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Review

The Implication of X-Linked Genetic Polymorphisms in Susceptibility and Sexual Dimorphism of Cancer

CHAROULA ACHILLA[1], THEODOSIOS PAPAVRAMIDIS[2], LEFTERIS ANGELIS[3] and ANTHOULA CHATZIKYRIAKIDOU[1]

[1]Laboratory of Medical Biology - Genetics, Faculty of Medicine, School of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece;
[2]First Propedeutic Department of Surgery, AHEPA University Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece;
[3]School of Informatics, Aristotle University of Thessaloniki, Thessaloniki, Greece

Abstract. *The X-chromosome is implicated in cancer development through various mechanisms, including X-inactivation defects, loss of heterozygosity, and germline and somatic alterations of X-linked genes. Sex is a key factor which influences cancer susceptibility as many cancer types show sexual dimorphism in their incidence. The aim of this review was to summarize the germline genetic polymorphisms lying on the X-chromosome that have been associated with cancer susceptibility and to evaluate their possible implication in cancer-related sexual dimorphism. PubMed and Web of Science were searched using the terms "X-chromosome", "polymorphism" and "cancer". The literature review revealed 39 articles reporting 33 genetic variants in 22 X-linked genes as being associated with cancer risk. Most of these genes interact with each other in a direct or indirect way, as GeneMANIA software revealed, demonstrating the complication of the mechanisms through which they are involved in tumorigenesis. Polymorphisms in eight genes [androgen receptor (AR), fibroblast growth factor 13 (FGF13), forkhead box P3 (FOXP3), L1 cell adhesion molecule (L1CAM), nudix hydrolase 11 (NUDT11), Shroom family member 2 (SHROOM2), transcription elongation factor A-like 7 (TCEAL7) and TIMP metallopeptidase inhibitor 1 (TIMP1)] are reported to have a sex-specific association with cancer susceptibility, which might explain the sexual dimorphism of certain cancer types. All of the above eight mentioned genes, with the exception of L1CAM, exhibit differences in their expression pattern between breast tumor (sex-specific)/thyroid tumor (sex-influenced) vs. normal tissues according to our analysis using GENT2 software. Additionally, differences in breast or thyroid tumor compared with normal tissues were also observed in five genes analyzed with GENT2 software that were previously related to sex-influenced cancer according to literature. Finally, the present review points out the need for the development of appropriate free and user-friendly statistical software in order to reduce bias/errors in statistical analyses and overcome researchers' reluctance to include X-chromosome variants in their genetic-association studies.*

Correspondence to: Anthoula Chatzikyriakidou, Assist. Professor of Medical Biology-Genetics, Faculty of Medicine, School of Health Sciences, Aristotle University, Thessaloniki, Greece. Tel: +30 2310999013, e-mail: chatzikyra@auth.gr

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The diploid human genome consists of 22 pairs of autosomal chromosomes, which have the same morphology in males and females, and one pair of sex chromosomes (X, Y) that differs between sexes due to the presence of two copies of the X-chromosome in females and in a single copy in males. The Y-chromosome is smaller than the X, representing the 2-3% of the haploid genome, while the X-chromosome represents 5%. The X-chromosome contains approximately 1,500 genes, most of which have no partner on the Y-chromosome. Only a few genes, located in the pseudoautosomal regions of the X-chromosome show homology with the Y-chromosome (1, 2). To ensure equal dosage compensation between sexes, one of the two X-chromosomes in each somatic cell of female mammals is transcriptionally silenced during embryonic development. The X-chromosome inactivation is initiated in the future X-inactivation center, a specific site on the long arm of the X-chromosome that ensures that all but one X-chromosome per

diploid genome are inactivated. The whole process is regulated by the X-inactive-specific transcript (*Xist*) gene which is located in the X-inactivation center. The *Xist* gene encodes a long non-coding RNA that is expressed by the X-inactive chromosome and coats it *in cis*. A series of subsequent chromatin modifications, including hypoacetylation of histone H4, accumulation of trimethylated histone H3, K9, and K27, and accumulation of histone variant macroH2A on the X-inactive chromosome, trigger gene silencing. The inactive X-chromosome, also called a Barr body, then localizes to the nuclear periphery. The X-chromosome inactivation occurs randomly either of the maternal or paternal X-chromosome. Therefore, females are a mosaic of two cell populations in which either the maternal or paternal alleles of X-linked genes are expressed. However, over 15% of human X-linked genes escape X-chromosome inactivation and are expressed from both the active and inactive X-chromosomes. Most of these genes lie on the short arm of the X-chromosome and form clusters (3, 4).

The X-chromosome inactivation is related to cancer, as many studies have shown that the inactive X-chromosome is epigenetically unstable in cancer cells. Disappearance of the inactive X-chromosome has been observed in many cancer types and is often accompanied by duplication of the active X-chromosome, while there is evidence for de-condensation and sporadic reactivation of the inactive X-chromosome in cancer cell lines. Both mechanisms lead to overexpression of X-linked genes which may be associated with cancer development and progression (2, 3). Moreover, defects in X-inactivation are common in many malignancies including cancer. Skewed X-chromosome inactivation is a non-random process characterized by the preferential inactivation of one X-chromosome. This process can lead to the expression of recessive traits in females heterozygous for X-linked disorders. A high incidence of skewed X-chromosome inactivation has been reported in females with ovarian, breast and lung cancer, indicating the presence of tumor-related genes on the X-chromosome (5).

Furthermore, loss of heterozygosity (LOH) of X-linked genes is also a common occurrence in carcinogenesis. LOH of tumor-suppressor X-linked genes has been reported in sex-specific cancer such as breast, ovarian and prostate cancer. LOH at the active X-chromosome may lead to the complete loss of function of tumor-suppressor genes, increasing cancer development. LOH of tumor-suppressor X-linked genes has also been associated with tumor aggressiveness in gastroenteropancreatic endocrine tumours (2, 6).

Somatic and germline alterations of genes on sex chromosomes may play a conducive role in tumorigenesis. The X-chromosome carries a significant number of oncogenes, tumor-suppressor genes and tumor-antigen genes. Mutations or dysregulation of these genes might be putative mechanisms for cancer development.

Given the above, we aimed to summarize the polymorphisms of X-linked genes that have been associated with cancer and evaluate their possible implication in sex disparities observed in susceptibility to several types of cancer.

