

Prostate cancer susceptibility and growth linked to Y chromosome genes

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1. ABSTRACT

The role of Y chromosome in prostate cancer progression and incidence is not well known. Among the 46 chromosomes, Y chromosome determines the male gender. The Y chromosome is smaller than the X chromosome and contains only 458 genes compared to over 2000 genes found in the X chromosome. The Y chromosome is prone to high mutation rates, created exclusively in sperm cells due to the highly oxidative environment of the testis. Y chromosome harbors epigenetic information, which affects the expression of genes associated with the incidence and progression of prostate cancer. In this review, we focus on Y chromosome related genetic abnormalities, likely to be involved in the development and progression of prostate cancer.

2. INTRODUCTION

Prostate cancer is the leading non-cutaneous cancer among men (1). About 1 in 7 men is diagnosed with prostate cancer at some point in his lifetime (2). Prostate cancer cells like other cancer cells migrate and metastasize. The small walnut shaped prostate gland produces seminal fluid required to nourish and transport sperm (3). Prostate cancer grows slowly and initially remains confined to the gland, however, in time will, like other tumors, metastasize (4). Metastasis usually occurs in the lymph nodes, bones, liver, lungs and brain

(5). Prostate cancers are mostly adenocarcinomas (6). Measuring the levels of prostate specific antigen (PSA) in men's blood is the standard screening practice for prostate cancer patients. An elevated level of PSA predicts the patient's risk of developing prostate cancer in future. Clinical presentations may include urinary difficulty, blood in the semen, bone pain, erectile dysfunction and discomfort in the pelvic region (7). A complete pathophysiology of prostate cancer is unclear (8). A Gleason score determines prostate cancer severity and is a system of grading prostate cancer tissue based on microscopic appearance (9). Gleason scores range from 2 to 10 and indicate how likely a tumor will spread. A low Gleason score means the cancer tissue is similar to normal prostate tissue and the tumor is less likely to spread; a high Gleason score indicates the cancer tissue is very different from normal prostate and is more likely to spread. Several factors contribute to prostate cancer, one major risk factor is increased age until 70 years and then declines thereafter (10). Another risk factor is gonorrhea; however, the reason for this association has not been established (11). Race and family history are also established risk factors, with men of African American ancestry having higher documented prostate cancer rates than Caucasian men (12). There are several risk factors associated with prostate cancer progression and incidence such as smoking (13), diet (14), family history (12) and environmental exposure (15).

Table 1. Racial differences are shown with genetic variance in patients with prostate cancer

Population	Genetic Variance	Relation to Prostate Cancer	References
White	n/a		(34)
African American	E3a	lineage associated with increased risk	(34)
Japanese	O3	lineage associated with increased risk	(34)
Latino	n/a		(34)
Ashkenazi Jewish	E, E1b1b, E1b1b1a1, E1b1b1b1	haplogroup protective effect against prostate cancer	(25)

Reports suggest prostate cancer develops in prostate cells that have abnormal repetitive mutations (16-19), understanding how these mutations are initiated will enable exploration of the factors determining mutation and its evolution. After spermatogenesis, sperm are stored in an oxidative environment in the testis contributes to mutational events. Chromosomes including Y chromosome goes through multiple cell divisions. Each cellular division provides an opportunity for mutation. Researchers reported a provisional association between Y chromosome modification and prostate cancer (20-24). Evidence found using computerized based method to gather population-based genetic information to establish the connection between Y chromosome gene alterations and prostate cancer after conducting analysis (23). Deep understanding of Y chromosome s and its genes may provide a link to prostate cancer and using different approaches to modulate the altered gene expression may have potential cure to prostate cancer. However, research regarding Y chromosome mutations is limited because of its size, high levels of repetitive genetic information and low levels of recombination (25). In reviewing the Y chromosome we hope to explore the potential role of the Y chromosome and associated genes in prostate cancer development.

