The landscape of 8q24 cytoband in gastric cancer (Review)

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Abstract. Worldwide, gastric cancer (GC) is estimated to be the fifth most common type of cancer type in both sexes, ranking sixth for new cases, with >640,850 cases per year, and fourth in terms of mortality rate. Cancer presents numerical and structural alterations in chromosomes, often through gains and losses of regions. In GC, there are multiple genetic alterations, in which those located in cytoband 8q24 have been frequently described; essential genes are present in this cytoband, regulating the homeostasis of crucial biological processes, such as the MYC gene, which induces expression of selective genes to promote cell growth and proliferation. Conversely, DNA sequence variations can also occur when a single nucleotide in the genome sequence is altered, and this is termed a single nucleotide polymorphism (SNP). These alterations, which can serve as a biological marker, are present in at least 1% of the population and assist in identifying genes associated with GC. In the present review, 12 genes present in cytoband 8q24 related to GC (NSMCE2, PCAT1, CASC19, CASC8, CCAT2, PRNCR1, POU5F1B, PSCA, JRK, MYC, PVT1 and PTK2) are discussed. The PSCA gene was cited more frequently than others; it has four known SNPs associated with GC (rs2978980, rs2294008, rs2976392 and rs9297976). Thus, these SNPs should be further studied in different populations to determine their risk value in patients with GC.

Contents

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1. Gastric cancer (GC)

Cancer is a group of genetic diseases characterized by the uncontrolled proliferation of heterogeneous cell populations with the ability to invade tissues locally and remotely from the site of origin (metastasis), responding to stimuli from the adjacent microenvironment and from the host organism. During oncogenesis, cancer not only escapes the host regulatory mechanisms, but also gains the ability to affect local and systemic homeostasis (1).

Cancer is the second leading cause of death worldwide; in 2022, 9,743,832 deaths were attributed to this disease, and it is estimated that the number of prevalent cases in 5 years will be 53,504,187 (2). Worldwide, GC is estimated to be the fifth most common cancer type in both sexes, ranking sixth for new cases, with 640,850 cases per year, and fourth in terms of mortality rate (GloboCan, 2020) (3).

The etiology of GC is complex, primarily due to genetic alterations and a set of factors (diet, lifestyle, genetics and socioeconomic factors). Significantly, 80% of cases are associated with infection with *Helicobacter pylori* (4,5).

Of note, <3% of GC cases are attributed to heredity causes, and these types of GC cancer cases include Hereditary GC (HGC), proximal polyposis of the stomach, and hereditary non-polyposis colorectal cancer (5). HGC is the best-known familial GC and is characterized by the loss of the CDH1 gene. Hereditary Diffuse GC (HDGC) is rare, with an incidence rate ranging from 0.3-3.1% in Korea and Japan. However, excluding the small portion of cases of familial GC syndrome, the risk of GC in those with a family history is three times higher vs. those with no history, which is higher than that for other adult solid cancer cases except ovarian cancer (6). Although family history is a systematically reported risk factor in GC, the molecular basis for familial clustering is unclear. Family members have shared exposure to carcinogens, (such as cigarette smoke and alcohol consumption), along with similar levels of hygiene, dietary habits (salty, spicy, and smoked

foods), bacterial virulence, including *Helicobacter pylori* $CagA^+$ and also genetic susceptibility (7).

Invasive GC is preceded by a long precancerous period, which can last for decades and thus provides ample opportunities to detect and treat precancerous lesions. When these lesions progress to an advanced stage, periodic endoscopic follow-ups should be performed to identify the lesions before they become invasive (8,9). Anatomic demarcations, histological differences, or both can be used to distinguish benign lesions from invasive lesions. Most relevant is the distinction between adenocarcinomas that arise from the cardia (the part of the stomach closest to the esophagus, cardia-GC) and other parts of the stomach (non-cardia-GC) (10). Currently, there are different histological classifications of GC, the most commonly used are the Lauren (11), Nakamura *et al* (12), Ming (8), Goseki *et al* (13), and the World Health Organization (WHO) classification systems (14).