Methodology

PubMed and Web of Sciences databases were searched using the key words "X-chromosome", "polymorphism" and "cancer". Then the CancerGenetics web database (http://www.cancer-genetics.org) was used and genes associated with cancer in the articles retrieved by the database search were categorized by chromosome. Thereafter, only the genes located on the X-chromosome were selected and a new search for each gene and its genetic association with cancer susceptibility was then performed in PubMed and Web of Science. Thirty-nine articles corresponding to the study's scope of X-chromosome variants association with cancer susceptibility were published during the period 2005-2020.

Germline Genetic Polymorphisms on the X-Chromosome Involved in Cancer

Genetic variants of genes lying on the X-chromosome have been proposed as candidate factors for increasing cancer susceptibility in a growing number of studies. Table I summarizes the genetic polymorphisms on the X-chromosome that have been associated with cancer risk in case–control studies. Genetic variants which have been detected in patients with cancer and have not been studied in a control group were not included in this review, as their involvement in cancer susceptibility is not clear.

The X-chromosome can be divided into six different strata according to the probability of genes escaping inactivation. Strata 1 to 5 contain regions that have very low, low, moderate, high and highest probability of escaping X-chromosome inactivation, respectively. On the other hand, genes located on the pseudoautosomal regions 1 and 2 (PAR1 and PAR2) always escape X-chromosome inactivation (4). The genetic polymorphisms on the X-chromosome that are implicated in cancer susceptibility reviewed here are observed in genes located in PAR1 locus and in strata with very low, low, and high probability of escaping X-chromosome inactivation.

Genetic Polymorphisms of Genes Located in the PAR1

Cluster of differentiation 99 (CD99). CD99 gene is a protein-coding gene which is located in PAR1 of X- and Y-chromosomes and escapes X-chromosome inactivation. This gene encodes a cell-surface glycoprotein involved in leukocyte migration, transport of surface molecules, T-cell adhesion, differentiation and apoptosis (7-9). High *CD99* expression is a key clinical feature of patients with Ewing sarcoma (EWS) and is routinely used as a prognostic marker (10). Martinelli

et al. evaluated the single nucleotide polymorphism (SNP) rs311059 C>T in *CD99* gene as a predisposing factor for EWS in children in an Italian population. Rs311059 is a non-coding SNP, but it may increase *CD99* expression through affecting *CD99* epigenetic regulation mechanisms. Another *CD99* variant (rs312257) identified in the same study was associated with better event-free survival in EWS patients, but more studies are needed to validate this finding (11).

Genetic Polymorphisms in Genes With Very Low Probability of Escaping X-Chromosome Inactivation

Angiotensin II receptor type 2 gene (AGTR2). An increasing number of studies have shown that the components of the renin–angiotensin system play a role in tumorigenesis. Angiotensin II is the main effector of the renin–angiotensin system acting through G-protein-coupled receptors, type 1 (*AGTR1*) and type 2 (*AGTR2*). *AGTR2* protein promotes tumor development by enhancing both malignant cell proliferation and tumor angiogenesis in renal cell carcinoma, gastric cancer and breast cancer (12-14). On the other hand, *AGTR2* expression is inversely correlated with cell proliferation and migration in colorectal cancer (15). A genetic variant in the *AGTR2* gene, rs5194 G>A, has been associated with aldosterone-producing adenoma. This SNP is located in the 3'-untranslated region (UTR) of the *AGTR2* gene. The risky A-allele may enhance the binding of *AGTR2* mRNA to micro-RNAs and lead to down-regulation of *AGTR2* mRNA, which may stimulate hyperplasia and overgrowth of adrenal cortical cells in patients with aldosterone-producing adenoma (16).

Androgen receptor (AR). Extensive evidence has highlighted the role of this gene in cancer susceptibility. This gene codes for AR, a steroid hormone receptor that acts as a transcriptional factor in androgen signaling. Up-regulation of the *AR* gene promotes tumorigenesis in many cancer types, including prostate, bladder, kidney cancer, lung, breast and liver cancer but its role in cancer metastasis is contradictory, acting either as a suppressor or stimulator (17). A trinucleotide cytosine-adenine-guanine (CAG) repeat expansion in exon 1 of the *AR* gene has been associated with cancer risk in different populations. Specifically, the CAG length is inversely correlated with transcriptional activity of the *AR* gene, meaning that short CAG repeats might promote tumorigenesis. These CAG repeats might serve as a biomarker of prostate cancer predisposition, especially in Asians and Caucasians, as carriers of short CAG repeat expansions have increased susceptibility to prostate cancer (18, 19).

Furthermore, a meta-analysis revealed short CAG repeat length to be associated with ovarian cancer risk in African Americans and Chinese, whereas the reverse association was observed in Caucasians and Italians, again, more studies are needed to validate these results (20). Moreover, a meta-analysis implicated CAG repeats in predisposition to breast cancer, with long CAG repeats increasing the risk of breast cancer in Caucasian women (21). Regarding CAG repeats in colorectal cancer, the findings are inconsistent, as long CAG repeats were associated with higher colorectal cancer risk in one study (22) and with increased colon cancer risk only in males (23), whereas no association between CAG repeats and colorectal cancer was revealed in another study (24).

In addition, exon 1 of the *AR* gene contains also a GGN microsatellite repeat polymorphism, the length of which varies among different populations. Short GGN repeat length has been reported to enhance *AR* expression (25). The association of this polymorphism with prostate cancer risk is unclear, as the results of two meta-analyses are contradictive. One study demonstrated that short GGN repeat length was associated with increased risk of prostate cancer, especially in Caucasians (19), while another meta-analysis revealed no association between GGN repeat length and prostate cancer susceptibility (26).

Glypican 3 (GPC3) and GPC4. Genetic polymorphisms in *GPC3* and *GPC4* have also been related to cancer susceptibility. These genes encode the GPC3 and GPC4 heparan sulfate proteoglycans involved in proliferation, migration, and cell survival modulation in several tissues. *GPC3* gene has controversial roles in cancer development, acting either as a tumor-suppressor gene in breast cancer, mesothelioma and ovarian cancer, or as an oncogene in other cancer types such as hepatocellular carcinoma (HCC), colorectal cancer, melanoma, Wilms tumor, neuroblastoma and salivary gland tumors (27, 28). A genetic polymorphism (rs2267531 G>C) in the promoter region of *GPC3* was associated with HCC in Egyptians. The risky allele C was found at a significantly higher frequency in patients with HCC compared to the control group and the C allele was correlated with higher *GPC3* gene expression (28).

