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SEX CHROMOSOME GENETICS '99
Gonadoblastoma, Testicular and Prostate Cancers, and the *TSPY* Gene

Yun-Fai Chris Lau

Division of Cell and Developmental Genetics, Department of Medicine, VA Medical Center, University of California, San Francisco

The role of the Y chromosome in oncogenesis of human cancers has been somewhat controversial. Both gain and loss of the Y chromosome in different leukemia, lymphoma, and solid tumors have been reported (Abeliovich et al. 1994; Brothman 1997; Dave et al. 1996; Geburek et al. 1997; Jackson-Cook et al. 1996; Kirk et al. 1994; Konig et al. 1994; Mertens et al. 1997; Riske et al. 1994; Watanabe et al. 1996). Conceivably, both oncogenes and tumor-suppressor genes exist on this chromosome, and they may act at different points during tumorigenesis, particularly for cancers of male-specific organs, such as the testis and the prostate. One scenario suggests that aberrant expression of an oncogene favoring cell proliferation may activate the early stages of tumorigenesis. These early events may be mediated by the duplication of all or part of the Y chromosome. The loss or repression of a tumor-suppressor gene may be essential for the tumor to acquire aggressive properties at later stages of cancer progression, possibly triggered by the loss of the Y chromosome. Unfortunately, most studies that have tried to define the role of the Y chromosomal loci in human cancers have relied on purely cytogenetic techniques—either classical or molecular. Many genomewide linkage studies have excluded the Y chromosome from their analyses (Cooney et al. 1997; Dunsmuir et al. 1998; Murray et al. 1994; Xu et al. 1998), since the bulk of the Y chromosome neither pairs with, nor recombines with, the X chromosome during meiosis. Hence, identification of oncogenic and tumor-suppressor loci on this chromosome has been lacking. Despite these difficulties, one cancer predisposition locus has been assigned to this chromosome—namely, the gonadoblastoma locus on the Y chromosome (GBY).

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Address for correspondence and reprints: Dr. Chris Lau, Division of Cell and Developmental Genetics, Department of Medicine, VAMC-111C5, University of California, San Francisco, 4150 Clement Street, San Francisco, CA 94121. E-mail: clau@itsa.ucsf.edu

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Genes on the Human Y Chromosome

Recent progress in positional cloning of Y-linked genes has provided a pool of candidate genes for gonadoblastoma. The 33 functional genes that are currently recognized on this chromosome (fig. 1) may be divided into three distinct groups. The first group consists of X-Y identical genes that are located on one of the two pseudoautosomal regions (PARs). PAR1 is situated on the telomere of the short arm and contains ~2.6 Mb of DNA. It harbors 10 genes that act in numerous pathways, including bone growth, cytokine signaling, cellular energy metabolism, melatonin synthesis, and cell surface antigen expression. PAR2, situated on the telomere of the long arm, contains 400 kb of DNA and includes two genes that encode an interleukin receptor and a synaptobrevin-like protein. Each gene in the PARs corresponds to an identical gene in the PARs of the X chromosome. A second group consist of X-Y homologous—but not identical—genes that are located on the nonrecombining region on the short and long arms of the Y chromosome. There are 10 single-copy genes in this group, most of which are ubiquitously expressed in many human tissues, including those of the testis and the prostate. It is still uncertain whether these X- and Y-homologous genes are functionally interchangeable. The third group includes 11 genes on the nonrecombining region. Except for the sex-determining region Y (*SRY*), all these genes are repeated on the Y chromosome. Some are candidates for the azoospermia factor (AZF; see McElreavey and Krausz (1999) [in this issue]). Exact functions for most of the genes on the nonrecombining region of the Y chromosome are still uncertain. Those that encode cytokine receptors, transcription factors, protein kinase, and phosphatase may influence cell proliferation and/or signal transduction and are good candidates for further studies on their probable involvement in oncogenesis of human and/or male-specific cancers.

Candidate Genes for the Gonadoblastoma Locus

Gonadoblastomas are gonadal neoplasms that consist of aggregates of germ cells and sex cord elements (Scully 1953, 1970). Although such tumors are rarely, if ever, found in normal males or females, in 46,XY testicular