GC can be divided into diffuse and intestinal GC based on its histological appearance as well as cardia and non-cardia-GC according to location. The epidemiological and molecular characteristics of GC differ according to the histological type and location of the tumor (6).

Intestinal-type GC (IGC) has well-defined structures or ductal chords surrounded by a zone of desmoplastic stroma. It forms adhesions or fibrous joint tissue within the tumor, with mixed inflammatory infiltration (15). IGC is observed more frequently in older adult patients and follows Correa's precancerous chain, which includes the following states: Atrophic gastritis, intestinal metaplasia and dysplasia (16). Tumor cells often have nuclei that are polymorphic and isochromatic with a coarse chromatin pattern; mitotic figures are thus easily detected. Intestinal-type carcinomas must be well or moderately differentiated, and diffuse-type adenocarcinomas have solitary or small groups of tumor cells without forming glandular structures (15).

Furthermore, Diffuse-type GC (DGC) occurs more frequently in younger patients, and there are no associations with atrophic gastritis or intestinal metaplasia (16). Clear cytoplasmic vacuoles may sometimes be observed. These cells that contain mucus push the nucleus to the periphery of the cell (signet ring cell carcinoma). The stroma formed is usually extensive, making it difficult to identify separate tumor cells on standard hematoxylin and eosin stains; additional keratin staining reveals the true extent of the tumor (15).

The pathogenicity of IGC has been well characterized and studied. However, diffuse GC (DGC) remains undefined, is considered genetically determined, and is less associated with environmental factors and the inflammatory cascade. Additionally, a minor proportion of DGC cases (1-3%) are inherently linked and associated with germline alterations in cell physiology, known as HDGC (7).

The stages of the precancerous cascade illustrated in Fig. 1 have been well characterized from the histopathological point of view. It is postulated that the progression from one stage to the next is determined by etiological factors linked to the inflammatory process and decades of progression (9). The stages of the precancerous cascade are non-atrophic gastritis, multifocal atrophic gastritis, complete intestinal metaplasia, incomplete intestinal metaplasia, dysplasia and adenocarcinoma (9).

Among the molecular pathogenesis, chromosome instability is involved (aneuploid, translocation, amplification, deletions and loss of heterozygosity), fusion genes, microsatellites instability (hypermethylation of promoters of DNA repair genes) and changes in gene expression profile (4,5,17).

2. Chromosomes and copy number alterations (CNA)

In humans, the genome consists of 23 pairs of chromosomes [22 autosomes (44 chromosomes and one pair of sex chromosomes (XX or XY), for a total of 46 chromosomes] located in the nucleus, as well as a small chromosome in each mitochondrion. Each human chromosome has a short arm ('p' for 'petit') and a long arm ('q' for 'queue'), separated by a centromere. The ends of chromosomes are called telomeres. Each chromosome arm is divided into regions, or cytogenetic bands, that can be observed using a microscope and special stains. The cytogenetic bands are labeled p1, p2, p3, q1, q2, q3, counting from the centromere to the telomeres. At higher resolutions, sub-bands can be identified within the bands. The sub-bands are also numbered from the centromere out toward the telomere. For example, the cytogenetic map location of the MYC gene is 8q24.21, which indicates it is located on chromosome 8, q arm, band 24, sub-band 21 and sub-sub-band 2. The ends of the chromosomes are labeled ptel and qtel. For example, the notation 8qtel refers to the end of the long arm of chromosome 8 (18).

CNA represent a genetic variation class involving cumulative somatic variations. CNA are defined as non-inherited genetic alterations in somatic cells (19). These unbalanced structural variants usually contain gains or losses. Their interpretation and the CNA report continue to be a topic of interest in health and disease and have an essential role in GC (19,20). The majority of gastric adenocarcinomas, similar to numerous other types of solid tumors, exhibit defects in the maintenance of genome stability, resulting in DNA CNA that may be analyzed using comparative genomic hybridization (21) and sequencing (22). Based on the aforementioned, it is a widespread phenomenon among humans, and several studies have focused on understanding these genomic alterations that are responsible for cancer. They may be used for its diagnosis and prognosis (23).