Another member of the glypican gene family, the *GPC4* gene, is also involved in cancer risk. The SNP rs1048369 C>T of *GPC4* leads to the coding amino acid Ala-Val (p.Ala442Val) mutation and its relationship with cancer susceptibility was studied in Chinese populations. The T-allele of rs1048369 was proposed as risk factor for Epstein–Barr virus-associated gastric cancer by influencing WNT signaling (29), while the C-allele was significantly more frequent in patients with Epstein–Barr virus-positive nasopharyngeal carcinoma (NPC) (30). This difference may be attributed to the different interaction of Epstein–Barr virus with GPC4 in different cancer types; the exact mechanism needs further investigation (30).

Interleukin-1 receptor-associated kinase 1 (IRAK1). IRAKs constitute a family of serine-threonine kinases involved in the signaling cascades of toll-like receptors (TLRs) and

Table I. *Genetic polymorphisms of X-chromosomal genes associated with cancer susceptibility.*

XCI	Gene	Location	Role (derived from http://www.tumorportal.org)	Polymorphism	Risky allele	Cancer type	Population	Ref
PAR1 (escape)	*CD99*	Xp22.33 and Yp11.2	Involved in leukocyte migration, T-cell adhesion, ganglioside GM1 and transmembrane protein transport, T-cell death by a caspase-independent pathway, rearrangement of the actin cytoskeleton.	rs311059 C>T	T	Ewing's sarcoma	Caucasian	11
Very low probability of escape	*AGTR2*	Xq23	Receptor for angiotensin II, programmed cell death mediation	rs5194 G>A	A	Adrenocortical*	Asian	16
	AR	Xq12	Steroid hormone receptor steroid acting as a transcriptional factor, involved in regulation of cell proliferation, motility, and apoptosis	CAG microsatellite	Short repeats	Prostate	Asian/Caucasian	18, 19
					Short repeats	Ovarian	AfricanAmerican/Asian Caucasian	20
					Long repeats			
					Long repeats	Breast	Caucasian	21
					Long repeats	Colorectal	Asian	22
					Long repeats		Caucasian/African American/Hispanic/ Asian/American Indian and Alaska Native	23
	GPC3	Xq26.2	Cell surface heparan sulfate proteoglycans, control of cell division and growth regulation	rs2267531 G>C	C	HCC	Egyptian	28
	GPC4			rs1048369 C>T	T	Gastric	Asian	29
					C	NPC	Asian	30
	IRAK1	Xq28	Serine/threonine kinase, IL1-induced NF-κB activation	rs3027898 C>A	A	Thyroid	Caucasian	32
	L1CAM	Xq28	Neuronal cell adhesion molecule, involved in neuronal migration and differentiation	rs4646263 C>A	A	Ovarian	Caucasian	40
	MAGEA1	Xq28	Cancer-testis antigens	rs3788749 C>T	T	Rectal	Asian	42
	MAGEA11			rs6641352 T>C	C	Renal cell	Asian	43
				rs6540341 C>T	T			
	PSMD10	Xq22.3	Regulatory component of the 26S proteasome, involved in cellular growth, proliferation and invasion	rs111638916 G>A	A	Gastric	Asian	48
	TCEAL7	Xq22.2	Transcriptional repressor of NF-κB signaling	rs5987515 T>A,G	T	Ovarian	Caucasian/African American/Hispanic/ Native American/ Asian/other	50
				rs5987724 A>C	A			
				rs5945971 T>C	T			
	XIAP	Xq25	Apoptosis inhibition	rs8371 C>T	C	ESCC	Asian	56
Low probability of escape	*F9*	Xq27.1	Plasma serine protease involved in blood coagulation	rs371000 C>T	T	NPC	Asian	57
	FGF13	Xq27.1	Involved in embryonic development, cell growth, morphogenesis, tissue repair, tumor growth and invasion	rs619373 G>A	A	Breast	Caucasian (European BRCA2+)	63
	FOXP3	Xp11.23	Involved in regulation, activation and differentiation of T-cells	rs3761548 C>A	A	Colorectal	Asian	71
					A	Lung	Asian	70
					A	Thyroid	Asian	72
					C	Endometrial	Asian	73
				rs5902434 (del/ATT)	del			
				rs2294021 C>T	CT heterozygosity	Breast	Asian	68
				rs2280883 T>C	T	Thyroid	Asian	72

Table I. *Continued*

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XCI	Gene	Location	Role (derived from http://www.tumorportal.org)	Polymorphism	Risky allele	Cancer type	Population	Ref
					T	HCC	Asian	66
					T	Lung	Iranian	76
				rs3761549 C>T	C	HCC	Asian	70
					T	Lung	Asian	76
	MAOA	Xp11.3	Mitochondrial enzyme, oxidative deamination of amines catalyzation	rs144551722 G>A	A	Glioblastoma	Caucasian	79
	NUDT10-NUDT11	Xp11.22	Involved in vesicle trafficking, maintenance of cell wall integrity, and mediation of cellular stress responses	rs5945572 A>G	A	Prostate	Caucasian, Asian, African	81
							Caucasian	82
				rs5945619 C>A,T	C	Prostate	Caucasian	85
							Jewish	84
							African	83
	TIMP1	Xp11.3	Inhibitor of the matrix metalloproteinases, promotes cell proliferation, anti-apoptotic function	rs4898 T>C	C	Breast	Asian	87
						Lung	Asian	88
High probability of escape	*ARHGAP6*	Xp22.2	Implication in regulation of actin polymerization at the plasma membrane during several cellular processes	rs5933886 C>T	C	NPC	Asian	57
	DMD	Xp21.1	Part of the dystrophin-glycoprotein complex, which bridges the inner cytoskeleton (F-actin) and the extracellular matrix	rs5927056 T>G	T	NPC	Asian	57
	SHROOM2	Xp22.2	Implication in endothelial sprouting, migration, and angiogenesis	rs5934683 T>C	T	Colorectal	Caucasian	93
				rs2405942 A>G	G	Prostate	Caucasian	95
	TLR7	Xp22.2	Involved in pathogen recognition and activation of innate immunity	rs179008 A>T	A	Hodgkin's disease	Caucasian/other	97
				rs179019 A>C	C	Urinary bladder	Asian	96