3. PROSTATE CANCER AND THE Y CHROMOSOME

3.1. The Y chromosome and genetic epidemiology

Epidemiologic data illustrates men have higher rates of cancer than females (26). In prostate cancer progression genetics (27), age (28), ethnicity (12), dietary factors (14), and environmental factors (15) all play a role. In terms of the Y chromosome and prostate cancer, there are several distinct disparities between certain groups such as African American men and their susceptibility to the disease (29). Interestingly, there has been a recent increase in the incidence of prostate cancer rates in Japanese men (30). These increased rates can be accounted for several external factors such as the change to a western diet, pollution and screening for disease. These factors may be related to environmental and genetic influences in Japanese immigrants in Hawaii (30). Globally, there has been a change to a more westernized diet that

could be having detrimental effects on these men's susceptibility to prostate cancer (31, 32). Moreover, in European ancestry population, 3,995 prostate cancer cases and 3,815 control cases were genotyped for Y chromosome binary markers (25). The Y chromosome based genetic information in different ethnic groups represented the incidence of prostate cancer in African American men is twice that of Caucasian men and 10 times higher in Japanese men (25). Similarly, other reports suggest higher incidence of prostate cancer in African American men (33). It was determined that risk variants of rs114798100 and rs111906923 - a new association signal are found exclusively in US men with African ancestry (33). These variants found close to long noncoding RNAs (lncRNAs) which are associated with prostate cancer. These lncRNAs include PRNCR1, PCAT1 and PCAT2 (33). Therefore, this may be the apparent disparities between men of African ancestry in terms of prostate cancer (33).

Furthermore, there is a connection between the rare haplogroup, E1b1b1c, which is associated with Ashkenazi Jewish ancestry and stage I prostate cancer (25). Additionally in a cohort study report, four different ethnic groups were selected from Hawaii and California (34). In one Japanese men study group, discovered to have a significant predisposition to prostate cancer, with high rates in younger individuals (35). These racial differences are shown Table 1. Based on the accumulated literature this is apparent the genetic variance in Y chromosome s play significant role in prostate cancer.

3.2. Genetic mutations

Prostate cancer patient's genome wide next generation sequencing analysis detected variants in chromosomal abnormalities (36). The genomic instability of 3.4. kb DYZ1 was observed in individuals with prostate cancer, cases of repeated abortion and males who were exposed to natural background radiation (37). The variation of DYZ1 in these males correlated with genetic constraints/anomalies. The mechanisms of genomic instability of DYZ1 is not well explored; however, it is understood that it plays a vital role in the structural integrity of the Y chromosome maybe by absorbing mutations, and can be used as a marker for Y chromosome integrity. There were well-defined deletions observed in three different regions

Table 2. Specific loci associated with prostate cancer found on the Y chromosome

Loci	High incidence of prostate cancer	References
rs114798100	High incidence of prostate cancer	(45)
rs111906923	High incidence of prostate cancer	(45)
allele 12 of DYS388	High incidence of prostate cancer	(45)
allele 14 of DYS439	Risk variant for prostate cancer in Europeans	(22)
rs1218582, rs119022336, rs4245739, rs3771570, rs761694, rs1894292, rs6869841, rs3096702, rs2273669, rs1933488, rs12155172, rs11135910, rs3850699, rs11568818, rs1270884, rs8008270, rs7141529, rs6844232, rs11650494, rs7241993, rs2427345, rs6062509, rs2405942	Low incidence of prostate cancer	(45)
allele 10 of DYS388	High incidence of prostate cancer in African Americans	(22)
8q24 region	High incidence of prostate cancer in African Americans	(22), (63)
PRNCR1	High incidence of prostate cancer in African Americans	(45, 64)
PCAT1	High incidence of prostate cancer in African Americans	(45, 65)
PCAT2		(45, 65)

(265, 773 and 275 bp) of DYZ1 when compared with DNA from normal males. Moreover, the copy number of DYZ1 was inconsistent and fluctuated below and above the normal range associated with an abnormal genotype (38). Additional reports explore the fate of DYZ1 in monozygotic male twins. It was determined that DYZ1 varied in both sequence polymorphisms and copy number between the twins. The sequence variation observed in germline and blood DNA of the same individual. Therefore, genetic changes in DYZ1 can be used as a marker (37).