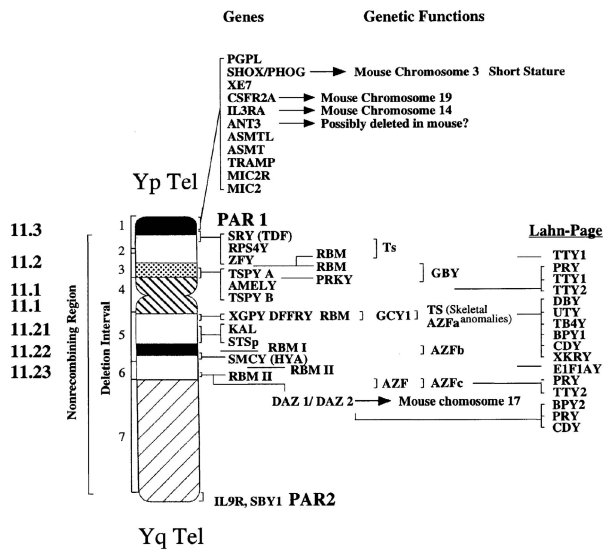

Figure 1 Genes on the human Y chromosome. This map represents an updated version of a figure presented at the Third International Workshop on Y Chromosome Mapping (Vogt et al. 1997). The Lahn-Page column indicates genes recently isolated by these investigators (Lahn and Page 1997). Other entries were derived from respective reports (Gianfrancesco et al. 1998; Ried et al. 1998; Esposito et al. 1999). The deletion intervals are drawn only approximately to the cytogenetic locations. See Vollrath et al. (1992) and Lahn and Page (1997) for a more precise assignment of deletion intervals.

feminization (Tfm) patients, or in 47,XXY or 46,XX males (all of whose testes are devoid of germ cells), gonadoblastomas develop in >30% of phenotypic females who harbor some Y-chromosomal materials in their genome (Verp and Simpson 1987; Sultana et al. 1995; Iezzoni et al. 1997). On the basis of these observations, Page (1987) postulated the existence of a GBY locus, on the Y chromosome, that predisposes the dysgenetic gonads of XY sex-reversed females to develop gonadoblastoma. Page further hypothesized that GBY acts as an oncogene only in the dysgenetic gonad and has a normal function in the testis. Since gonadoblastomas recapitulate germ cell/support cell architecture, Page suggested that GBY might well function in or prior to spermatogenesis of the normal testis.

The mapping of the underlying gene for this condition has proved unexpectedly complex. Using a panel of DNAs from sex-reversed and gonadoblastoma patients, Page had initially mapped the GBY locus to deletion intervals 3 on the short arm and 4B–7 on the long arm of this chromosome (fig. 1; also see Page 1987). Subsequent studies by Tsuchiya et al. (1995) further sublocalized the GBY locus to a small region at intervals 3E–3G proximal to and 4B at the centromere. These investigators estimated the GBY critical region to be ~1–2 Mb on the short arm of the human Y chromosome (fig. 1, dotted area on Yp). Salo et al. (1995), however, mapped the GBY locus within 4 Mb of DNA between intervals 4B at and 5E proximal to the centromere on the long arm of the Y chromosome.

These various findings led Tsuchiya et al. (1995) to speculate that more than one gene may be implicated in gonadoblastoma, and it is also possible that some relevant gene is present in multiple copies that are distributed across the Y chromosome. However, it remains uncertain whether the discrepancy between regions for GBY sublocalized by the two groups arose because of inversion polymorphisms on the Y chromosome (Vogt et al. 1997). Despite the elusive location of GBY, the isolation of many of the Y chromosome genes (Lahn and Page 1997; Vogt et al. 1997) has provided a pool of candidates for GBY.

The small region defined by Tsuchiya et al. (1995) contains seven known genes: amelogenin Y (*AMELY*), RNA binding motif (*RBM*), protein kinase Y (*PRKY*), protein tyrosine phosphatase (PTP)-BL related Y (*PRY*), testis transcripts Y1 and Y2 (*TTY1* and *TTY2*), and testis-specific protein Y-encoded (*TSPY*). Both *TTY1* and *TTY2* consist of repetitive DNA sequences, and their transcripts lack any apparent protein-coding sequences (Lahn and Page 1997), so these genes may serve no crucial function. *AMELY*, like its X-linked homologue, *AMELX,* encodes an enamel protein (Lau et al. 1989) that is exclusively expressed in the developing tooth bud (Salido et al. 1992). Hence, neither of these gene products is likely to affect cell proliferation in the gonad. *RBM* is a repeated gene with functional sequences that are mostly located in interval 6 on the long arm (Ma et al. 1993). Only a few copies are located within the GBY critical region. The RBM protein contains an RNA-binding motif, from which it derives its name, and it localizes primarily to the nuclei of spermatogenic cells (Elliott et al. 1997). As discussed by McElreavey and Krausz (1999), RBM is postulated to act in the nuclear metabolism of newly synthesized RNA (Elliott et al. 1998) and may underlie the azoospermia defect that has been mapped to interval 6 (Ma et al. 1993; Vogt et al. 1997). Although its transcripts have been detected in gonadoblastoma tissues (Tsuchiya et al. 1995), *RBM* is an unlikely candidate for GBY, since most of its functional units are located outside the GBY critical region. *PRKY* and its X homologue, *PRKX*, encode members of the cAMP-dependent serine/threonine protein kinase family (Klink et al. 1995; Schiebel et al. 1997). *PRY* is a newly identified repeated gene whose product displays some similarity to PTP-BL (Lahn and Page 1997). Other copies of *PRY* are found in interval 6, outside the GBY critical region.