AGTR2: Angiotensin II receptor type 2; *AR*: androgen receptor; *ARHGAP6*: Ras homolog GTPase-activating protein 6; *BRCA2*: BRCA2 DNA repair-associated; *DMD*: Duchenne muscular dystrophy; ESCC: esophageal squamous cell carcinoma; *F9*: factor 9; *FGF13*: fibroblast growth factor 13; *FOXP3*: forkhead box P3; *GPC3*: glypican 3; *GPC4*: glypican 4; HCC: hepatocellular carcinoma; *IRAK1*: interleukin-1 receptor-associated kinase 1; *L1CAM*: L1 cell adhesion molecule; *MAGEA1*: melanoma antigen gene A1; *MAGEA11*: melanoma antigen gene A11; *MAOA*: monoamine oxidase-A; NFκB: nuclear factor kappa B; NPC: nasopharyngeal carcinoma; *NUDT10*: nudix hydrolase 10; *NUDT11*: nudix hydrolase 11; PAR1: pseudoautosomal region 1; *PSMD10*: proteasome 26S subunit non-ATPase 10; *SHROOM2*: Shroom family member 2; *TCEAL7*: transcription elongation factor A-like 7; *TIMP1*: tissue inhibitor matrix metalloproteinase 1; *TLR7*: toll-like receptor 7; XCI: X-chromosome inactivation; *XIAP*: X-linked inhibitor of apoptosis protein. *Aldosterone-producing adenoma.

interleukin-1 receptors. The first member of the family, *IRAK1*, has a crucial role in cancer, as its expression is elevated in many solid tumor types and hematological malignancies and is often correlated with metastasis or poor prognosis (31, 32). A recent study in a Greek population correlated the genetic polymorphism rs3027898 C>A, in the 3′-UTR of *IRAK1* with papillary thyroid cancer (PTC) risk. The frequency of the minor allele A was higher in patients with PTC compared to controls, and after adjusting for sex, the A-allele was found to be the risky allele only in men, suggesting a possible role of rs3027898 in PTC development (32). The same polymorphism was also associated with autoimmune diseases in a large number of studies (33-36).

L1 cell-adhesion molecule (L1CAM). A key factor in tumorigenesis in many cancer types, this gene encodes *L1CAM* transmembrane protein, which is a neuronal cell adhesion molecule involved in cell migration, adhesion and differentiation (37). *L1CAM* gene has a significant role in cancer initiation and progression, as alterations in its expression can affect cancer cell migration, invasion, growth and metastasis (38, 39). An *L1CAM* intron SNP, rs4646263

C>A, was associated with susceptibility for epithelial ovarian cancer. Carriers of the AA genotype were at higher risk of developing epithelial ovarian cancer but the mechanism involved remains unclear (40).

Melanoma antigen gene A1 (MAGEA1) and MAGEA11. The *MAGE* gene family is a known for its role in cancer as its members are tumor biomarkers and targets of immunotherapies. Type I MAGEs (MAGEA, -B, and -C subfamily members) are cancer testis antigens located on the X-chromosome and involved in cancer immunity (41). Genetic association between MAGEs and cancer susceptibility was revealed in two case–control studies. In the first study, the minor T-allele of the rs3788749 SNP on *MAGEA1* was more frequent in patients with colorectal cancer and when tumor location was taken into account, this correlation was observed only in patients with rectal cancer. Thus, the rs3788749 C>T polymorphism was proposed as a rectal cancer biomarker, since the T-allele seems to increase *MAGEA1* gene expression through its independent functioning as a binding site for transcription factors (42).

The second study identified an association between two intronic SNPs (rs6641352 T>C and rs6540341 C>T) on *MAGEA11* gene and renal cell carcinoma (RCC) risk. Carriers of the minor alleles of these SNPs, C and T, respectively, showed increased susceptibility to RCC compared to those homozygous for the major alleles, indicating a possible contribution of these two SNPs to RCC development (43).

Proteasome 26S subunit non-ATPase 10 (PSMD10). PSMD10, encoding the enzyme also known as gankyrin, is a component of the 19S regulatory cap of the 26S proteasome which is involved in diverse biological processes, including cellular growth, proliferation, and invasion. Several studies have reported that *PSMD10* gene is up-regulated in a variety of cancer types and have established its role as a candidate oncogene and a tumor biomarker (44-47). Liu *et al*. investigated the involvement of a SNP located in the 3′UTR of *PSMD10* gene (rs111638916 G>A) in gastric cancer development. They concluded that the minor A-allele of rs111638916 may act as a tumor-promoting factor and increase gastric cancer risk through affecting post-transcriptional regulation of *PSMD10* mRNA by *miR-505*. Carriers of the GA and AA genotypes had also larger tumor size and higher risk of metastasis, suggesting an association between the rs111638916 SNP and clinical features of gastric cancer (48).

Transcription elongation factor A-like 7 (TCEAL7). This gene codes for the cell death-regulatory protein TCEAL7, which acts as a transcriptional repressor of nuclear factor-kappa-B signaling. It has been reported that the *TCEAL7* gene is down-regulated in ovarian, breast, brain, prostate, non-small-cell lung and gastric cancer, as well as glioblastoma, and may function as a tumor-suppressor gene (49). In a case–control study, Peedicayil *et al*. reported three SNPs (rs5987515, rs5987724, rs5945971) upstream of the *TCEAL7* gene that may affect ovarian cancer susceptibility. They found that the minor alleles of these SNPs were significantly associated with reduced risk of invasive serous ovarian cancer, and therefore they may have a role in the development of this cancer type (50).

X-linked inhibitor of apoptosis protein (XIAP). Genes of the XIAP apoptotic signaling pathways are also implicated in tumorigenesis. *XIAP* inhibits cell death mainly through blocking apoptosis. Overexpression of *XIAP* has been validated in many cancer types and has been linked to cancer development and poor prognosis (51-55). Furthermore, SNP rs8371 C>T in the 3'-UTR of the *XIAP* gene was associated with esophageal squamous cell carcinoma susceptibility in a Chinese case–control study. The T-allele was observed at lower frequencies in patients compared to the control group, suggesting its protective role in susceptibility (56).

