            | Lahn and Page 1997 [3] |
| UTY         | Yq: 3C   | Ubiquitous TRY motif, Y | infertility | +            | Lahn and Page 1997 [3] |
| TR4Y        | Yq: 3D   | Thymosin α4,Y isoform | infertility? | +            | Lahn and Page 1997 [3] |
| BPT1*       | Yq: 3G   | basic protein, Y1 | Turner? | +            | Reijo et al. 1995 [17] |
| CEPY        | Yq: 3L,6Y | chromodomain,Y | infertility | −            | Lahn and Page 1997 [3] |
| XRRX        | Yq: 3L   | XK-related, Y | infertility? | −            | Reijo et al. 1995 [17] |
| RBM5*       | Yp:q     | RNA-binding motif, Y | infertility? | −            | Ma et al. 1993 [15] |
| SMCY        | Yp: 3P   | Selected Mouse cDNA,Y | unknown | +            | Agulnik et al. 1994 [16] |
| EIF1AI      | Yq: 3Q   | Translation initiation factor 1A,Y | infertility? | +            | Lahn and Page 1997 [3] |
| DAZZ*       | Yq: 8F   | Deleted in azoospermia | infertility? | −            | Reijo et al. 1995 [17] |
| VCY2        | Yq: 6A   | variably charged protein, Y2 | infertility | −            | Reijo et al. 1995 [17] |
| ILSR        | XPA      | Interleukin 9 receptor | unknown | +            | Vermeesch et al. 1997 [29] |
| SYBR1*      |          | Synaptotagmin-like 1 | unknown | +            | Kozmik et al. 1995 [30] |
| HSPB2V3      |          | Human-sprouty 3 | unknown | +            | Ciccododicola et al. 2006 [31] |
| CXorf1*     |          | CXorf1 | unknown | +            | Ciccododicola et al. 2000 [31] |

*Testis-specific genes or families.

Note: All genes expressed specifically in the testis are present in multiple copies dispersed throughout the euchromatic portion of the Y chromosome. Exceptional is SRY, which is expressed specifically in the testis but present in single copy.
BIOLGICAL FUNCTIONS OF THE HUMAN Y CHROMOSOME

Several phenotypes have been associated with the non-recombing portion of the Y chromosome. For obvious reasons, most of these are male-specific and make the Y a specialised chromosome during human evolution. The most characterising features of this chromosome remain its implication in human sex determination and in male germ cell development and maintenance.

SRY gene and sex determination

The first indices that the Y chromosome was involved in male sex determination came from the observation that XY or XXY (Klinefelter syndrome) individuals develop testes whereas XX or XO (Turner’s syndrome) individuals develop ovaries (Jacobs and Strong [32]). Later, studies showing that mice XX presenting a male phenotype carried a small portion of the Y chromosome supported the proposition that a master gene involved in male sex determination was carried by the Y chromosome (Goodfellow and Darling [33]). In 1990, the gene responsible for testicular determination, named SRY (Sex-determining Region on the Y chromosome), was finally identified (Sinclair et al. [2]). SRY was cloned by isolation of small fragments of translocated Y on XX sex-reversed patients. This gene is located on the short arm of the Y chromosome close to the pseudoautosomal boundary. It comprises a single exon encoding a protein of 204 amino acids which presents conserved DNA-binding domain (the HMGI-box: High Mobility Group), suggesting this protein regulates gene expression. This gene has been shown to be essential for initiating tests development and the differentiation of the indifferent, bipotential, gonad into the testicular pathway. Moreover, SRY has been proposed to be the master gene regulating the cascade of tests determinism. Although many genes and loci have been proposed to interact with SRY protein, such as WT-1 (Wilms’ tumour gene), SF-1 (Steroidogenic Factor 1) and SOX-9, the question of how these genes are regulated, if so, by SRY is still unanswered.

Anti-Turner syndrome effect

Turner syndrome is characterised by a female 45 X karyotype or monosomy X. The principal manifestations of this syndrome are growth failure, infertility, anatomic abnormalities, and selective cognitive deficits. This human genetic disorder is ascribed to haplo-insufficiency of genes of the X chromosome that are common to both X and Y. These genes must escape X-inactivation because otherwise no difference will be observed between 45, X and 46, XX females. Secondly, in 46, XY these genes must have a male counterpart on the Y chromosome, thus, these genes are regulated, if so, by SRY is still unanswered.

Genes controlling spermatogenesis

Torpole and Zuffardi [4] reported the occurrence of grossly cytogenetically detectable de novo deletions in six azoospermic individuals, describing for the first time the role of the Y chromosome in spermatogenesis. These observations led the authors to postulate the existence of a locus, called AZoosperma Factor (AZF), on Yq11 required for a complete spermatogenesis since the seminal fluid of these patients did not contain mature spermatozoa. The location of AZF in Yq11 was further confirmed by numerous studies at cytogenetic and molecular level (see [36–38]). Once the molecular map by Vergnaud et al. [7] became available, AZF was localised to the deletion interval 6, a region in band q11.23. The publication of about 200 Y-specific STS, allowed by Vollrath et al. [8], allowed a much simpler Y chromosome screening for microdeletions to be performed. Thus, the original AZF region was further subdivided into three different nonoverlapping subregions in Yq11 associated with male infertility, named AZFa, AZFb, and AZFc (Vogt et al. [39]). Each one of these regions contains several genes proposed as candidate genes involved in male infertility.