Currently, we cannot exclude the possibility that mutation and/or aberrant expression of *PRKY* or *PRY* are responsible for the predisposition of the dysgenetic go-

nads of XY females to gonadoblastoma. Protein kinases often act as signal transducers for growth factor and cytokine receptors, whereas phosphatases counterbalance their effects (see Hunter 1998*a,* 1998*b*, for review). Indeed, there is ample precedent that activated protein kinases can serve as oncoproteins and that protein phosphatases can act to suppress tumor formation (see, e.g., Myers and Tonks 1997). Hence, either PRKY or PRY may possess growth-regulatory functions, but the biological functions of these proteins are not yet understood.

The remaining candidate locus for gonadoblastoma is *TSPY,* a multicopy gene that is located primarily in the GBY critical region at interval 3, as defined by deletion mapping (Arnemann et al. 1987, 1991; Zhang et al. 1992; Vogt et al. 1997). Several homologous copies have also been mapped on proximal intervals 4 and 5 on the long arm. *TSPY* expression has been detected in gonadoblastoma tissues (Tsuchiya et al. 1995). Significantly, as detailed below, recent studies provide circumstantial evidence supporting a role for *TSPY* as an oncogene. For this reason, *TSPY* has emerged as the most likely candidate for GBY.

TSPY Is Evolutionarily Conserved on the Mammalian Y Chromosome

Approximately 20–40 copies of *TSPY* or of similar sequences cluster at two locations—TSPYA and TSPYB—within interval 3 on the short arm of the human Y chromosome (Vogt et al. 1997). Additional copies are also present in interval 4/5 on the long arm. Each copy of the gene consists of six exons distributed over 2.8 kb (Schnieders et al. 1996) and is embedded in a 20-kb tandemly repeated unit (Zhang et al. 1992; Manz et al. 1993). The number of functional units in this array is uncertain, but, in most cases, 35–45-kb DNA fragments from the region direct the expression of a normal-sized TSPY transcript in transfected cells (Zhang et al. 1992). Hence, all necessary *cis*-acting transcription and RNA-processing signals appear to be present in most *TSPY* repeat units.

Homologues of *TSPY* also map to the Y chromosome in other mammals, including primates, artiodactyls, and rodents (Conrad et al. 1996; Kim et al. 1996; Vogel et al. 1997, 1998*a;* Glaser et al. 1998; Mazeyrat and Mitchell 1998), and in all cases these genes exhibit a similar structural organization (Vogel et al. 1997; Mazeyrat and Mitchell 1998). Two functional copies of *Tspy* are found on the rat Y chromosome (Mazeyrat and Mitchell 1998), although the mouse carries only a single, poorly expressed copy of the *Tspy* gene, which contains numerous in-frame stop codons within its coding sequence. This sequence almost certainly represents a pseudogene (Mazeyrat and Mitchell 1998; Vogel et al. 1998*a*), but other related cDNAs have recently been isolated from both human and mouse (Vogel et al. 1998*b*), and one or more homologous genes may function in place of the Y-linked *Tspy* in the mouse.

Normal and Abnormal Expression of *TSPY* in the Testis

TSPY transcripts have also been detected in fetal testis as early as the 22d week of gestation in humans (Zhang et al. 1992), and expression persists through adulthood. TSPY occurs in the adult testis as a 33-kD protein and as a phosphoprotein with an apparent molecular weight of 38 kD (Schnieders et al. 1996; author's unpublished data). Immunohistological staining with a specific antibody localizes the TSPY epitope primarily to the cytoplasm of a subset of spermatogonial cells and around the basal lamina of the seminiferous tubules of the adult testis (Schnieders et al. 1996). Interestingly, spermatogonial cells that express TSPY appear to be paired with adjacent cells that show lower expression. TSPY signals are also observed in the nuclei of a relatively small proportion of spermatogonial cells. Schnieders et al. (1996) hypothesize that TSPY regulates the normal proliferation of spermatogonia and marks the entry of the spermatogonia into the meiotic differentiation. Significantly, TSPY is detected with higher intensity in spermatogonia at early stages of testicular tumorigenesis, in carcinoma in situ of the testis (Schnieders et al. 1996), and in seminomas (fig. 2). These results suggest that TSPY is aberrantly expressed in tumors with germ cell origins. Conversely, XY females, who exhibit Tfm as a result of mutations in the androgen-receptor gene, show positive TSPY staining in a much-reduced number of residual spermatogonia in their testes. Hence, TSPY expression appears to depend on spermatogenic activity and a proper hormonal environment. This postulate is reasonable since spermatogenesis is greatly influenced by male hormones (see reviews, McLachlan et al. 1996; Yong et al. 1988). If TSPY indeed serves a vital function in directing the spermatogonial stem cells to enter meiotic division, it is conceivable that its expression is regulated by androgen and androgen receptor.