In the present review, CNA research on samples of patients with GC is discussed. In a previous investigation, it was noted that the 8q24 cytoband exhibited alterations (24), and thus this cytoband's role in this neoplasia is reviewed below. The complete sequence of chromosome 8 has 145,138,636 bases, the NCBI RefSeq access key corresponding to the GRCh38.p14 version of the human genome is NC_000008.11, the chromosome has 34 cytobands, 2,388 genes, and 4,651 proteins. Chromosome 8 has 103 genes related to cancer; 22 of these genes are in cytoband 8q24, and seven of these genes are reported to be associated with stomach cancer (25,26) (Table I; 27-49).

3. 8q24 cytoband genes and single nucleotide polymorphisms (SNPs)

Alterations in the 8q24 cytoband have been associated with multiple conditions, including cancer; several mechanisms have been proposed, including chromosomal translocations (50), viral integration (51), identification of nucleotide variations (51-53), and variations in the number of copies (24). The 8q24.21 cytoband is one of the most studied due to its association with various types of cancer or complex diseases; this locus has very few protein-coding genes and is rich in long non-coding RNAs (lncRNAs) (54).

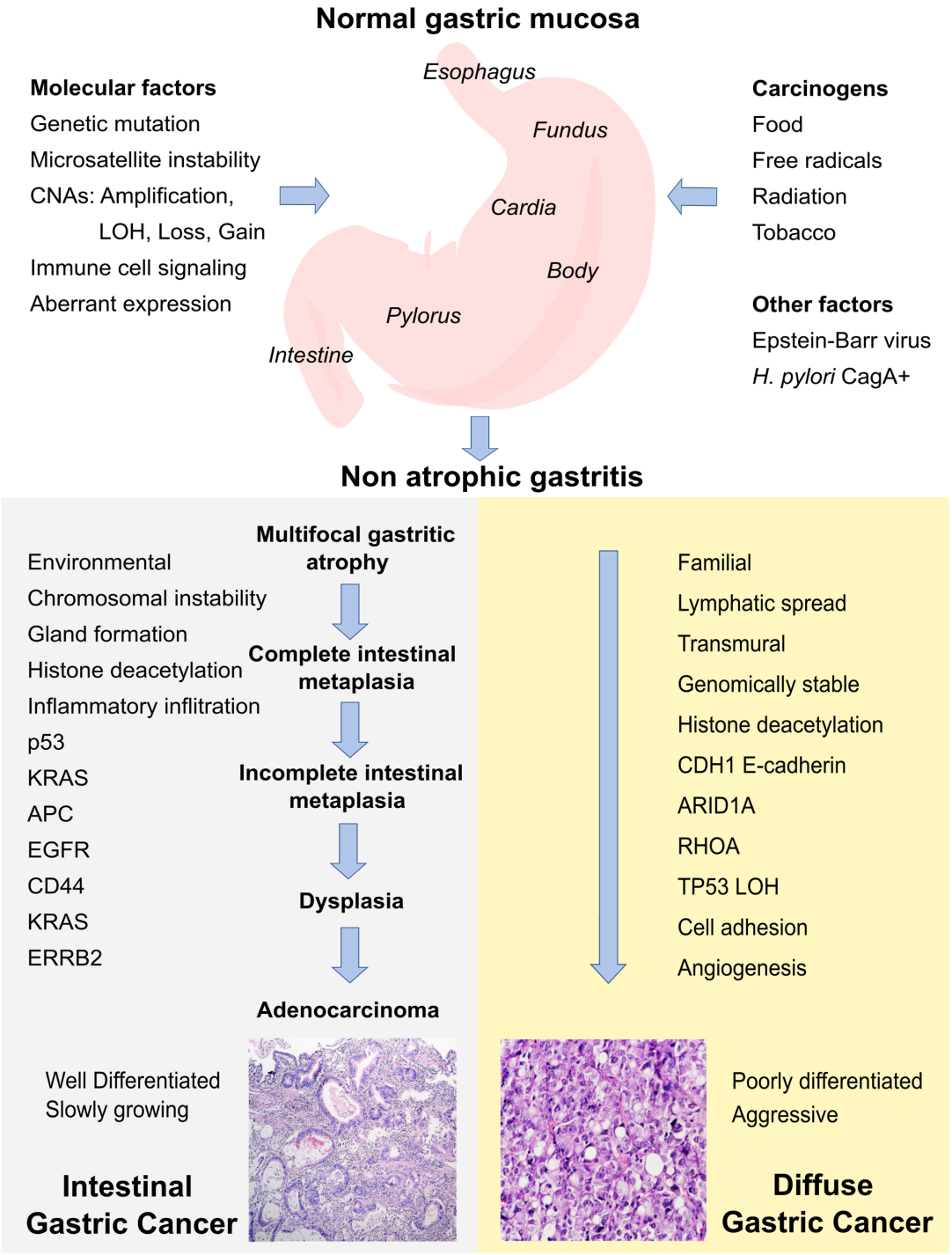