3.2.1. Loss of Y chromosome

Age related loss of the Y chromosome is a well-known phenomenon in normal hematopoietic cells. Swedish men blood samples (approximately 6000) and medical records examined using single-nucleotide polymorphism (SNP) array analysis in order to quantify the loss of the Y chromosome (LOY) in blood cells for potential causes of LOY (39). The association between LOY rate and other variables includes age, education level, exercise, smoking and cholesterol levels. The same research group also hypothesized that LOY potentially gives cells a proliferative advantage presumably through elimination of tumor suppressor genes on the Y chromosome (40). Recent report suggest that LOY in cancer patients is more significant predictor than age, however age does not contribute to even increased number of subjects with detectable LOY in cancer patients cohort (26). The higher rates of LOY is associated with death at a younger age and more susceptibility to cancer (41). LOY may contribute to compromising the cancer fighting abilities of immune cells (26). However, another study suggested that, who smoke occasionally have less LOY rates than chain smokers (35). Complete loss of the Y chromosome was reported in seminal vesicles of 28 prostate cancer

patients and 11 bladder cancer patients (42). However, loss of the Y chromosome has been reported in only 12 prostate cancer tissue microarray containing samples of 3,261 patients treated with radical prostatectomy, no significant associations found between LOY and patient age, tumor stage and risk of PSA recurrence (41). Y chromosome loss was significantly higher than expected percent seen in lymphocytes, which may be indicative of aging rather than alteration in the prostate due to carcinogenesis. The loss of the Y chromosome in epithelial cells is a predictive biomarker for prostate cancer in men (41). Available literature suggest that loss of Y chromosome and its genes are closely associated with immunosurveillance modification and various cancers.

3.2.2. Y chromosome loci

The Y chromosome has specific loci genetically linked to familial prostate cancer inheritance (22). On the Y chromosome, 51 sequence tagged sites were screened on coding region of SRY gene related with male-specific region and sequence and copy number variations in DYZ1 gene in LNCaP and DU145 prostate cancer cells (43). Though both of these cell lines were derived from different origins; LNCaP cells (androgen dependent metastasize to lymph nodes) and DU145 (androgen independent, from brain metastasis) prostate cancer cells. In another study, Malaysian men with prostate cancer reported to have four Y-linked short tandem repeats (STRs) were; DYS388, DYS435, DYS437 and DYS439 on the DYS loci (31). STRs, referred to as microsatellites or simple sequence repeats (SSRs; are stretches of DNA) that contain core repeated sequences between two and seven nucleotides in length (20). Men who have allele 12 of DYS388, allele 14 of DYS439, or haplotype CAAA are more likely to develop prostate

cancer; and that those belonging to lineages with allele 10 of DYS388 or haplotype AABC were more resistant to develop prostate cancer (33). In another study, 23 prostate cancer susceptibility loci were identified (44). Table 2 summarizes Y chromosome related loci. These loci were able to explain approximately 30 percent of the familial risk for the disease (44). Another specific region of the Y chromosome that contains risk variants for prostate cancer is the 8q24 region. This observation was made after using fine mapping identified a rare variation of the risk region of 8q24 when prostate cancer patients were compared to healthy control subjects (45).

3.2.3. Y chromosome splice variants

Splice variation or alternative splicing is a process resulting in multiple transcripts generated from a single gene (46). The effect of splice variation of Y chromosome genes has not been well-characterized (47). However, Lysine (K)-specific demethylase 5D (KDM5D), is one gene found on the Y chromosome, located in the AZFb region that encodes for a JmjC-domain-containing protein. The KDM5D gene is capable of demethylating di and tri-methyl H3K4, a known Y chromosome suppressor. Two novel splice variants of KDM5D were detected with lengths of 2650bp and 2400bp corresponding to proteins in DU-145 human prostate cancer cell line (24). Silencing these variants increased the growth of prostate cancer cells and reduced cell-mediated death. These variants reduced cell-mediated death. Playing a role in RNA processing, protein synthesis, apoptosis, cell cycle and cell growth, variants of KDM5D are promising targets for tumor specific chemotherapeutics (24).