The AZFa region is located in proximal Yq within the deletion interval 5 and its molecular extension has been roughly estimated between 1 and 3 Mb. Several genes have been identified in this region: Dead Box Y (DBY), Ubiquitous TPR motif Y (UTY), Yosome B4Y isoform (T4Y), and the homologue of the Drosophila Developmental gene Fats Facets (DFFFRY). The first three genes have no apparent specialised functions and they seem to be involved in cellular “housekeeping.” By contrast, the DFFRY gene has been proposed to play a role in gametogenesis. It encodes a protein involved in desubuquitination (the process by which proteins are tagged for degradation) and mutations in the Drosophila homologue of the gene cause a sterile phenotype (Fischer-Vize et al. [40], Brown et al. [41]).

The AZFb region is located between deletion interval 5 and proximal deletion interval 6, and its molecular extension has been estimated to be similar to that of the AZFa region (1–3 Mb). Five genes have been so far described within this interval: RNA-binding motif (RBM), Chromodomain Y (CDY), XK Related Y (XKRT), eukaryotic translation initiation factor 1A (eIF-1A), and Selected Mouse cDNA on the Y (SMCY). The RBM gene encode germ cell specific nuclear proteins containing RNA binding motif and it is present in multiple copies along the Y. However, not all of these copies are functional and most may be pseudogenes. It has been strongly proposed as a candidate infertility gene since its expression is testis-specific, it is recurrently deleted in azoospermic men and it seems to be specifically expressed in spermatogonia and primary spermatocytes (Ma et al. [15], Elliot et al. [42]). Other two genes are expressed specifically in adult testis and are recurrently deleted in infertile males, the CDY and the XKRT.

The AZFc region is located in the proximity of the heterochromatin region distal to Yq11 and its molecular extension is about 500 kb (Reijo et al. [17]). This region contains the DAZ (Deleted in AZoosperma) gene cluster, two copies
of the PTP-BL Related Y (PPY), Basic Protein Y2 (BPY2), as well as copies of CDY and RBM. DAZ encodes a testis-specific RNA binding protein (Reijo et al. [17]) and contains seven tandem repeats of 24 aa unit. DAZ is present in at least six to nine copies, all being located within AZFc. It is homologous to an autosomal gene on chromosome 3, with a single DAZ repeat, named DAZL1 (DAZ like-autosomal 1) which is also specifically expressed in the testis. It has been hypothesized that DAZ originated from a translocation and subsequent amplification of this ancestral autosomal gene. (Reijo et al. [43], Saxena et al. [44]). Cooke et al. [45] described the homologue of the human Y-linked DAZ gene, named Dazla (DAZ like autosomal), in the mouse where is located on chromosome 17. Dazla presents an RNA-binding domain with 89% of homology with DAZ and is expressed specifically in the testis and ovaries (see [45, 43]). Knock-out mice for this gene have been shown to be infertile in both the two sexes (Ruggiu et al. [46]). These observations suggested Dazla as an important gene in mouse gametogenesis. Although DAZ has been proposed as the cause of the AZFc phenotype, other genes must be involved since deletions within AZFc region without including DAZ have been recently reported (see [47–49]). The other genes identified within this region, PRY, BPY2, and TTY2, all also present a single DAZ repeat, named DAZL1 (DAZ like-autosomal 1). DAZ is present in at least seven tandem repeats of 24 aa unit. DAZ is expressed in gonadoblastoma, in spermatogonias at early stages of testicular tumorigenesis, in carcinoma in situ of the testis, in seminoma and prostate cancers. These observations strongly suggest that this Y-linked gene may predispose germ cells to other oncogenic events in the multistep process of tumorigenesis.

**Conclusion Remarks**

The Y is unique under many aspects. It is always in the haploid state, is full of repeated sequences but it is responsible for important biological roles such as sex determination and male fertility. Moreover, the Y chromosome is a powerful tool to study human populations and evolutionary pathways. The nonrecombining portion of the Y retains a record of the mutational events that have occurred along male lineages throughout evolution. This is because it is holsandrically transmitted, from father to son, without recombination at meiosis. Thus, the study of the different mutations this molecule has accumulated along its evolution may be highly informative in deducing the histories of human populations (see [55–61]). In conclusion, it is time to change the opinion about this singular chromosome. Although the Y chromosome has been studied for more than 30 years, it is considered by many to have little relevance, except in very limited circumstances. The Y has not only demonstrated to be extremely informative in disentangling the history of human populations but it also has essential biological roles that make this chromosome an important component of the human genome.

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