Figure 1. Top: illustration of the normal gastric mucosa, stomach parts, molecular factors, and carcinogens. Bottom right: diffuse gastric cancer and certain factors that participate in the development of the neoplasia. Bottom left: gastric intestinal cancer, the precancerous chain, and certain factors that influence the development of neoplasia. CNA, copy number alterations.

The latter play a range of roles in transcription and translation; however, a number of the identified variants in these regions have been insufficiently studied. The study of this locus has presented several difficulties since most of the lncRNAs in 8q24.21 are not evolutionarily conserved, and there are no mouse orthologs (55).

Currently, repositories such as ENSEMBL (56) and UCSC (57) allow the consultation of different cytobands of the human genome in their different versions. Additionally, BioMart is a tool that provides an interface for accessing database collections, which allows annotating or obtaining genomics, genetics and proteomics records, amongst other tools. With the BioMart data mining tool (58), an analysis of 8q24 (GRCh38.p13) was performed; it has a length of 138.9 megabase pairs (Mbp) and seven segments, of which q24.3 is the longest (6.2 Mbp) and the one with the most significant number of coding genes, pseudogenes and small RNAs, and q24.11 is the smallest (1.6 Mbp) (Table II).

The 8q24 cytoband has 509 genes: 172 coding genes and 337 non-coding genes; among the non-coding ones, lncRNAs, microRNAs, miscellaneous RNAs, small nucleolar RNAs,

Table I. Gastric cancer-related genes.