3.2.4. Y chromosomes and related genes

Reports suggest that certain genes present on the Y chromosome have a connection to the incidence of prostate cancer (44). Prostate cancer known to have complex polygenetic properties. Experimentally 15 genes on Y chromosome were observed link to prostate cancer (48). In these genes; SRY, XKRY2, AMELY, UTY, DDX3Y and EIF1AY were observed replaced by BPY2 and RPS4Y1 in cancer network. BPY2 found on Y chromosome, interacts with ubiquitin protein ligase E3A, which may be involved in male germ cell development and infertility. RPS4Y1 encodes for the protein Y isoform 1, which is related the function of ribosomes; organelles involved in protein translation. The roles of following genes are summarized in Table 3 and represented increased expression in prostate cancer. Next, 19 genes on Y chromosome are linked to prostate cancer; however, 12 genes have already been identified as having a putative role in prostate cancer. These genes were identified using an independent co-expression network approach to reconstruct normal and cancerous stages

(49). The genes, which represented low expression on the Y chromosomes are summarized in Table 4. The most prominent genes in prostate cancer are BPY2, UTY, SRY and EIF1AY (48).

3.2.5. Y Chromosome and tumor suppressor genes

Prognosis of prostate cancer requires sequence of events leading to the development of tumor and metastasis. To deal with such successive events we need to have good modulators of prognostic markers and tumor suppressor genes. KDM5D and MSY, represses gene expression associated with cell invasion (50) (Table 5). The male specific protein is believed to be involved in inter- and intra-sexual communication (51), and found to specifically repress invasion-associated genes MMP1, MMP2, MMP3, MMP7 when demethylated (50). These genes are involved in extracellular matrix degradation and occurs under normal physiological conditions such as embryonic development, reproduction, and tissue remodeling (52). However, matrix metalloproteinases play major role in arthritis as well as in cancer metastasis. Suppression of these genes may control metastasis (53). The suppressor KDM5D was significantly down regulated in metastatic prostate tissues compared to normal prostate tissues (51). Therefore, we emphasize Y chromosome gene involvement in suppressing prostate cancer. Low levels of this gene were associated with slow disease progression. Moreover, in metastatic prostate cancer these genes are frequently deleted (50). These findings highlight the role Y chromosome mediated transcriptional regulation plays in the prevention of prostate cancer metastasis (50).

3.2.6. Alleles

Allele is a variant form of a gene and micro-allele is a short tandem repeat with a fractional value. Micro-alleles sometimes referred as microvariants as fractional markers or partial repeats. Micro variant alleles DYS458 sequence of DYZ1 gene are over expressed in individuals with prostate cancer. Moreover report suggested that allele 12 of DYS393 and allele 19 of DYS458 might have a protective effect in patients. However, patients carrying allele 13 of DYS393 appeared to have an increased risk to prostate cancer (38). A recent report found a significant amount of prostatic cancerous tumors had recurrent, non-coding sequences of genes (38). The analyzed genome sequences from non-indolent prostate tumors represented recurrent molecular aberrations and novel prognostic translocations, inversions and epigenetic events (54). Further in-depth knowledge of short tandem repeat allele may add more information to genetic profiling of prostate cancer by overcoming from resistance or susceptibility.