Aberrant Expression of *TSPY* in Prostate

The testis-specific expression that inspired the naming of *TSPY* (Arnemann et al. 1987, 1991) is not absolute. Expression in somatic cells was not considered in our initial study, although we detected specific transcripts from this gene in a highly metastatic melanoma cell line, HT-144, derived from a 29-year-old male patient (Zhang et al. 1992). The observation of TSPY in testicular tumors has now led us to reexamine the expression of this gene in other male-specific cancers, such as those of the

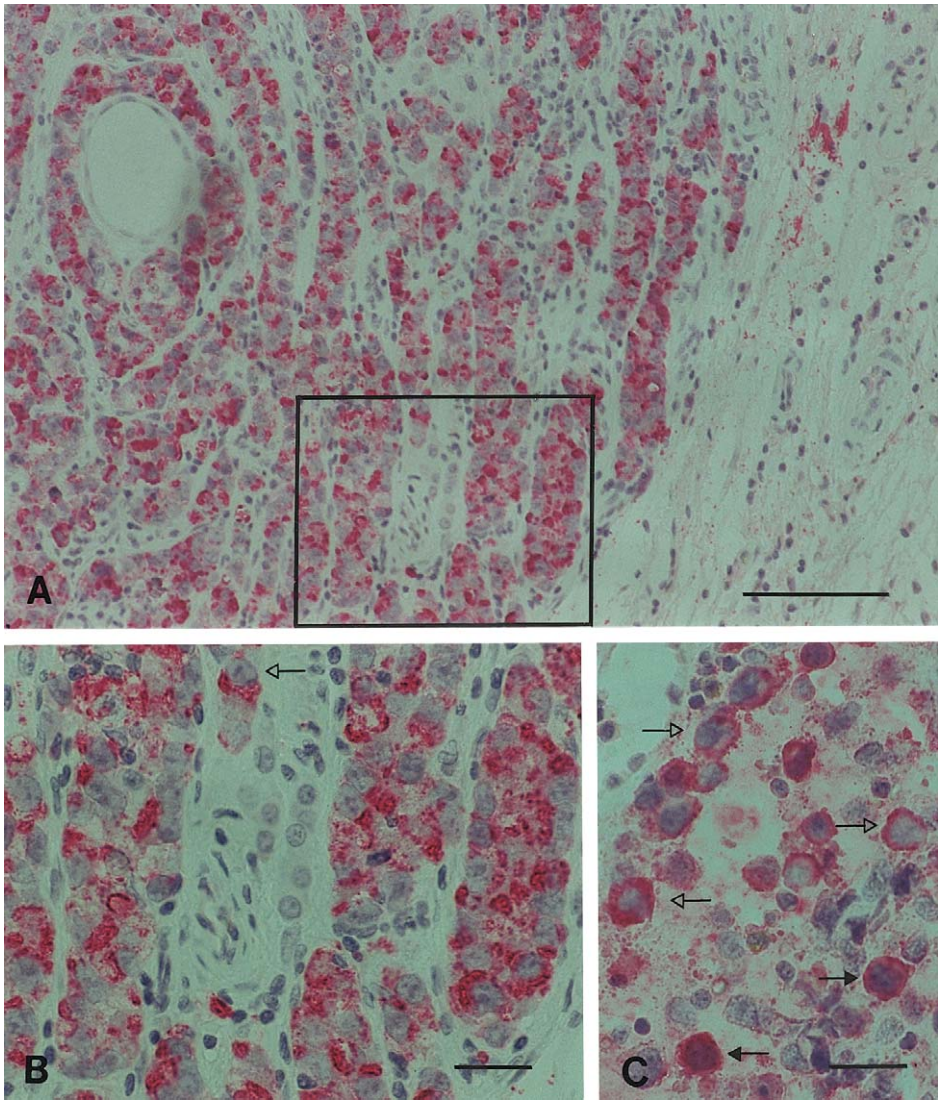

Figure 2 Localization of TSPY on tumor cells of human seminoma specimens by immunostaining. A highly specific antibody against a recombinant TSPY protein (Zhang et al. 1992) was used in immunostaining with two human seminoma specimens (Kömüves et al. 1998). A secondary antibody conjugated with the alkaline phosphatase was used for visualization of TSPY protein locations (red). The slides were counterstained with hematoxylin-eosin (greenish blue). *A*, Specific signals were observed on the cancerous region (e.g., boxed area) which, under higher magnification as in *B*, showed specific antibody staining of the large seminoma cells with characteristic vesicular nuclei. *C*, A second specimen showing specific immunostaining of TSPY protein in both cytoplasm (open arrows) and nucleus (solid arrows) of the tumor cells. Bar represents 200 μm in *A* and 25 μm in *B* and *C*.

prostate. Using both in situ mRNA hybridization and immunostaining techniques, we have demonstrated a preferential expression of TSPY in the epithelial cells at the cancerous regions of prostate cancers of high and low Gleason grades (Y.-F. C. Lau and L. G. Kömüves, unpublished data). These findings strongly suggest that aberrant expression of *TSPY* may also be involved in tumorigenesis of the prostate gland. Further, we also observed an up-regulation of *TSPY* expression in the responsive prostatic cell line, LNCaP, with stimulation by androgen (Y.-F. C. Lau and J. Q. Zhang, unpublished data). These latter results further support the hypothesis that *TSPY* (or some copies of its functional units) is regulated by male hormone and its receptor in the prostate as well as the testis.

