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# GALECTIN-3 GENE VARIANTS AND PROTEIN-LIGANDS INTERACTIONS IN CANCER PATHOPHYSIOLOGY

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**ABSTRACT:**

**Background**: Galectin-3 (gal-3), encoded by *LGALS3*, is a carbohydrate-binding protein that plays a pivotal role in cancer by influencing initiation, progression, and metastasis. Genetic variants in *LGALS3*, specifically Single Nucleotide Polymorphisms (SNPs), have been reported as potential contributors to cancer risk. This study aims to conduct a comprehensive systematic review to investigate the association between SNPs in the *LGALS3* and the risk of developing cancer.

**Method and Results**: The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines for a comprehensive systematic review. A systematic search was conducted across PubMed, Scopus, and ISI Web of Science databases, without language or publication date restrictions, up to July 2023. Only full-text articles relevant to the objective were included. The initial search yielded 152 articles, and after eliminating duplicates, reviewing titles and abstracts, 13 articles met the inclusion criteria. These articles included 3 studies of reproductive cancers, including breast, cervical, and prostate cancer, 3 of gastrointestinal cancers, including gastric and colorectal cancer, 2 of respiratory cancers, including non-small cell lung cancer (NSCLC) and laryngeal squamous cell carcinoma (LSCC), 3 of nervous system cancer including gliomas, glioblastoma and skull base chordoma (SBC) and 2 of endocrine cancer including thyroid cancer. These studies were conducted in various Asian and Caucasian populations. The two most commonly studied SNPs of *LGALS3, i.e.,* rs4644 and rs4652, were examined, along with the analysis of rs11125, rs7157768, rs8013027, and rs17128230.

**Conclusions:** SNP rs4644 exhibited an association with breast cancer in Asian and Caucasian populations. Similarly, this SNP was documented to be associated with prostate, thyroid cancer, and glioblastoma in German, Italian, and Chinese populations. rs4652 was found to be associated with cervical, gastric, gliomas, glioblastoma, SBC, and NSCLC in the Chinese cohort. In Turkish population, significant differences in genotypic frequency distribution for rs4644 and rs4652 were observed in colorectal cancer patients compared to controls. Furthermore, rs11125 was associated with cervical cancer in the Chinese population. These findings emphasize the importance of SNP research in understanding cancer. Further extensive research in SNPs concerning cancer is imperative for a deeper comprehension of disease susceptibility and the development of therapeutic strategies.

**Keywords:** Angiogenesis, Apoptosis, Gal-3, Cell motility, Cell proliferation, Ligands.

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## 1. INTRODUCTION

Numerous cancers stand as the foremost drivers of mortality worldwide. Genetic alterations emerge as a crucial factor in the complex pathophysiology of cancer, acting in concert with many environmental risk factors. Genetic factors, especially Single Nucleotide Polymorphisms (SNPs), are gaining importance in cancer research as they impact cancer susceptibility, initiation, progression and treatment response. Different SNPs of various DNA repair genes, oncogenes, and tumor repressor genes have been reported till date, associated with various cancers. Apart from these genes, galectin-encoding genes have emerged as significant contributors to cancer development. Notably, galectins play a multifaceted role in cancer development through modulation of angiogenesis, cell adhesion, migration. Galectins, a family of animal lectins, are carbohydrate-binding proteins that bind to β-galactoside containing glycans (1,2). Based on the structure, galectins are divided into three subtypes- prototypical, chimera-type, and tandem-repeat type. Gal-3, a 31kDa protein, is the only chimera-type galectin (1). It consists of the extended N-terminal region that is linked to the C-terminal CRD. It is encoded by the *LGALS3*, located at chromosome 14q22.3. It consists of six exons and five introns. Exon I and II encode 5' untranslated region (UTR). Exon II also contains a translation initiation site along with the first six amino acids, including methionine as the initial amino acid residue. Exon III encodes the N-terminal of the protein. The C-terminal of the protein is encoded by exons IV, V, and VI (2,3). Gal-3, a multifunctional protein, engages with a diverse array of extracellular, cytoplasmic, and nuclear ligands, thereby exerting a significant influence on cancer development. It promotes tumorigenesis through its involvement in cell proliferation by modulating gene expression, enhancing cell adhesion, metastasis, and inhibiting apoptosis. Reportedly, the two most common SNPs of *LGALS3* in various cancers, rs4644 and rs4652, are located in the exon III of *LGALS3*, causing a missense change. In rs4644 variant, histidine substitutes the proline by replacing C with A/G at the 191 coding position. On the other hand, rs4652 variant encodes proline instead of threonine at the 292 position, replacing A with C. In addition, rs11125 SNP, located in Exon VI, also leads to missense variation. It encodes for histidine instead of glutamine, with T replacing A at 603 position. The intronic SNPs rs7157768 (G/C) in intron I, rs8013027(C/G) in intron V and rs17128230 (C/T) in intron III have also been studied. This comprehensive review aims to provide a critical analysis of the studies reporting the association of SNPs of *LGALS3* in a wide spectrum of cancer types to gain deeper insights into their potential implications for the development, progression, and prognosis of different cancer types.