Table 3. Genes associated with high expression in prostate cancer found on the Y chromosome

Genes	Full Name	Role	References
BPY2	Basic Charge, Y-Linked, 2	Cell growth	(48, 62)
RPS4Y1	Ribosomal Protein S4, Y-Linked	Cell growth	(48, 62, 66)
NLGN4Y	Neurologin 4 Y linked	Cell growth	(48, 67)
VCY1B	Variable Charge, Y-Linked 1B	Cell growth	(48)
RBM1Y	RNA Binding Motif Protein, Y-Linked, Family 1, Member E	Cell growth	(48)
ZFY	Zinc Finger Protein,		
Y-Linked	Cell growth	(48, 62)	
TMSB4Y	Thymosin Beta 4, Y-Linked	Cell growth	(48, 67, 68)
XKRY2	XK Related, Y-Linked 2	Cell growth	(48, 69)
GPI	Glucose-6-Phosphate Isomerase	Tumor growth	(49, 70)
SMAD3	SMAD Family Member 3	Prostate cancer cell growth	(49, 70)
HMGB2	High Mobility Group Box 2	Cell growth castration-resistant in prostate cancer	(49)
SF1	Steroidogenic factor 1	Promotes aggressive growth of castration-resistant prostate cancer cells by stimulating steroid synthesis and cell proliferation.	(49, 71-73),
IL10RB	Interleukin 10 Receptor Subunit Beta	Benign prostate hyperplasia	(49, 74)
RPS4Y1	Ribosomal Protein S4, Y-Linked	Protein synthesis	(48, 62, 66, 75)
FGFR1	Fibroblast Growth Factor Receptor 1	Tissue development	(49, 76)
MYB	Transcriptional activator Myb	Proliferation and differentiation of hematopoietic progenitor cells	(49, 77)
KLK3	Kallikrein-3	Biomarker for prostate cancer	(49, 78, 79)
HEXA	Hexosaminidase Subunit Alpha	Protein synthesis	(49, 80)
OLFM1	Olfactomedin 1	Nerve tissue	(48)
CYL1B	Chromodomain Y-Linked 1B	Gene repression	(48)
SFN	Stratifin	Cell growth	(49, 81, 82)
CD44	CD44 Blood molecule (Indian Blood Group)	Cell migration	(49, 83)
Slug	Snail family transcriptional repressor 2	Antiapoptosis Activity	(50, 84)
UBE3A	Ubiquitin Protein. Ligase E3A	Targeting for cell degradation	(49, 85)
TSPY	Testis Specific Protein, Y linked	Prostate cancer cell progression	(59) (60) (55)
H3K4	Histone H3 Lysine 4	Cell Growth	(51, 86)
CYORF15B	Chromosome Y Open Reading Frame 15B	Cell Growth	(48)
PRY2	PTPN13-Like, Y-Linked 2	Cell Growth	(48)
DAZ4	Deleted In Azoospermia 4	Cell growth	(48)
PRKY	Protein Kinase, Y-Linked, Pseudogene	Cell Growth	(48)
PCDH11Y	Protocadherin 11 Y-Linked	Cell Growth	(48)

Table 4. Genes associated with high expression in prostate cancer found on the Y chromosome

Genes	Full Name	Role	References
RB1	RB Transcriptional Corepressor 1	Negative regulator of the cell cycle	(49, 87, 88)
FAS	Fas Cell Surface Death Receptor	Apoptosis	(49)
SRY	Sex-Determining Region Y	Prostate cancer cell growth	(48, 89, 90)
XKRY2	XK Region, Y linked	Prostate cancer cell growth	(48, 89, 90)
AMELY	Amelogenin, Y linked	Prostate cancer cell growth	(48, 62)
UTY	Ubiquitously Transcribed Tetratricopeptide Repeat Containing, Y linked	Prostate cancer cell growth	(48, 62, 67, 68)
DDX3Y	DEAD-Box Helicase 3, Y-Linked	Prostate cancer cell growth	(48)
EIF1AY	Eukaryotic Translation Initiation Factor 1A, Y-Linked	Prostate cancer cell growth	(48, 62, 68)
USP9Y	Ubiquitin Specific Peptidase 9, Y-Linked	Cell growth, prevent protein degradation	(48, 67)