TSPY, the SET Oncoprotein, and Other Cyclin B–Binding Proteins

The involvement of *TSPY* in cell proliferation and tumorigenesis is further reinforced by its homology to the *SET* oncogene on 9q34. *SET* was initially identified

in a patient with acute undifferentiated leukemia, who harbored an intrachromosomal translocation on chromosome 9 (von Lindern et al. 1992). This translocation fused the 3′ end of *c-SET* with another oncogene, *CAN*, to create a *SET-CAN* chimera that encodes a 155-kD putative oncoprotein. The two normal c-SET transcripts of 2.0 and 2.7 kb differ only in their 3′ untranslated domains and are predicted to encode an identical 32-kD protein. Immunoprecipitation analysis demonstrates that c-SET is a nuclear phosphoprotein of 39 kD that is widely expressed in numerous tissues and cell types (Adachi et al. 1994), including the testis.

SET has also been identified as the template-activating factor, TAF-1 (Nagata et al. 1995), and as a potent inhibitor of protein phosphatase 2A (PP2A; Li et al. 1996). TAF-1 was defined because of its role in stimulating initiation and elongation in adenovirus core DNA. PP2A is an abundant, multifunctional serine/threonine–specific phosphatase that stimulates the replication of both SV40 DNA replication and chromosomal DNA (Lin et al. 1998). PPA2 antagonizes cdc2/cyclin B complexes, which regulate the progression of cells past the G_2 stage of the cell cycle; hence, inhibition of PPA2 and cessation of DNA replication may be required for the onset of mitotic division. Indeed, Kellogg et al. (1995) have demonstrated that SET and related proteins, such as nucleosome assembly protein 1 (NAP-1), interact specifically with mitotic cyclin B. Hence, SET may serve a normal function in cell cycle regulation, and its fusion with CAN may generate an oncogenic protein that promotes leukemic cell proliferation.

The homology of TSPY with SET was initially noted by Tsuchiya et al. (1995) and subsequently characterized by Schnieders et al. (1996). Currently, there are 23 members of the SET/NAP-1 family of cyclin B–binding proteins, as defined by their homologies to a 194-residue conserved domain. The TSPY proteins share homology to the amino half of this consensus domain, whereas the SET homology extends 42 additional residues toward the carboxyl terminus. Along with the homology between these classes of proteins, the fact that TSPY and SET proteins are of similar molecular weights and exist as phosphoproteins (Adachi et al. 1994; Schnieders et al. 1996; J. Zhang and Y.-F. C. Lau, unpublished data) make it tempting to speculate that TSPY serves a specialized role in the testis, related to that of SET. Preliminary studies conducted in our laboratory suggest that TSPY binds to human cyclin B and is phosphorylated by p34cdc2/cyclin B complex in vitro (J. Zhang and Y.-F. C. Lau, unpublished data). These observations, if confirmed in vivo, would further support the model that interactions between TSPY and cyclin B direct spermatogonia to enter meiosis.

Is *TSPY* an Oncogene?

TSPY possesses several interesting features that fit the profile for the long-sought gonadoblastoma gene. First, most of its repeat units have been mapped to the GBY critical region(s), including intervals 3E–3G and 4/5 (Page 1987; Salo et al. 1995; Tsuchiya et al. 1995). Second, its expression in spermatogonial cells in normal testis (Schnieders et al. 1996) suggests a function early in spermatogenesis, as predicted by Page (1987) in his original hypothesis. Third, *TSPY* is up-regulated in gonadoblastoma tissues (Tsuchiya et al. 1995), as well as in certain testicular and prostate cancers (Schnieders et al. 1996; Y.-F. C. Lau and L. G. Kömüves, unpublished data). Finally, *TSPY* expression is drastically reduced in the dysgenetic gonads of patients with 46,XY Tfm, who rarely develop gonadoblastomas.

If *TSPY* is an oncogene, how might it contribute to development of gonadoblastoma or testicular or prostate cancer? Given the multiplicity of *TSPY* genes on the Y chromosome, it is difficult to envision how the mutation of a single copy of the gene could confer oncogenic potential, although such a strong, dominantly acting mutation is conceivable. More likely, the oncogenic function of *TSPY* may be explained by its aberrant or inappropriate expression either in somatic cells (e.g., epithelial cells of the prostate) that are incapable of entering meiotic differentiation or in germ cells (e.g., dysgenetic gonads) that are in an environment unsuitable for spermatogenesis.