## 2.METHODS

### Search Strategy

This systematic review was conducted following the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations. Online Databases, *i.e.,* PubMed, Scopus and ISI Web of Science, were searched systematically for eligible studies published till July 2023. The following search query was used in the online databases: [(Gal-3 or Gal-3 or *LGALS3*) (genetic variants or polymorphisms or SNPs) and cancers]. Restriction on the publication period and language was not applied.

### Inclusion and Exclusion criteria

Studies were considered eligible for inclusion if they evaluated the association between SNPs and the risk of developing cancer in patients. Studies without access to full text were excluded.

## 3.RESULTS

### Search results

The initial search of the PubMed, ISI Web of Science, and Scopus databases yielded a total of 152 articles. Following the elimination of duplicate entries, a comprehensive review of the title and abstract was conducted on 111 articles. Among these, 13 articles aligned with the established inclusion criteria. Notably, 88 articles were excluded due to their lack of relevance to the study's objectives, and 1 full text was not available for analysis. Of the remaining articles, 5 articles failed to provide information on SNPs, 2 articles did not investigate the association between SNPs and cancer and 2 articles examined polymorphisms in breast cancer cell lines rather than in human subjects. The process of the literature search and study selection is given in detail in the flowchart in figure 1.

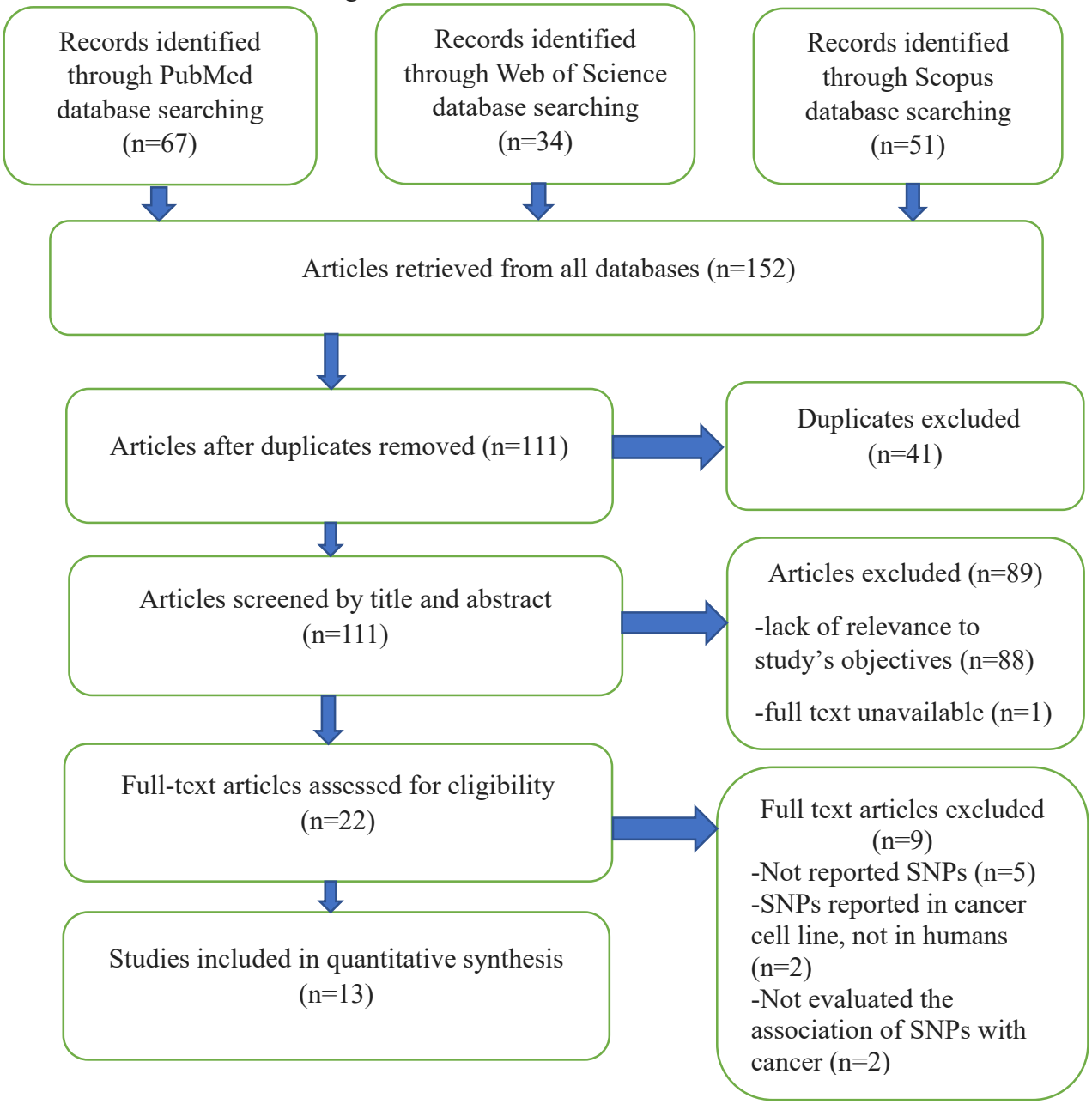


**Figure 1:** Flowchart of selection of studies to be included in the systematic review.

### Characteristics of studies

Characteristics of the 13 included studies are reported in table 1. These were case-control studies published from 2006 to 2021. No further studies were published for a time period from

January 2022 to July 2023. These 13 studies were carried out in seven different populations. Among them, six studies focused on Asian populations, including participants of Chinese and Japanese descent. The other six studies were conducted on populations of Caucasian origin, which included participants from Turkey, Germany, Italy, and Portugal. One study examined both Caucasian and Asian populations together. Three exonic SNPs rs4644, rs4652 and rs11125, and three intronic SNPs rs7157768, rs8013207 rs17128230 have been studied in different cancers, including breast, cervical, colorectal, gastric, glioma, glioblastoma, laryngeal squamous cell (LSCC), Non-small cell lung cancer (NSCLC), prostate, thyroid and skull base chordoma (SBC).