Genetic Polymorphisms in Genes With a Low Probability of Escaping X-Chromosome Inactivation

Factor 9 gene (F9). An X chromosome-wide association study for SNPs in a Chinese population (57) revealed genetic association of *F9* with NPC risk, which was validated in Taiwanese (58) and Malaysian replication cohorts (59, 60). This gene encodes factor IX protein, a plasma serine protease which circulates as a zymogen and is involved in blood coagulation (61). Combined analysis of the three population groups revealed that an intron *F9* polymorphism, rs371000 C>T, was associated with NPC risk only in males (57).

Fibroblast growth factor 13 (FGF13). The FGF gene family has a crucial role in regulating cellular proliferation, migration, and differentiation. FGF13 protein has an oncogenic activity, as its overexpression is involved in tumor development and progression in many cancer types, including pancreatic endocrine carcinoma, melanoma, multiple myeloma and lung cancer (62). Furthermore, in a genome-wide association study, the intron *FGF13* rs619373 G>A variant was associated with increased breast cancer risk in BRCA2 DNA repair-associated (*BRCA2*) mutation carriers, with the A-allele being the risky variant (63).

Forkhead box P3 (FOXP3). *FOXP3* encodes a transcription factor involved in regulation, activation, and differentiation of T-cells. Alterations in *FOXP3* expression were found in autoimmune diseases, benign tumors, and carcinomas. *FOXP3* is up-regulated in colorectal cancer, non-small lung cancer, thyroid cancer, melanoma and cervical cancer. On the other

hand, high levels of FOXP3 are associated with good prognosis in breast, prostate and gastric cancer (64). The association of two *FOXP3* promoter polymorphisms, rs3761549 C>T and rs3761548 C>A, with cancer susceptibility has been investigated in many studies in Asian populations but the results were conflicting (65-69). However, a meta-analysis of these studies revealed the rs3761549 (C>T) and rs3761548 (C>A) polymorphisms not to be associated with the risk of breast cancer but with the risk of HCC and non-small-cell lung cancer, respectively (70). Additional studies indicated that the minor A-allele of rs3761548 is a risk factor for colorectal cancer and differentiated thyroid cancer (71, 72), while it is related to lower risk of endometrial cancer (73). Moreover, the same allele was associated with autoimmune diseases susceptibility (74, 75). Regarding the rs3761549 polymorphism, although the major C-allele has been associated with HCC risk, a study in an Iranian population revealed a possible involvement of the T-allele in susceptibility to lung cancer (76). These results might be explained by the dual role of *FOXP3* gene in carcinogenesis, acting either as a transcriptional activator or repressor (73, 76). Another *FOXP3* promoter polymorphism, rs5902434 (del/ATT), and especially the ATT/ATT genotype, may act as a protective factor reducing endometrial cancer risk in Chinese women (73). The same polymorphism has also been associated with low risk of recurrent respiratory papillomatosis, a benign neoplasm of the larynx and trachea (77). Additionally, the intron *FOXP3* rs220883 T>C polymorphism appeared to reduce the risk of differentiated thyroid cancer (C-allele) (72) and to increase the susceptibility to hepatitis B-related HCC and small-cell lung cancer (T-allele) (66, 76). Finally, the heterozygous genotype of the intronic rs2294021 C>T polymorphism was reported to interact with skewed X-chromosome inactivation and elevate breast cancer predisposition by breaking the balance between FOXP3-controlled immune tolerance and tumor suppression (68).

Monoamine oxidase-A (MAOA). This gene encodes the mitochondrial enzyme which degrades monoamine neurotransmitters, such as serotonin and norepinephrine, by the production of hydrogen peroxide. Previous studies have documented that up-regulation of the *MAOA* gene promotes cancer development and progression in prostate cancer, renal cell carcinoma, classical Hodgkin lymphomas, glioma and non-small cell lung cancer, while reduced *MAOA* levels may serve as a biomarker for cholangioma and HCC prognosis (78). A recent study proposed the rs144551722 G>A polymorphism, which lies in the promoter region of the *MAOA* gene, as a predictive biomarker for glioblastoma in males (79).

Nudix hydrolase 10 (NUDT10) and NUDT11. NUDT10 and *NUDT11* genes encode two diphosphoinositol polyphosphate phosphohydrolases involved in a variety of biological processes, including vesicle trafficking, maintenance of cell wall integrity, and mediation of cellular stress responses (80). A meta-analysis assessed that a *NUDT10 -NUDT11* intergenic polymorphism, rs5945572, is associated with prostate cancer susceptibility. More specifically, the minor G-allele of rs5945572 increases prostate cancer susceptibility and may promote prostate carcinogenesis *via* multiple signaling pathways (81). This association was confirmed not only in patients with sporadic, but also in those with hereditary prostate cancer (82). Another SNP in the same genetic region, rs5945619, was also reported to be associated with prostate cancer risk in several studies, suggesting a significant role of the *NUDT10-NUDT11* intergenic region in prostate cancer susceptibility (83-85).

Tissue inhibitor matrix metalloproteinase 1 (TIMP1). TIMP1 gene inhibits the proteolytic activity of matrix metalloproteinases and is involved in cell proliferation and anti-apoptotic activity. *TIMP1* overexpression is associated with cancer progression and poor patient prognosis in papillary thyroid carcinoma, cutaneous melanoma, and gastric, breast, lung and colorectal cancer (86). The rs4898 T>C *TIMP1* missense variant has been proposed as a predictive marker for breast and lung cancer, as the C-allelic frequency was increased in patients of both cancer types compared to controls in a Taiwanese population (87, 88). After adjusting for gender, the distribution of rs4898 genotypes did not differ significantly between males and females, so this polymorphism was reported not to contribute to the sex disparities in lung cancer susceptibility (88).

Genetic Polymorphisms in Genes With a High Probability of Escaping X-Chromosome Inactivation

Ras homolog GTPase-activating protein 6 (ARHGAP6). ARHGAP6 is a novel protein involved in regulation of actin polymerization in several cellular processes. It has been reported in *in vitro* and *in vivo* studies that ARHGAP6 has an inhibitory effect on the cell growth and metastasis of cervical carcinoma and lung cancer (89, 90) and might serve as a biomarker for colorectal cancer development and progression (91). An intron SNP on *ARHGAP6* gene (rs5933886) showed correlation to NPC predisposition, but only in females (57).