The reason for such aberrant expression is currently unknown. If *TSPY* is indeed regulated by androgen and its receptor, misexpression could result either from mutations within the regulatory elements of one or a few of its transcriptional units or from inappropriate signaling, perhaps prompted by changes in the hormonal environment in the testis or prostate. The aberrant expression of *TSPY*, however, only predisposes the dysgenetic gonads (in gonadoblastoma), abnormal spermatogonia (in testicular cancer), or somatic epithelial cells (in prostate cancer) to other oncogenic events in the multistep process of carcinogenesis (Knudson 1997). TSPY may contribute to such predisposition by potentiating cell proliferation. This hypothesis provides a basis for further evaluation of *TSPY* as a potential Y-linked proto-oncogene.

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References

Abeliovich D, Yehuda O, Ben-Neriah S, Or R (1994) Loss of Y chromosome: an age-related event or a cytogenetic marker of a malignant clone? Cancer Genet Cytogenet 76:70–71

Adachi Y, Pavlakis GN, Copeland TD (1994) Identification and characterization of SET, a nuclear phosphoprotein encoded by the translocation break point in acute undifferentiated leukemia. J Biol Chem 269:2258–2262

Arnemann J, Epplen JT, Cooke HJ, Sauermann U, Engel W, Schmidtke J (1987) A human Y-chromosomal DNA sequence expressed in testicular tissue. Nucleic Acids Res 15: 8713–8724

Arnemann J, Jakubiczka S, Thuring S, Schmidtke J (1991) Cloning and sequence analysis of a human Y-chromosome-derived, testicular cDNA, TSPY. Genomics 11:108–114

Brothman AR (1997) Cytogenetic studies in prostate cancer: are we making progress? Cancer Genet Cytogenet 95: 116–121

Conrad C, Hierl T, Glaser B, Taylor K, Zeitler S, Chandley AC, Schempp W (1996) High-resolution fluorescence in situ hybridization of RBM- and TSPY-related cosmids on released Y chromatin in humans and pygmy chimpanzees. Chromosome Res 4:201–206

Cooney KA, McCarthy JD, Lange E, Huang L, Miesfeldt S, Montie JE, Oesterling JE, et al (1997) Prostate cancer susceptibility locus on chromosome 1q: a confirmatory study. J Natl Cancer Inst 89:955–959

Dave BJ, Hopwood VL, Spitz MR, Pathak S (1996) Sex chromosome abnormalities in lung cancer patients. Cancer Genet Cytogenet 87:24–28

Dunsmuir WD, Edwards SM, Lakhani SR, Young M, Corbishley C, Kirby RS, Dearnaley DP, et al (1998) Allelic imbalance in familial and sporadic prostate cancer at the putative human prostate cancer susceptibility locus, HPC1. CRC/BPG UK Familial Prostate Cancer Study Collaborators. Cancer Research Campaign/British Prostate Group. Br J Cancer 78:1430–1433

Elliott DJ, Millar MR, Oghene K, Ross A, Kiesewetter F, Pryor J, McIntyre M, et al (1997) Expression of RBM in the nuclei of human germ cells is dependent on a critical region of the Y chromosome long arm. Proc Natl Acad Sci USA 94: 3848–3853

Elliott DJ, Oghene K, Makarov G, Makarova O, Hargreave TB, Chandley AC, Eperon IC, et al (1998) Dynamic changes in the subnuclear organisation of pre-mRNA splicing proteins and RBM during human germ cell development. J Cell Sci 111:1255–1265

Esposito T, Gianfrancesco F, Ciccodicola A, Montanini L, Mumm S, D'Urso M, Forabosco A (1999) A novel pseudoautosomal human gene encodes a putative protein similar to Ac-like transposases. Hum Mol Genet 8:61–67

Geburek BM, Kollmorgen TA, Qian J, D'Souza-Gburek SM, Lieber MM, Jenkins RB (1997) Chromosomal anomalies in stage D1 prostate adenocarcinoma primary tumors and lymph node metastases detected by fluorescence in situ hybridization. J Urol 157:223–227

Gianfrancesco F, Esposito T, Montanini L, Ciccodicola A, Mumm S, Mazzarella R, Rao E, et al (1998) A novel pseudoautosomal gene encoding a putative GTP-binding protein resides in the vicinity of the Xp/Yp telomere. Hum Mol Genet 7:407–414

Glaser B, Grutzner F, Willmann U, Stanyon R, Arnold N, Taylor K, Rietschel W, et al (1998) Simian Y chromosomes: species-specific rearrangements of DAZ, RBM, and TSPY versus contiguity of PAR and SRY. Mamm Genome 9: 226–231