	Gene	ID	Chr	Summary	(Refs.)
1	ADGRB1[a]	575	8q24.3	Angiogenesis is controlled by a local balance between stimulators and inhibitors of new vessel growth and is suppressed under normal physiologic conditions. Angiogenesis is essential for the growth and metastasis of solid tumors.	(27)
2	AGO2	27161	8q24.3	This gene encodes a member of the Argonaute family of proteins which play a role in RNA interference. The encoded protein is highly basic and contains a PAZ domain and a PIWI domain. It may interact with Dicer1 and play a role in short-interfering-RNA-mediated gene silencing. Multiple transcript variants encoding different isoforms have been found for this gene.	(28)
3	CYP11B1	1584	8q24.3	This gene encodes a member of the cytochrome P450 superfamily of enzymes. The cytochrome P450 proteins are monooxygenases that catalyze numerous reactions in drug metabolism and synthesize cholesterol, steroids, and other lipids.	(29,30)
4	CYP11B2	1585	8q24.3	This gene encodes a member of the cytochrome P450 superfamily of enzymes. The cytochrome P450 proteins are monooxygenases that catalyze numerous reactions in drug metabolism and synthesize cholesterol, steroids, and other lipids.	(31)
5	HSF1	3297	8q24.3	The product of this gene is a transcription factor rapidly induced after temperature stress and binds heat shock promoter elements (HSE). This protein plays a role in the regulation of lifespan.	(32)
6	RECQL4	9401	8q24.3	The protein encoded by this gene is a DNA helicase that belongs to the RecQ helicase family.	(33)
7	SCRIB	23513	8q24.3	The mammalian protein is involved in tumor suppression pathways. As a scaffold protein involved in cell polarization processes, this protein binds to numerous other proteins.	(34)
8	PTK2[a]	5747	8q24.3	This gene encodes a cytoplasmic protein tyrosine kinase, which is concentrated in the focal adhesions between cells growing in the presence of extracellular matrix constituents.	(35)
9	PTP4A3[a]	11156	8q24.3	This gene encodes a member of the protein-tyrosine phosphatase family. Protein tyrosine phosphatases are cell signaling molecules that play regulatory roles in various cellular processes.	(36)
10	PSCA[a]	8000	8q24.3	This gene encodes a glycosylphosphatidylinositol-anchored cell membrane glycoprotein. This gene is up- regulated in numerous prostate cancers and is also detected in bladder and pancreas cancers. This gene includes a polymorphism that results in an upstream start codon in some individuals; this polymorphism is thought to be associated with a risk for certain gastric and bladder cancers-alternative splicing results in multiple transcript variants.	(37)
11	EXT1	2131	8q24.11	This gene encodes an endoplasmic reticulum-resident type II transmembrane glycosyltransferase involved in the chain elongation step of heparan sulfate biosynthesis.	(38)
12	RAD21	5885	8q24.11	This protein is a nuclear phospho-protein, which becomes hyperphosphorylated in the cell cycle M phase. The highly regulated association of this protein with mitotic chromatin, specifically at the centromere region, suggests its role in sister chromatid cohesion in mitotic cells.	(39)
13	CCN3 (NOV)	4856	8q24.12	The protein encoded by this gene is a small, secreted cysteine-rich protein and a member of the CCN family of regulatory proteins. CNN family proteins associate with the extracellular matrix and play an important role in cardiovascular and skeletal development, fibrosis, and cancer development.	(40)
14	TNFRSF11B	4982	8q24.12	The protein encoded by this gene is a member of the TNF-receptor superfamily.	(41)

Table I. Continued.

	Gene	ID	Chr	Summary	(Refs.)
15	HAS2	3037	8q24.13	Hyaluronan or hyaluronic acid (HA) is a high molecular weight unbranched polysaccharide synthesized by various organisms, from bacteria to mammals, and is a constituent of the extracellular matrix. Changes in the serum concentration of HA are associated with inflammatory and degenerative arthropathies such as rheumatoid arthritis.	(42)
16	MTSS1[a]	9788	8q24.13	Predicted to be involved in the cellular response to fluid shear stress, negative regulation of epithelial cell proliferation, and urogenital system development. Predicted to act upstream of or within several processes, including actin filament polymerization; adherents junction maintenance; and magnesium ion homeostasis, which are in the actin cytoskeleton.	(43)
17	RNF139	11236	8q24.13	This gene was found to be interrupted by a t(3:8) translocation in a family with hereditary renal and non-medullary thyroid cancer. Studies of the Drosophila counterpart suggested that this protein may interact with tumor suppressor protein VHL and COPS5/JAB1, a protein responsible for the degradation of tumor suppressor CDKN1B/P27KIP.	(44)
18	CCDC26	137196	8q24.21	No data	(45)
19	MYC[a]	4609	8q24.21	This gene is a proto-oncogene and encodes a nuclear phosphoprotein that plays a role in cell cycle progression, apoptosis, and cellular transformation.	(46)
20	PVT1[a]	5820	8q24.21	This gene represents a long non-coding RNA locus identified as a candidate oncogene. Increased copy number and overexpression of this gene are associated with numerous cancers, including breast and ovarian cancers, acute myeloid leukemia, and Hodgkin lymphoma.	(47)
21	CCN4 (WISP1)	8840	8q24.22	This gene encodes a WNT1 inducible signaling pathway (WISP) protein subfamily member, which belongs to the connective tissue growth factor (CTGF) family. It is expressed at a high level in fibroblast cells and overexpressed in colon tumors. It also attenuates p53-mediated apoptosis in response to DNA damage by activating the Akt kinase.	(48)
22	NDRG1	10397	8q24.22	The protein encoded by this gene is a cytoplasmic protein involved in stress responses, hormone responses, cell growth, and differentiation. The encoded protein is necessary for p53-mediated caspase activation and apoptosis.	(49)

ADGRB1, adhesion G protein-coupled receptor B1; PTK2, protein tyrosine kinase 2; PTP4A3, protein tyrosine phosphatase 4A3; PSCA, prostate stem cell antigen; MTSS1, MTSS I-BAR domain containing 1; PVT1, Pvt1 oncogene; Chr, chromosome; [a], stomach cancer related-genes.

small nuclear RNAs, and processed, unprocessed, polymorphic pseudogenes were identified (Table SI).