Duchenne muscular dystrophy (DMD). This gene is the largest human gene and codes for dystrophin protein, which is part of a protein complex that links the intracellular cytoskeleton network to the extracellular matrix. *DMD* dysregulation is involved in the pathogenesis of sarcoma, leukemia, lymphoma, melanoma, carcinoma and nervous system cancer (92). In an X-chromosome-wide association study, the intron SNP rs5927056 T>G on the *DMD* gene was associated with NPC susceptibility, with the minor G allele

to be the risky variant. This polymorphism might alter regulatory motifs and affect *DMD* expression and thus contribute to NPC predisposition (57).

Shroom family member 2 (SHROOM2). A meta-analysis of five genome-wide association studies revealed an association of the rs5934683 polymorphism in the promoter region of the *SHROOM2* gene with colorectal cancer susceptibility (93). The *SHROOM2* gene is involved in endothelial sprouting, migration, and angiogenesis. The *SHROOM2* gene is implicated in carcinogenesis of esophageal squamous cell carcinoma and NPC, acting as a tumor-suppressor gene (94). Moreover, a meta-analysis identified a correlation between the *SHROOM* intron SNP rs2405942 A>G and prostate cancer risk, which was then confirmed in the replication stage of the same study (95). However, an association study by Cremers *et al.* did not validate this finding (82).

Toll-like receptor 7 (TLR7). This gene encodes an endosomal receptor that has a key role in innate and adaptive immunity. This protein has been studied due to its immunostimulatory action that can be used in antitumor therapy (96). The rs179008 A>T *TLR7* polymorphism has been proposed to have a protective effect on the risk of Hodgkin disease in individuals carrying the minor T-allele (97). Another *TLR7* SNP, rs179019 A>C, has been associated with increased susceptibility to urinary bladder cancer (UBC) in males, but more studies are needed to confirm this finding (96). This polymorphism has also been proposed as a predisposing factor for systemic lupus erythematosus (98, 99).

Interaction Between Genes Involved in Cancer Susceptibility

The study of the interactions among the genes described above may provide a better overview of their implication in cancer susceptibility. GeneMANIA (http://genemania.org) is a flexible user-friendly web site for generating hypotheses about gene function, analyzing gene lists and prioritizing genes for functional assays. The 22 corresponding genes from Table I were submitted to GeneMANIA and their interaction network is shown in Figure 1. The interaction network shows direct and indirect interactions among the 22 genes (co-expression, shared protein domains, co-localization, pathway, and predicted interactions). Co-expression means that two genes are linked if their expression levels are similar across conditions in a gene-expression study. Shared protein domains are a protein interaction type in which the genes are linked because their protein products have the same protein domain. Moreover, two genes are considered to be 'linked' if they are both expressed in the same tissue or identified in the same cellular location (co-localization) or if their products participate in the same reaction within a pathway (pathway). Finally, the interaction network shows the predicted functional relationships between genes, which may be protein interactions.

In detail, *CD99* shows similar expression level to *IRAK1*, *TIMP1* and *GPC4,* and has the same protein domain and predicted interaction with *IRAK1*. Regarding the heparan sulfate proteoglycans *GPC3* and *GPC4*, *GPC3* has a similar expression level to *DMD*, *SHROOM2*, *MAGEA1* and *MAOA*, while *GPC4* shows co-expression with *CD99* and *DMD*. *GPC3* and *GPC4* also share the same protein domain. *AR* is co-expressed with *DMD* and participates in the same pathway with *F9*. *SHROOM2* has similar expression levels to *GPC3* and *MAOA* and the same protein location as *MAGEA1*. Furthermore, *MAGEA1* and *MAGEA11* are co-expressed and share the same protein domain, while *MAGEA1* also has the same protein location as *SHROOM2* and *L1CAM*. Co-expression is also observed between *XIAP* and *PMSD10*. Moreover, *IRAK1* participates in the same pathway as *TLR7* and has predicted interaction with *XIAP*. From the remaining genes, *FOXP3, TCEAL7* and *NUTD11* show only indirect interactions in the network, while *FGF13*, *AGTR2* and *ARHGAP6* have neither direct nor indirect interactions (Figure 1).

The multiple interactions among the 22 genes described in Table I demonstrate the complicated way in which these genes are involved in cancer susceptibility and illustrate that these genes may contribute to tumorigenesis through their interplay. A gene polymorphism may not contribute to cancer susceptibility directly, but it is possible that it can affect cancer development, indirectly affecting expression of other genes. Specifically, alterations in gene expression caused by a polymorphism can affect the expression of other genes participating in the same pathway or alter the balance among genes that are co-expressed, promoting tumorigenesis, Moreover, a combination of genetic variants in genes that interact with each other may promote tumorigenesis. Taking into account that most of these genes are located in regions with low or very low probability of escaping X-chromosome inactivation, random or skewed X-chromosome inactivation events further complicate the understanding of the mechanisms involved in cancer development.

Sexual Dimorphism in Cancer

Sex is a significant factor that affects the incidence, progression and treatment responses of various diseases including cancer. Sex disparities have been observed not only in sex-specific cancer, but also in a variety of other cancer types. Generally, there is a male predominance in cancer susceptibility for many cancer types, such as hematological malignancies, head and neck squamous cell cancer, and esophageal, urinary bladder and liver cancer. On the other hand, females have an increased risk of developing thyroid, gallbladder, biliary tract and anal cancer (100). Sex disparities in cancer susceptibility are believed to be the result of both physiological and genomic differences between the sexes (101).