Hunter T (1998*a*) Anti-phosphatases take the stage. Nat Genet 18:303–305

———(1998*b*) The Croonian Lecture, 1997. The phosphorylation of proteins on tyrosine: its role in cell growth and disease. Philos Trans R Soc Lond B Biol Sci 353:583–605

Iezzoni JC, Von Kap-Herr C, Golden WL, Gaffey MJ (1997) Gonadoblastomas in 45,X/46,XY mosaicism: analysis of Y chromosome distribution by fluorescence in situ hybridization. Am J Clin Pathol 108:197–201

Jackson-Cook C, Bae V, Edelman W, Brothman A, Ware J (1996) Cytogenetic characterization of the human prostate cancer cell line P69SV40T and its novel tumorigenic sublines M2182 and M15. Cancer Genet Cytogenet 87:14–23

Kellogg DR, Kikuchi A, Fujii-Nakata T, Turck CW, Murray AW (1995) Members of the NAP/SET family of proteins interact specifically with B-type cyclins. J Cell Biol 130: 661–673

Kim HS, Takenaka O (1996) A comparison of TSPY genes from Y-chromosomal DNA of the great apes and humans: sequence, evolution, and phylogeny. Am J Phys Anthropol 100:301–309

Kirk JA, VanDevanter DR, Biberman J, Bryant EM (1994) Y chromosome loss in chronic myeloid leukemia detected in both normal and malignant cells by interphase fluorescence in situ hybridization. Genes Chromosomes Cancer 11: 141–145

Klink A, Schiebel K, Winkelmann M, Rao E, Horsthemke B, Ludecke HJ, Claussen U, et al (1995) The human protein kinase gene PKX1 on Xp22.3 displays Xp/Yp homology and is a site of chromosomal instability. Hum Mol Genet 4: 869–878

Knudson AG (1997) Hereditary predisposition to cancer. Ann N Y Acad Sci 833:58–67

Kömüves LG, Hanley K, Jiang Y, Elias PM, Williams ML, Feingold KR (1998) Ligands and activators of nuclear hormone receptors regulate epidermal differentiation during fetal rat skin development. J Invest Dermatol 111:429–433

Konig JJ, Teubel W, van Dongen JW, Romijn JC, Hagemeijer A, Schroder FH (1994) Loss and gain of chromosomes 1, 18, and Y in prostate cancer. Prostate 25:281–291

Lahn BT, Page DC (1997) Functional coherence of the human Y chromosome. Science 278:675–680

Lau EC, Mohandas TK, Shapiro LJ, Slavkin HC, Snead ML (1989) Human and mouse amelogenin gene loci are on the sex chromosomes. Genomics 4:162–168

Li M, Makkinje A, Damuni Z (1996) The myeloid leukemia-associated protein SET is a potent inhibitor of protein phosphatase 2A. J Biol Chem 271:11059–11062

Lin XH, Walter J, Scheidtmann K, Ohst K, Newport J, Walter G (1998) Protein phosphatase 2A is required for the initi-

ation of chromosomal DNA replication. Proc Natl Acad Sci USA 95:14693–14698

Ma K, Inglis JD, Sharkey A, Bickmore WA, Hill RE, Prosser EJ, Speed RM, et al (1993) A Y chromosome gene family with RNA-binding protein homology: candidates for the azoospermia factor AZF controlling human spermatogenesis. Cell 75:1287–1295

Manz E, Schnieders F, Brechlin AM, Schmidtke J (1993) TSPY-related sequences represent a microheterogeneous gene family organized as constitutive elements in DYZ5 tandem repeat units on the human Y chromosome. Genomics 17: 726–731

Mazeyrat S, Mitchell MJ (1998) Rodent Y chromosome TSPY gene is functional in rat and non-functional in mouse. Hum Mol Genet 7:557–562

McElreavey K, Krausz C (1999) Male infertility and the Y chromosome. Am J Hum Genet 64:928–933 (in this issue)

McLachlan RI, Wreford NG, O'Donnell L, de Kretser DM, Robertson DM (1996) The endocrine regulation of spermatogenesis: independent roles for testosterone and FSH. J Endocrinol 148:1–9

Mertens F, Johansson B, Hoglund M, Mitelman F (1997) Chromosomal imbalance maps of malignant solid tumors: a cytogenetic survey of 3185 neoplasms. Cancer Res 57: 2765–2780

Murray JC, Buetow KH, Weber JL, Ludwigsen S, Scherpbier-Heddema T, Manion F, Quillen J, et al (1994) A comprehensive human linkage map with centimorgan density; Cooperative Human Linkage Center (CHLC). Science 265: 2049–2054

Myers MP, Tonks NK (1997) PTEN: sometimes taking it off can be better than putting it on. Am J Hum Genet 61: 1234–1238

Nagata K, Kawase H, Handa H, Yano K, Yamasaki M, Ishimi Y, Okuda A, et al (1995) Replication factor encoded by a putative oncogene, set, associated with myeloid leukemogenesis. Proc Natl Acad Sci USA 92:4279–4283