**Reproductive Cancers**

Reproductive cancers, including cervical, breast, and prostate cancer, are significant health challenges with diverse implications for affected populations. These cancers are influenced by genetic factors, and specific gene polymorphisms of *LGALS3* have been investigated for their associations with cancer risk and prognosis, shedding light on the intricate relationship between genetics and the development and progression of these reproductive malignancies.

**Breast cancer**

The genotype analysis of the non-synonymous SNP rs4644 in cancer-free and breast cancer patients was performed and correlated with the incidence of breast cancer in Caucasian and Asian populations (4). For Caucasian and Asian patients, the odds ratio for breast cancer for the C/C genotype compared to the A/A genotype was 2.7; 95% CI=1.4-4.9; p=0.001 and 94.6; 95% CI=10.0-892.4; $p<0.001$, respectively. The study also involved variant analysis in human breast cancer cell lines. The normal human fibroblast cell lines (HS68 and IMR90) and the normal human breast epithelial cell line (MCF10A) were both found to be homozygous for the C allele. Tumorigenic human breast cancer cell lines MDA-MB-231, MDA-MB-435, SUM 149, SUM 1315, and SUM 102 were homozygous for the A allele, while MDA-MB-468 was heterozygous carrying both alleles. The non-synonymous change from C to A leads to the replacement of proline to histidine, making the resulting protein susceptible to cleavage by matrix metalloproteinases (MMP). Normal breast tissue showed no evidence of gal-3 cleavage. However, most of the invading cell clusters in the infiltrating lobular carcinoma tested positive for the cleaved product. The non-synonymous change was further demonstrated to confer the resistance to cisplatin-induced apoptosis in the transfected BT-547 breast cancer cell line, while the cell clones with wild-allele C were highly susceptible to drug-induced apoptosis. In experimental studies, gal-3 null cells transfected with gal-3 carrying histidine residue at the 64th position led to the acquisition of tumorigenicity and a metastatic phenotype, while cells transfected with gal-3 carrying proline residue at the 64th position showed lower tumorigenicity, with reduced angiogenesis and enhanced apoptosis.