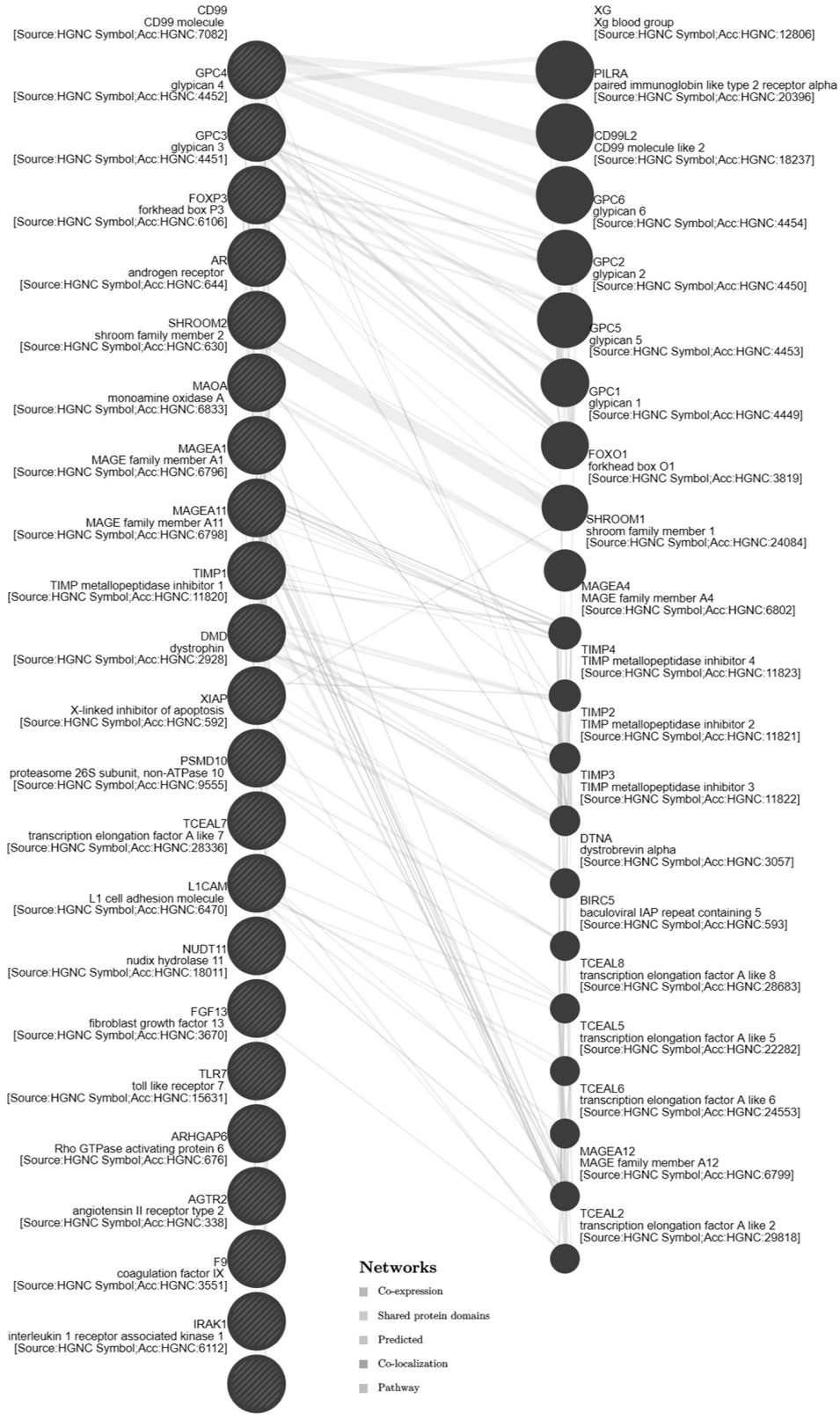

Figure 1. *Interaction network of the 22 X-chromosome-linked genes (left column), the polymorphisms of which are involved in cancer susceptibility. The right column shows other genes which participate in the indirect interactions among the 22 X-linked genes (http://genemania.org).*

Physiological differences. The main reason for the physiological differences leading to different cancer susceptibility between males and females is sex hormones. Sex steroid hormones derive from cholesterol and include the androgens (testosterone), estrogens (17β-estradiol, estriol, and estrone) and progestogens. Sex hormones act through four types of receptors: the estrogen receptors *ERα*, *ERβ* and G protein-coupled estrogen receptor 1 (*GPER1*), and the *AR*. By binding to these receptors, sex hormones are involved in cell-signaling pathways affecting cancer susceptibility through various mechanisms (101). Most of these mechanisms influence immune surveillance, cancer stem cell self-renewal, the tumor microenvironment, and the regulation of systemic metabolism. In many cancer types, such as head and neck squamous cell carcinoma, colonic, glioma, skin, esophageal and non-small-cell lung cancer, significant differences in incidence are observed when comparing males or postmenopausal females with premenopausal females, suggesting a mechanism of sex hormone-mediated tumor development (102). Sex hormone signaling often has controversial roles in regulating cancer development. For example, estrogen signaling has a protective role in HCC, reducing the cancer risk in females, while in many other cancer types, such as of the breast and the female reproductive system, it promotes carcinogenesis (103). Moreover, studies have shown that sex-related hormones, such as prolactin, gonadotropins (Luteinizing hormone and Follicle stimulation hormone) and gonadotropin-releasing hormone have a role in tumor development in prostate, ovarian and breast cancer (102).

Genomic differences. The main reason for the genomic differences in cancer susceptibility between sexes is the sex chromosomes. As described previously, the X-chromosome carries a significant number of genes involved in tumorigenesis. The presence of these genes in a single copy in males and in two copies in females, in combination with random, skewed or escaping X-chromosome inactivation events and LOH in females, is a mechanism that explains the differences in cancer predisposition between sexes. Alterations on the Y-chromosome, sex-specific expression of protein-coding genes and micro-RNAs, and differences in epigenetic profiles of autosomal and sex chromosome genes can also alter the cancer incidence rate between males and females (101). This part of the review focuses on the possible implication of genetic polymorphisms on the X-chromosome, described above, in sex disparities in cancer susceptibility.

Polymorphisms on the X-chromosome and sex disparities in cancer susceptibility. Polymorphisms in eight genes (*AR*, *FGF13*, *FOXP3*, *L1CAM*, *NUDT11*, *SHROOM*, *TCEAL7, TIMP1*) described in Table I were associated with sex-specific cancer, such as prostate cancer in males, and breast or ovarian cancer in females (referred to as sex-restricted in Table II).