Table 5. Genes associated with prostate cancer tumor suppression

Genes	Full Name	Role	References
KDM5D	Lysine Demethylase 5D	Tumor suppressor	(48, 91)
MSY	Male-specific region of the Y chromosome	Tumor suppressor	(50)

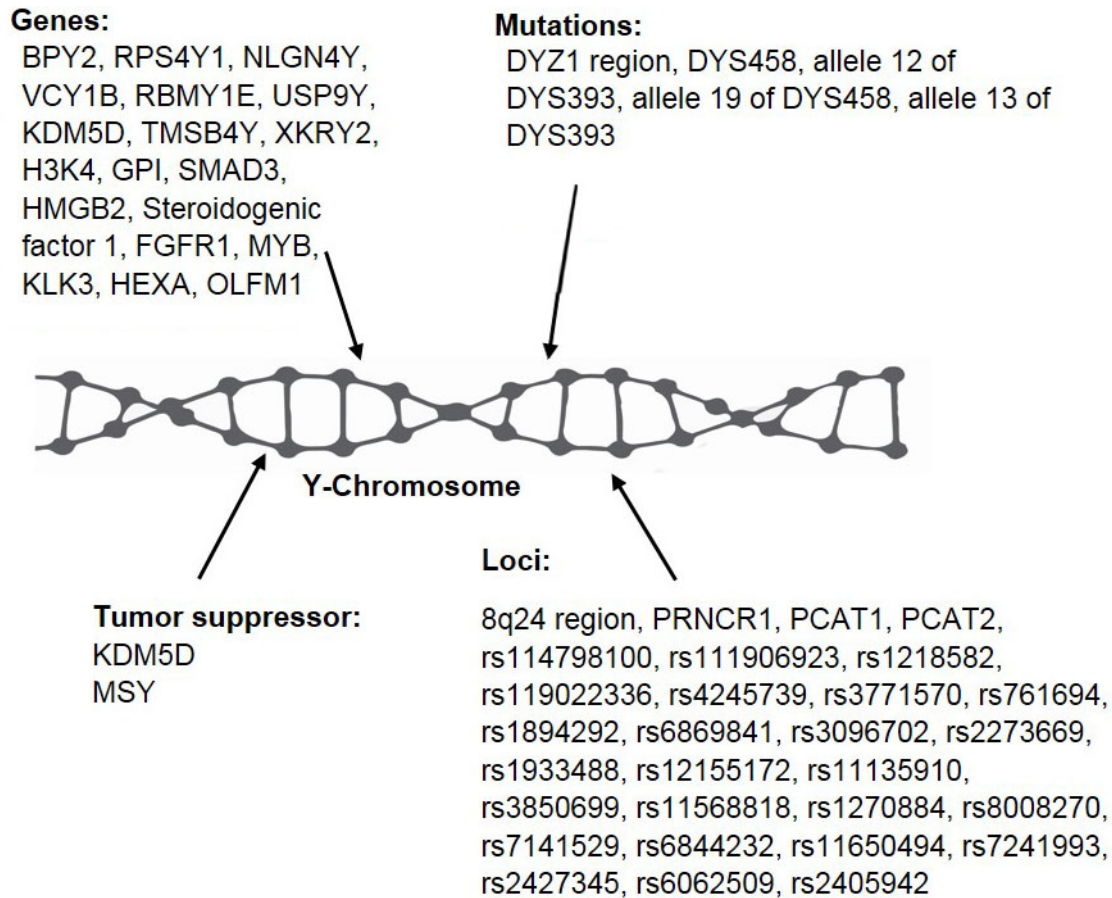


Figure 1. Y chromosome related genes, loci, mutations and involved tumor suppressor genes.