**TABLE 1: Association of *LGALS3* polymorphisms with various cancers**

| Types of cancer | Population | Study type | Polymorphism Studied (Method used) | Polymorphism Associated | Number of Individuals | Results | References |
|---|---|---|---|---|---|---|---|
| Breast cancer | Caucasian and Asian | Case-control study | rs4644 (P64H) (C>A) (PCR-RFLP) | rs4644 | 338 Caucasian (144 patients and 194 controls) and 140 Asian (61 patients and 79 controls) | H allele was associated with increased risk in both races. | Balan et al., 2008(4) |
| Cervical cancer | Chinese | Case-control study | rs4644 (C>A), rs4652 (A>C) rs11125 (A>T) (PCR-RFLP) | rs11125 rs4652 | 126 patients and 102 controls | Allele C of rs4652 and allele T of rs11125 were associated with increased risk. | Fang et al., 2017 (5) |
| Prostate cancer | German | Case-control study | rs4644(P64H) (C>A) (qPCR and RFLP-PCR) | rs4644 | 510 patients and 490 controls | H allele was associated with increased risk | Meyer et al., 2013(6) |
| Gastric cancer | Japanese<br>Chinese | Case-control study<br>Case-control study | rs4644 (C>A) rs4652 (A>C) (PCR-SSCP and sequencing)<br>rs4644 (C>A), rs4652 (A>C) (MALDI-TOF MS) | -<br>rs4652 | 51 patients and 25 controls<br>479 patients and 459 controls | No association was observed<br>rs4652 CA/AA genotype was associated with | Okada et al., 2006 (7)<br>Shi et al., 2017(8) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | increased risk | |
| Colorectal cancer | Turkish | Case-control study | rs4644 (C>A), rs4652 (A>C) (PCR-RFLP) | rs4644 rs4652 | 119 patients and 117 controls | Significant difference between the genotypic frequency distribution was observed. CA/CC genotype of rs4644 more in patients and AC genotype of rs4652 in patients | Korkmaz et al., 2016 (9) |
| Non-small cell lung cancer (NSCLC) | Turkish | Case-control study | rs4644 (C>A), rs4652 (A>C) (qPCR) | - | 65 patients and 95 controls | No association was observed | Terzioglu-Usak et al., 2021 (10) |
| Laryngeal Squamous cell carcinoma (LSCC) | Turkish | Case-control study | rs4644 (C>A), rs4652 (A>C) (PCR-RFLP) | rs4652 | 74 patients and 97 controls | Allele C of rs4652 was found to be associated with the LSCC. | Horozoglu et al., 2021 (11) |
| Gliomas | Chinese | Case-control study | rs4644 (C>A), rs4652 (A>C) (PCR-RFLP) | rs4652 | 190 patients and 210 controls | Allele A of rs4652 was associated with increased risk | Chen et al., 2012 (12) |
| Glioblastoma | Chinese | Case-control study | rs4644 (C>A), rs4652 (A>C) rs7157768 (G>C), rs8013027 (C>G), | rs4644 rs4652 | 961 patients and 1351 controls | rs4644 AA genotype and rs4652 CC genotype associated with the | Wang et al., 2018 (13) |