The most studied genes of this cytoband are those belonging to the MYC family (8q24.21: c-MYC, l-MYC, and n-MYC). The c-MYC proto-oncogene is affected in almost 20% of the different types of cancer, and it is suspected that it may be related to the functioning of other genes (59). It is a coding gene that participates in cell division and multiplication, maturation and apoptosis. To date, when searching for information on '8q24 cytoband AND cancer' in PubMed (https://www.ncbi.nlm.nih.gov/pmc/), 248 articles were found (April 2023). When exploring the combination '8q24 cytoband AND GC', 73 articles were found; however, when performing an advanced search (selecting the 'Title and Abstract' options) in PubMed with the combination '8q24 AND cancer' a total of 1,553 articles were found, whereas when using '8q24 AND GC' as the search term, only 50 articles were returned (Table SII). Based on these analyses, Fig. 2 was constructed, which serves as an axis for the following parts of the present review.

A total of three genes (pink rectangles) are demonstrated in Fig. 2: MYC, PVT1 and PTK2, which have been reported to be altered in GC (Table I), and nine genes (yellow rectangles) in which SNP alterations in GC have been described; the cytobands in which they were located were 8q24.13, 8q24.21 and 8q24.3. The information on all these cytobands can be found in Table SIII.

A total of seven genes related to GC are in cytoband 8q24 (ADGRB1, MTSS1, MYC, PSCA, PTK2, PTP4A3, and PVT1; Table I). The present bibliographic analysis determined the most frequently cited 12 genes (NSMCE2, PCAT1, CASC19, CASC8, CCAT2, PRNCR1, POU5F1B, PSCA, JRK, MYC, PVT1 and PTK2) (Table SIII). The genes that were present in both search strategies were MYC, PVT1, PTK2 and PSCA, and of these, the PSCA gene was the most cited in GC articles.

The PSCA gene has four SNPs: i) rs2978980, which is located at a functional enhancer in the 8q24.3 GC-susceptibility