Table II. *Differences in expression profiles of X-chromosome genes associated with cancer between normal and breast or thyroid tumor tissues (http://gent2.appex.kr).*

Gene	Association with cancer type	*p*-Value	
		Breast	Thyroid
AR	Sex-restricted	**<0.001**	**<0.001**
FGF13	Sex-restricted	**<0.001**	**<0.001**
L1CAM	Sex-restricted	0.841	0.331
NUDT11	Sex-restricted	**<0.001**	0.565
SHROOM2	Sex-restricted	**<0.001**	**0.002**
TCEAL7	Sex-restricted	**<0.001**	**<0.001**
TIMP1	Sex-restricted	**<0.001**	0.477
FOXP3	Sex-restricted, sex-influenced	**<0.001**	**0.006**
IRAK1	Sex-influenced	**<0.001**	0.751
TLR7	Sex-influenced	**<0.001**	**<0.001**
MAGEA11	Sex-influenced	0.998	0.297
F9	Sex-influenced	**<0.001**	0.136
ARHGAP6	Sex-influenced	**<0.001**	**<0.001**
MAOA	Sex-influenced	**<0.001**	**<0.001**

See Table I for gene descriptions. Statistically significant *p*-values are shown in bold.

As far as sex-influenced cancer, Jiang *et al*. reported that the frequency of the AA or AC *ge*notypes of the *FOXP3* rs3761548 (C>A) polymorphism was increased in females compared to males. These genotypes were associated with differentiated thyroid cancer risk (72). Taking into account that thyroid cancer incidence has a male to female ratio of 1:4 (100), rs3761548 may explain the increased incidence of thyroid cancer in females. Moreover, the rs3027898 risky A-allele on the *IRAK1* gene was correlated with PTC risk in males. In male controls, the major rs3027898 C-allele was more frequent compared to in females, leading to high *IRAK1* expression, which may act as a protective factor for PTC in males (32).

Another SNP, rs179019, on the *TLR7* gene may increase UBC susceptibility in males. In females, no significant difference in the allelic frequency for rs179019 was observed between patients with UBC and the control group (96). As UBC has higher prevalence in males compared to females, with a male to female ratio of 4:1 (96), it is of great importance to investigate the possible role of the rs179019 polymorphism in increasing UBC risk in males.

Furthermore, two other polymorphisms of the *MAGEA11* gene (rs6641352 T>C and rs6540341 C>T) were associated with RCC risk in the overall population and after performing gender-stratified analysis, rs6641352 showed stronger association with RCC in males, in contrast to rs6540341 in females (43). RCC frequency did not differ much between sexes (male to female ratio 1.5:1) (43), therefore more studies are needed to confirm these findings and clarify how these polymorphisms contribute to RCC cancer risk in the two sexes.

Additionally, the study of Zuo *et al*. revealed two X-linked SNPs, rs371000 C>T on the *F9* gene and rs5933886 on the *ARHGAP6* gene to be associated with NPC susceptibility. The rs371000 polymorphism was shown to increase risk of NPC only in males, while rs5933886 had a protective effect on NPC risk in females. Given that there is a male predominance in NPC incidence (male to female ratio of 2-3:1), these polymorphisms may contribute to the gender disparities in NPC susceptibility (57).

Finally, the rs144551722 G>A polymorphism on the *MAOA* gene was associated with glioblastoma risk only in males. As glioma is more common in males compared to females (male to female ratio 1.4:1), this SNP might have a role in the differences observed in glioma risk between sexes (79).

A confirmation of the sex-associated involvement of the above reviewed genetic polymorphisms in cancer susceptibility may be indirectly derived from studying gene expression in normal compared to certain tumor tissues. Taking as examples breast cancer and thyroid cancer, a female-specific cancer and a cancer with high female to male incidence ratio, respectively, the expression levels of the sex-influenced and sex-restricted genes described above were studied in breast and thyroid cancer. Specifically, for this analysis the GENT2 database (http://gent2.appex.kr) was used, which is a platform for exploring gene-expression patterns across normal and tumor tissues. Most of these genes have significantly altered expression in breast or thyroid tumor compared with normal tissues as shown in Table II. Thus, this finding may enforce the association of some of the genes discussed above with sex-limited or sex-influenced cancer types.

Statistical Analysis of X-Chromosome Genetic Association Studies

In case–control genetic association studies, many statistical methods for testing the association between autosomal markers and phenotype have successfully been established. However, due to the different inheritance patterns of X-chromosome-linked traits and the X-chromosome inactivation process, there is a lack of statistical tools for handling X-chromosome genotypic data. As a result, in most studies, the X-chromosomal variants are either incorrectly analyzed or completely excluded from analysis. Recently, many statistical models for testing X-chromosomal associations have been developed. Zheng *et al*. proposed several approaches for analyzing X-chromosomal variants (104) and Clayton was the first who incorporated the random X-inactivation process in X-chromosome data analysis (105). Other methods have taken into account the different patterns of X-chromosome inactivation and the deviations from Hardy–Weinberg equilibrium (106). Different methods for testing Hardy–Weinberg equilibrium on the X-chromosome have also been developed (107). In addition, Gao *et al*. introduced the XWAS software toolset, which facilitates the integration of X-chromosome data in genome-wide association studies, combining several previously proposed statistical models (108). However, this software does not incorporate the skewed X-chromosome inactivation pattern.

Even though there are efforts to reduce mistakes in X-chromosome genetic association studies, it is obvious that there is a lack of a standardized, complete, and user-friendly method to analyze X-chromosome genomic data. Therefore, current genetic association studies of X-chromosome-linked variants may have bias or errors in their analyses or may conceal the reluctance of researchers to include X-chromosome variants in their studies.

Conclusion

In summary, this study reviewed genetic polymorphisms on the X chromosome that affect cancer susceptibility. Some of these polymorphisms have a sex-specific association with cancer risk. This suggests that the X-chromosome may have different genetic effects on the two sexes, which may partly explain the sexual dimorphism observed in the incidence of many cancer types. It is of primary importance to point out that the statistical analysis of the X-chromosome genotype–phenotype associations is susceptible to bias due to the presence of a single allele in males and non-random, skewed or escaping X-chromosome inactivation events in females. The genes highlighted in this review are located in different regions regarding the X-chromosome inactivation process, with most genes having a high probability of becoming inactivated and fewer genes escaping inactivation. Considering that there is a lack of available tools for analyzing X-chromosome genotypic data and taking into account the specific traits of the X-chromosome inactivation process and inheritance, the need for the development of appropriate free and user-friendly statistical software in order to reduce bias or errors in the resultant associations is great.

Conflicts of Interest

None declared.

Authors' Contributions

CA and AC were responsible for conducting the literature research, extracting, and analyzing data, interpreting results and writing the review. AC, TP and LA reviewed the article.

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