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|---|---|---|---|---|---|---|---|
| | | | rs17128230 (C>T)<br>(MALDI-TOF MS) | | | increased risk | |
| Skull base chordoma (SBC) | Chinese | Case-control studies | rs4644 (C>A), rs4652 (A>C)<br>(Sequencing) | rs4652 | 48 patients and 66 controls | Allele A and AA genotype of rs4652 was associated with increased risk | Tian et al., 2018 (13) |
| Thyroid cancer | Italian<br><br>Portuguese | Case-control study<br><br>Case-control study | rs4644 (C>A), (q-PCR)<br>rs4652 (A>C),(PCR-SSCP and Sequencing) | rs4644<br><br>- | 1142 patients and 1223 controls<br><br>55 patients and 45 controls | rs4644 AA genotype was associated with reduced risk<br><br>No association was observed | Corrado et al., 2021 (14)<br><br>Martins et al., 2006 (15) |

PCR-RFLP: Polymerase Chain Reaction-Restriction Fragment Length Polymorphism, PCR-SSCP: Polymerase Chain Reaction-Single-Strand Conformation Polymorphism, MALDI-TOF MS: Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry, qPCR: Quantitative Polymerase Chain Reaction

**Cervical Cancer**

After breast, cervical cancer is the second most frequent reproductive malignancy in women, accounting for 275,000 annual fatalities. *LGALS3* polymorphisms, *i.e.,* rs4644, rs4652, and rs11125 were investigated for their associations with cervical cancer risk and prognosis in Chinese populations (5). The genotypic frequencies of the rs4652 CC+CA and rs11125 AT+TT in cervical cancer patients were significantly higher than controls ($p<0.05$). Allele C of rs4652 (OR=1.474; 95% CI=1.017–2.136; p=0.048) and allele T of rs11125 (OR=4.677; 95% CI= 2.432–8.993; $p<0.001$) were found to be associated with the increased risk of cancer. There was no statistically significant difference in the genotype distribution and allele frequency for rs4644 ($p>0.05$). SNPs rs4652 and rs11125 also correlated with FIGO staging, differentiation grades, clinical staging, lymph node metastasis (LNM), and mode of treatment, while rs4644 only correlated with tumor diameter. The follow-up revealed that the patients with CC+CA genotype of rs4652 (54.63%) had a lower 5-year survival rate than those with AA type (88.89%), with a higher recurrence rate. As opposed to AT+TT genotype (42%) patients, AA genotype (71.05%) patients with rs11125 showed greater 5-year survival rates and lower recurrence rates. Multivariate Cox analysis of risk factors for overall survival (OS) and disease-free survival (DFS) of patients with cervical cancer revealed LNM was the only independent factor associated with OS ($p<0.05$), while the CC+CA genotype of rs4652, the AT+TT genotype of rs11125, and the treatment modality were all associated to OS and DFS independently ($p<0.05$).

**Prostate Cancer**

Prostate cancer is the most common cancer in men. A study conducted in the German population investigated the rs4644 (Pro64His) SNP of *LGALS3* and SNPs of other 9 candidate genes involved in apoptosis including *ATM* (Ser49Cys), *BID* (Ser56Cys), *CASP8* (Asp302His), *CASP10* (Val410Ile), *RASSF1* (Ser133Ala), *TP53* (Arg72Pro), *TP53AIP1* (Ala7Val), *BCL2* (-938C/A) and *MDM2* (SNP309) (6). With minor allele frequencies ranging from 0.06 to 0.44, seven polymorphisms in the genes *BCL2, CASP8, CASP10, TP53, HDM2, LGALS3*, and *RASSF1* were common. The most convincing evidence for a difference in allelic distribution between patients and controls, consistent with a minor allele's protective impact, was provided by rs4644 in *LGALS3*. There was a significant difference in the allelic distribution of rs4644 between patients and controls. In prostate cancer patients, carriers of the histidine variation were markedly underrepresented, indicating a protective impact of this alteration (OR=0.82; 95% CI =0.69-0.99; p=0.04). The findings were best explained by a dominant model (p=0.01) in which just one A allele was required to provide the protective effect (OR=0.71; 95% CI=0.54-0.92; p=0.01), and the effect was most evident in those diagnosed before the age of 60 (OR=0.52; 95% CI=0.31-0.85; p=0.01). While there were some trends towards a potential risk effect for the rare allele of rs2279115 in *BCL2* (p=0.07) and a potential protective effect for the rare allele of rs13010627 in *CASP10* (p=0.08), the other polymorphisms did not differ significantly between cases and controls. Under a dominant model, the D302H variation of *CASP8* also seemed to be connected to a protective effect in the group with higher Gleason scores (p=0.03).