4. EXPERIMENTAL MODELS:

There are limited animal models available to determine the Y-linked nature of prostate cancer. Various transgenic mice models recapitulate different aspects of prostate cancer development and metastasis. The TSPY (testis specific protein, is Y-linked), is a proto-oncogene involved in the onset and progression of several human cancers such as skin, liver and prostate (55). Moreover, TSPY's binding partner EEF1A is elevated in clinical cases of prostate cancer compared to latent prostate cancer or non-cancerous cases. These findings suggest the expression of TSPY is associated with the growth and progression of prostate cancer. Y chromosome of rat harbors a single functional copy of TSPY gene, and this is only expressed in elongating spermatids while the human TSPY is primarily expressed in spermatogonia and spermatocytes (56, 57). Later Schubert *et al.* generated a transgenic mouse line (58), which was harboring 50 copies of human TSPY gene

on Y chromosome of the mouse, known as TgTSPY9. More detail about TgTSPY9 transgene, it was 8.2.-kb transgene contains 2.9.5-kb the promoter region, 2.8.-kb structural gene and 2.4.5-kb 3' flanking sequence of the human TSPY gene. Like human TSPY gene, it was expressed at early stages of spermatogenesis in spermatogonia and spermatocytes (58). There are potential limitations with available mouse models of prostate cancer in mimicking the ectopic expression of TSPY, when Y-located TSPY transgene (TgTSPY9) was introduced to LADY mouse model of prostate cancer. TgTSPY9 transgene was expressed in FoxA1-negative hypercellular stroma of LADY mice prostate, conversely in human clinical prostate cancer specimens TSPY is expressed in FoxA1-positive epithelial cells (59).

Another approach utilizes mice by transplanting non myelo-ablative MHC-matched; single Y chromosome-encoded, or multiple minor histocompatibility antigen-mismatched hematopoietic cells (52). Transplanting

allogeneic hematopoietic stem cells synergized with vaccination to cure prostate cancer (60). However, this approach is not well understood enough to be used as a method to treat solid tumors (60).

One report, which evaluated the role of genes on Y chromosome in human prostate cancer using athymic nude mice (61). Histidinol gene tagged Y chromosome was transferred into parental PC-3 cells lacking Y chromosome. TSA-FISH was able to detect Histidinol gene on the Y chromosome. Tumorigenicity of these PC-3 hybrids were evaluated *in vivo* and *in vitro*. PC-3 hybrid injected mice showed tumor growth in only one mouse; however, tumors grew in all mice injected with parental PC-3 cells. Results showed the addition of Y chromosome prevented tumor formation in athymic nude mice, and blocked tumorigenesis in-vitro (61).

5. SUMMARY AND CONCLUSIONS

Available studies suggest the involvement of the Y chromosome in contributing to the development of prostate cancer (Figure 1). Prostate cancer risk and susceptibility are associated with several epidemiological factors. Mutations on DYZ1 region of the Y chromosome can act as a marker for the disease (37, 41). Specific alleles found on the DYZ1 region were associated with an increased risk to prostate cancer while other alleles shown protective effects. Another abnormality seen in prostate cancer was LOY (39). LOY correlates with incidence of prostate cancer. The Y chromosome encodes for numerous genes associated with prostate cancer such as BPY2 and RPS4Y1 (48). These genes are upregulated during prostate cancer, associated with cell growth, and may contribute to tumor progression and metastasis. Other genes on the Y chromosome, specifically CDY1B, RB1, SFN and TNFRSF25 are downregulated in prostate cancer (48). These genes specifically reduce cell growth and promote apoptosis so the low expression may suppress prostate cancer progression. Silencing of KDM5D splice variants increased prostate cancer cell growth and reduced apoptosis in DU-145 cells (24). Furthermore, tumor suppressor effects on the Y chromosome revealed that genes; KDM5D and MSY act as tumor suppressors and are down regulated in metastatic prostate (50, 62).

Based on published research articles, Y chromosome mutations may play a significant role in prostate cancer progression. Once we have in-depth knowledge about the pathophysiology of the mutations, then we may have novel solutions to prevent or reverse these genetic alterations.

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