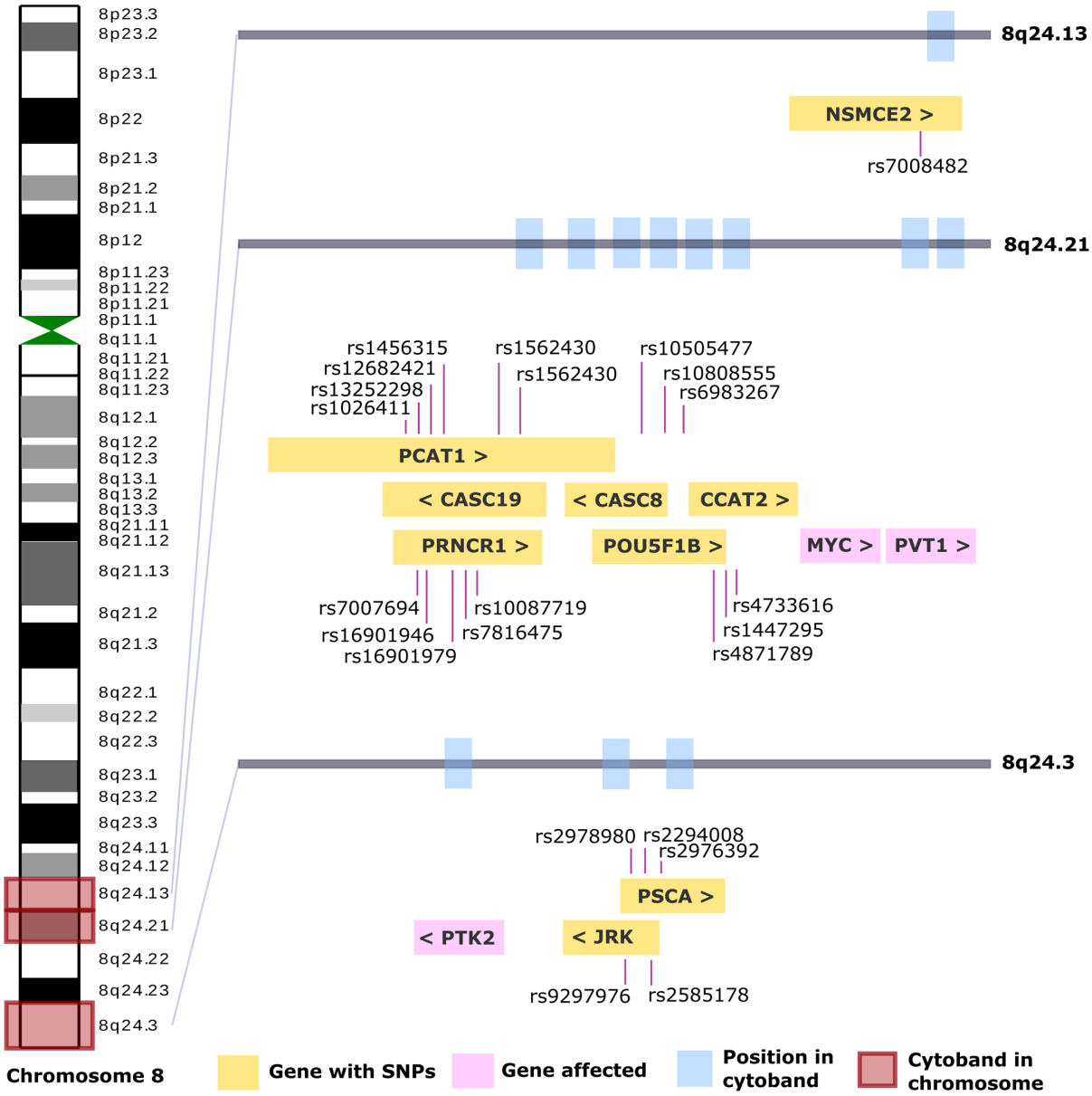

Figure 2. The complete chromosome 8 is shown on the left side, the centromeres are shown in green, and of the 40 cytobands, three are highlighted in red as they are most commonly affected in GC. Each affected cytoband has a gray bar with blue rectangles, indicating the affected genes. In the yellow rectangles, the genes and their SNP identified in GC are observed, and in pink, those that present an alteration, such as CNV. GC, gastric cancer; SNP, single nucleotide polymorphism; CNV, copy number variation; NSMCE2, NSE2 (MMS21) homolog, SMC5-SMC6 complex SUMO ligase; PCAT1, prostate cancer associated transcript 1; CASC19, cancer susceptibility 19; CASC8, cancer susceptibility 8; CCAT2, colon cancer associated transcript 2; PRNCR1, prostate cancer associated non-coding RNA 1; POU5F1B, POU class 5 homeobox 1B; PVT1, Pvt1 oncogene; PSCA, prostate stem cell antigen; PTK2, protein tyrosine kinase 2; JRK, jrk helix-turn-helix protein; >, sense; <, antisense.

locus (60,61); ii) rs2294008, the T allele of which is a risk allele for diffuse-type GC (62); iii) rs2976392, which is associated with alterations in apoptosis/proliferation (63); iv) rs9297976, which can potentially be recommended as a criterion for identifying high-risk groups for the development of GC (64).

4. SNPs and the risk of cancer

A SNP is a genomic variant at a single base position in DNA. Numerous studies have focused on identifying the mechanisms of specific SNPs in a genome on health, disease, drug responses, and other traits in SNPs can occur in promoters, exons, introns, untranslated regions (UTRs), amongst other regions; the molecular mechanisms that may be affected are described in Table III.