In cervical cancer, rs4652 and rs11125 polymorphisms were linked to increased cancer risk and prognosis, with specific genotypes affecting survival rates. Breast cancer was notably affected by the rs4644 polymorphism, which increased cancer risk in both Caucasian and Asian populations and influenced the susceptibility of gal-3 to cleavage and resistance to cisplatin-induced apoptosis. Conversely, prostate cancer saw a protective impact of the rs4644 polymorphism, with carriers of the histidine variation having a reduced risk, particularly in those diagnosed before the age of 60.

## Gastrointestinal Cancers

Gastrointestinal cancers encompass a spectrum of malignancies affecting the digestive system. Specifically, the SNPs within the *LGALS3* have been extensively studied in the context of gastric and colorectal cancer, offering crucial insights into the genetic factors influencing these particular cancer types.

### Gastric Cancer

Gastric cancer is a significant health concern with varying prevalence across different populations. Genetic factors, including polymorphisms in *LGALS3* have been implicated in gastric cancer susceptibility and prognosis. The associations of gal-3 SNPs, *i.e.,* rs4644 and rs4652, with gastric cancer were studied in Japanese and Chinese populations. In the Japanese, it was observed that there were no statistically significant disparities in the genotype frequencies of rs4644 and rs4652 between controls and gastric cancer patients (p=0.664 and p=0.839 for rs4644 and rs4652 respectively)(7). However, the study did uncover a compelling correlation between gal-3 expression and specific clinicopathological features of gastric cancer, such as nodal status (p=0.0495), lymphatic invasion (p=0.0086), pathological stage (p=0.0433) and two key histological parameters, *i.e.,* tumor histological type (p=0.0001) and tumor grading (p=0.0001). Gal-3 expression did not exhibit significant associations with demographic factors like age and gender or tumor characteristics such as status or vascular invasion. Furthermore, the study revealed no substantial correlation between gal-3 expression and the proliferation potential of cancer cells, as assessed by the Ki-67 Labelling Index. Moreover, it was found that compared to the high gal-3 expression group, the low gal-3 expression group's cumulative survival rate was considerably lower (p=0.0002).

Conversely, in the Chinese population, it was found that rs4652 CA/AA carriers showed a significant increase in their susceptibility to gastric cancer (OR=1.51; 95% CI= 1.05-2.18; p=0.03) (8). However, the genotypic distribution of rs4644 did not show significant differences between gastric cancer patients and controls. Moreover, the genotypic distribution of rs4644 and rs4652 as well as haplotype distribution, were not associated with the overall clinicopathological characteristics of gastric cancer patients. Furthermore, a strong correlation was observed between P-glycoprotein 1 (Pgp) expression level and genotypic distributions of rs4652.

### Colorectal Cancer

The rs4644 and rs4652 variations of the *LGALS3* were also examined in relation to histopathological and clinical characteristics of colorectal cancer (9). There was a different distribution of *LGALS3* variant rs4644 genotypes between the patient and control groups (p=0.0260). The CC genotype with a mucinous component was more prevalent than those without a mucinous component for the rs4644 variant of the *LGALS3*. Studies indicated that colorectal patients with mucinous components have worse prognoses than those without such components. Similarly, the distribution of the rs4652 variant genotypes in the patient and control groups was significantly different (p=0.0390). In addition, the frequency of the CCCT haplotype of the rs4644 *LGALS3* variant and the rs214250 *AXIN1* variant was significantly greater in the patient group compared to the control group (18.5% vs 9.4%, OR= 1.966; 95%CI= 0.999-3.871; p=0.044). When compared to the control group, the patient group showed significantly lower frequencies of the AACC haplotype of rs4652 of *LGALS3* and the rs214250 variant of the *AXIN1* (3.4% vs. 13.7%, OR= 0.246; 95%CI=0.085-0.713; p=0.004). The CCAACT haplotype was shown to be considerably more prevalent in the patient group than in the control group in triple haplotyping of the rs4652 and rs4644 variants of the *LGALS3* and the rs214250 variant of the *AXIN1* (12.6% vs. 4.3%, OR= 2.95; 95%CI= 1.108- 7.855; p=0.022). Moreover, in comparison to the controls, the patient's serum gal-3 level was significantly higher (5.90.69ng/ml vs. 0.790.01ng/ml, p=0.001).