Page DC (1987) Hypothesis: a Y-chromosomal gene causes gonadoblastoma in dysgenetic gonads. Development 101 Suppl:151–155

Ried K, Rao E, Schiebel K, Rappold GA (1998) Gene duplications as a recurrent theme in the evolution of the human pseudoautosomal region 1: isolation of the gene ASMTL. Hum Mol Genet 7:1771–1778

Riske CB, Morgan R, Ondreyco S, Sandberg AA (1994) X and Y chromosome loss as sole abnormality in acute non-lymphocytic leukemia (ANLL) [published erratum appears in Cancer Genet Cytogenet 1994 Sep;76(2):161]. Cancer Genet Cytogenet 72:44–47

Salido EC, Yen PH, Koprivnikar K, Yu L-C, Shapiro LJ (1992) The human enamel protein gene amelogenin is expressed from both the X and the Y chromosomes. Am J Hum Genet 50:303–316

Salo P, Kaariainen H, Petrovic V, Peltomaki P, Page DC, de la Chapelle A (1995) Molecular mapping of the putative gonadoblastoma locus on the Y chromosome. Genes Chromosomes Cancer 14:210–214

Schiebel K, Mertz A, Winkelmann M, Glaser B, Schempp W, Rappold G (1997) FISH localization of the human Y-homolog of protein kinase PRKX (PRKY) to Yp11.2 and two pseudogenes to 15q26 and Xq12→q13. Cytogenet Cell Genet 76:49–52

Schnieders F, Dork T, Arnemann J, Vogel T, Werner M, Schmidtke J (1996) Testis-specific protein, Y-encoded (TSPY) expression in testicular tissues. Hum Mol Genet 5: 1801–1807

Scully R (1953) Gonadoblastoma: a gonadal tumor related to the dysgerminoma (seminoma) and capable of sex-hormone production. Cancer 6:445–463

———(1970) Gonadoblastoma: a review of 74 cases. Cancer 25:1340–1356

Sultana R, Myerson D, Disteche CM (1995) In situ hybridization analysis of the Y chromosome in gonadoblastoma. Genes Chromosomes Cancer 13:257–262

Tsuchiya K, Reijo R, Page DC, Disteche CM (1995) Gonadoblastoma: molecular definition of the susceptibility region on the Y chromosome. Am J Hum Genet 57:1400–1407

Verp MS, Simpson JL (1987) Abnormal sexual differentiation and neoplasia. Cancer Genet Cytogenet 25:191–218

Vogel T, Boettger-Tong H, Nanda I, Dechend F, Agulnik AI, Bishop CE, Schmid M, et al (1998*a*) A murine TSPY. Chromosome Res 6:35–40

Vogel T, Dechend F, Manz E, Jung C, Jakubiczka S, Fehr S, Schmidtke J, et al (1997) Organization and expression of bovine TSPY. Mamm Genome 8:491–496

Vogel T, Dittrich O, Mehraein Y, Dechend F, Schnieders F, Schmidtke J (1998*b*) Murine and human TSPYL genes: novel members of the TSPY-SET-NAP1L1 family. Cytogenet Cell Genet 81:265–270

Vogt PH, Affara N, Davey P, Hammer M, Jobling MA, Lau YF, Mitchell M, et al (1997) Report of the Third International Workshop on Y Chromosome Mapping 1997. Heidelberg, Germany, April 13–16, 1997. Cytogenet Cell Genet 79:1–20

Vollrath D, Foote S, Hilton A, Brown LG, Beer-Romero P, Bogan JS, Page DC (1992) The human Y chromosome: a 43-interval map based on naturally occurring deletions. Science 258:52–59

von Lindern M, van Baal S, Wiegant J, Raap A, Hagemeijer A, Grosveld G (1992) Can, a putative oncogene associated with myeloid leukemogenesis, may be activated by fusion of its 3′ half to different genes: characterization of the set gene. Mol Cell Biol 12:3346–3355

Watanabe A, Kawachi Y, Nishihara T, Uchida T, Setsu K, Hikiji K (1996) Extra Y chromosome in T-cell acute lymphoblastic leukemia. Cancer Genet Cytogenet 89:85–87

Xu J, Meyers D, Freije D, Isaacs S, Wiley K, Nusskern D, Ewing C, et al (1998) Evidence for a prostate cancer susceptibility locus on the X chromosome. Nat Genet 20: 175–179

Yong EL, Ghadessy F, Wang Q, Mifsud A, Ng SC (1998) Androgen receptor transactivation domain and control of spermatogenesis. Rev Reprod 3:141–144

Zhang JS, Yang-Feng TL, Muller U, Mohandas TK, de Jong PJ, Lau YF (1992) Molecular isolation and characterization of an expressed gene from the human Y chromosome. Hum Mol Genet 1:717–726