These alterations, as shown, affect the control of transcription and/or translation of the genes. These sequence changes can be insignificant or very relevant, affecting key molecules or 'checkpoints' of cellular homeostasis and leading to a predisposition to specific diseases such as various types of cancer, particularly in GC.

In the present review, 12 genes present in cytoband 8q24 related to GC (NSMCE2, PCAT1, CASC19, CASC8, CCAT2, PRNCR1, POU5F1B, PSCA, JRK, MYC, PVT1 and PTK2) are discussed. The PSCA gene was cited more frequently than others; it has four known SNPs associated

Table II. Description of the 8q24 cytoband. Information obtained from BioMart.

	Cytobands						
Features	q24.11	q24.12	q24.13	q24.21	q24.22	q24.23	q24.3
Start Chr	116700000	118300000	121500000	126300000	130400000	135400000	138900000
End Chr	118300000	121500000	126300000	130400000	135400000	138900000	145138636
Length (Mbp)	1.6	3.2	4.8	4.1	5.0	3.5	6.2
Protein coding	7	13	26	5	16	2	103
rRNA pseudogene	0	1	0	0	0	0	1
lncRNA	4	11	37	29	26	8	68
miRNA	1	1	6	7	3	0	16
snoRNA	1	1	2	2	2	0	2
snRNA	0	1	5	6	0	2	1
miscRNA	2	2	2	3	4	0	4
Processed pseudogene	1	7	15	6	13	2	10
Unprocessed pseudogene	1	0	0	0	1	1	2
Transcribe processed pseudogene	0	0	1	1	0	0	0
Polymorphic pseudogene	0	0	0	0	0	0	1
Transcribe unitary pseudogene	0	0	0	0	0	0	2
Transcribe unprocessed pseudogene	0	0	0	0	0	0	2
Unitary pseudogene	0	0	0	0	0	0	1

Chr, chromosome; lncRNA, long non-coding RNA; miRNA, microRNA; snoRNA, small nucleolar RNA; snRNA, small nuclear RNA; miscRNA, miscellaneous RNA.

Table III. Molecular mechanisms of region-based SNP on cancer susceptibility.

SNP regions	Possible molecular mechanism	Unclear issues
Promoter	Genetic regulation: promoter activity (TATA box, transcription-factor binding ability)	The interaction between genetic and epigenetic elements
	Epigenetic regulation: DNA methylation, histone modification	Effect of SNPs on DNA methylation status
Exons	Non-synonymous cSNPs: coding protein structure and function	Detail mechanism at the biochemical and cellular level
	Synonymous cSNPs: secondary structure conformation translation dynamics	Mechanism of the kinetics of translation
Introns	cis-regulatory elements mRNA splicing genomic imprinting long non-coding RNAs chromatin looping	Detail functions of cis-regulatory elements and splicing
UTRs	5'-UTRs: protein translation and transcription activity	How SNPs in the 5'-UTR affect the efficiency of translation
	3'-UTRs: Regulate mRNA degradation and translation	How does the 3'-UTR affect miRNA binding sites
Non-definite regions	Long-range cis-regulation tRNA and rRNA	The ways polymorphisms affect long-range cis-regulation, tRNA and rRNA

Taken from (65); SNP, single nucleotide polymorphism; UTR, untranslated region.

with GC (rs2978980, rs2294008, rs2976392 and rs9297976). Thus, these SNPs should be further studied in different populations to determine their risk value in patients with GC.

5. Conclusions

Alterations in cytoband 8q24 can occur at the structural level (deletions, insertions and translocations, among other types), at the functional level (genes and proteins), and at the SNP level, which can translate to a risk of suffering from a disease depending on the base that is mutated, that is, if it occurs in an oncogene or tumor suppressor gene and the function of the affected gene. In GC, mutations in the PSCA gene and the presence of SNPs are consistent and are thus deserved of further study.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

VLS and HAVS, participated in the analysis of results, preparation, writing, and discussion of the manuscript. MERT was responsible for the design of the present study. VLS, HAVS and MERT supervised, critically reviewed, edited and wrote the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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