Research in Japanese and Chinese populations on *LGALS3* variations and their impact on gastric cancer susceptibility and prognosis demonstrated complex relationships. In Japanese individuals, specific gene variants, *i.e.,* rs4644 and rs4652, were not directly associated with gastric cancer risk, but gal-3 expression was linked to crucial clinicopathological features and patient survival. Conversely, in the Chinese population, the rs4652 polymorphism was associated with increased gastric cancer susceptibility, while rs4644 did not exhibit a significant influence. The colorectal cancer study further revealed unique *LGALS3* variant distributions (rs4644 and rs4652) linked to distinct histopathological characteristics, suggesting potential connections between these genetic variations and disease prognosis.

**Respiratory Cancers**

Lung cancer, a leading global cause of cancer-related deaths, comprises two primary types: NSCLC and small cell lung cancer (SCLC). NSCLC accounts for the majority of cases, often diagnosed at advanced stages (10). Furthermore, LSCC ranks as the second most prevalent cancer in the respiratory tract, following lung cancer. Studies have been conducted to examine the role of *LGALS3* SNPs in assessing the risk of developing NSCLC and LSCC.

**NSCLC**

The relationship between a genetic variant of *LGALS3, i.e.,* rs4644 and rs4652, and NSCLC risk development and prognosis was examined. It was revealed that neither the rs4644 nor the rs4652 variations showed any statistical differences in the genotype and allele frequency distributions between the patients and the controls in Turkish population (10). No correlation was found between the genotype of the rs4644 variant and the characteristics of the disease, such as tumor stage, lymph node metastases, perineural invasion, angiolymphatic invasion, and vascular invasion. For NSCLC patients with the AA genotype of the rs4652 mutation, there was evidence of angiolymphatic invasion ($p=0.04$). Furthermore, higher serum levels of gal-3 were seen in the patients with the CA and CC genotypes of the rs4644 variation compared to the controls ($p<0.0001$). Additionally, individuals with the rs4652 AC and AA genotypes had higher serum levels of gal-3 compared to controls ($p<0.0001$). Patients with NSCLC with the AC genotype of both rs4644 ($p=0.03$) and rs4652 ($p=0.019$) variations had higher serum levels of gal-3 in the presence of vascular invasion than in the absence. It was demonstrated in the multivariant analysis that smoking and serum gal-3 levels may be risk factors for NSCLC that influence the diagnosis independently of variations in gal-3 distribution. For each NSCLC patient, the level of gal-3 mRNA expression was assessed in the tumor tissue and contrasted with the surrounding healthy tissue of the same participant. However, this difference was not statistically significant ($p=0.4959$). In addition, the patients with different rs4644 and rs4652 genotypes did not have statistically significantly different survival rates ($p=0.625$ and $p=0.349$). Moreover, high serum levels of gal-3 were found to be an independent surrogate marker for poorer survival, according to multivariate analysis (Hazard ratio, HR=5.106; 95% CI= 0.956-27.267; $p=0.056$).

**LSCC**

The association of two SNPs of LGALS3 rs4644 and rs4652 with LSCC in the Turkish population was also evaluated (11). In the rs4644 variant of *LGALS3*, there was no difference in genotypic ($p=0.364$) or allelic frequency ($p=0.145$) between the patient and control groups. No statistically significant variation in genotypes was observed between the patient and control for the rs4652 variant of *LGALS3* ($p=0.053$). In the patients compared to the control group, a greater frequency of the C allele for rs4652 was observed ($p=0.017$). When compared to the early tumor stage, patients with advanced tumor stage had a greater prevalence of homozygous genotypes (CC/AA) of rs4652 ($p=0.017$). In contrast to individuals without reflux, patients with reflux were shown to have a higher proportion of homozygous genotypes ($p=0.036$). Patients with positive family histories of laryngeal cancer were shown to have greater rates of

CC genotype carriage of rs4644 than patients with negative family histories (p=0.036). Logistic regression results revealed that among patients carrying the C allele of rs4652, there was a statistically significant difference between the advanced tumor stage and the early tumor stage (p=0.015).

In the Turkish population, the genetic variations rs4644 and rs4652 showed no significant differences between patients and controls in NSCLC. However, they did reveal associations with critical clinical factors, *i.e.,* vascular invasion and angiolymphatic invasion in the case of NSCLC. Moreover, in the context of LSCC, the presence of the C allele in rs4652 was significantly linked to advanced tumor stages, providing valuable insights into disease progression in the Turkish population.

**Cancer of Nervous System**

*LGALS3* SNPs was also studied in nervous system cancers, including SBC, gliomas and the highly aggressive subtype, glioblastoma. These investigations into *LGALS3* SNPs provide essential insights into the genetic component, with the potential to reshape strategies in order to manage these complex neuro-oncological conditions.

**Gliomas and glioblastoma**

Gliomas are a type of primary brain tumor that originates from glial cells in the brain or spinal cord. Glial cells are supportive cells that surround and support the neurons in the central nervous system. A case-control study conducted in the Han Chinese population evaluated the association of two SNPs of gal-3 rs4644 and rs4653 with gliomas (12). The patients with gliomas were divided into three subgroups based on their histological diagnoses: 79 astrocytomas (including diffuse astrocytoma, anaplastic astrocytoma, or other astrocytoma other than glioblastomas), 26 other gliomas (including oligodendrogliomas, ependymomas, or mixed gliomas), and 85 glioblastomas. No significant difference was observed between the genotypic and allelic frequency in both patients and controls for rs4644. However, a significant difference was observed in the case of rs4652. AA genotype was more prevalent in patients than controls (42.1% vs 29.0%, p=0.02). Moreover, the frequency of the A allele was higher in patients than controls (61.8% vs 45.0%, p=0.01). After adjusting for age, sex, smoking status, histology, stage, and therapy status, multivariable analyses revealed a substantially increased risk for gliomas in AA genotype carriers of rs4652 (OR= 2.11, 95% CI= 1.14-3.11, p=0.01, compared with C/C). When compared to CC, the AC genotype had a lower chance of developing gliomas (OR=1.23; 95% CI= 0.99-1.78; p=0.071). AA genotype was also found to be associated with higher tumor grade. Moreover, no significant difference was observed in the genotypic and allelic frequency of patients with different gliomas according to histology type. Follow-up analysis after treatment revealed that rs4652 was found to be associated with the OS, not rs4644. Patients with AA genotype (22.2±3.8 months) were found to have a lower OS period than the AC/CC genotype (38.3±7.9 months) (p=0.04).

The association of the SNPs of *LGALS3,* i.e., rs4644, rs4652, rs7157768, rs8013027, and rs17128230 with the risk of developing the glioblastoma, a subtype of gliomas and resistance to radio-chemotherapy was also evaluated in Chinese population (13). There were significant differences observed in the allele frequencies of two SNPs (rs4644 and rs4652) among the studied five SNPs between patients and controls (p=0.037 and 0.028, respectively). It was found that in the dominant-effect model, CA+CC homozygotes of rs4652 were substantially linked with a higher susceptibility to glioma compared to wild-type carriers (adjusted OR=1.19, 95%CI=1.00-1.42). In the recessive-effect model, the homozygous variant genotype AA of rs4644 was individually linked to a higher risk of gliomas (AA vs. AC+CC: adjusted OR=2.10, 95%CI=1.22-3.62). Additionally, stratification studies for the two *LGALS3* variations (rs4652 and rs4644) were carried out utilizing the histological subcategories (glioblastoma and other gliomas). Both the CC genotype of rs4652 and the AA genotype of rs4644 were associated with

a significantly higher risk of glioblastoma, according to the codominant model (OR=1.44, 95% CI=1.01-2.06 and OR=2.81, 95% CI=1.46-5.38, respectively). In a recessive model, the AA genotype of rs4644 also showed an elevated correlation with risk in only glioblastoma patients, not in other glioma subgroups (OR=2.81, 95%CI=1.47-5.36). It was established using *LGALS3* positive T98G and U251 cells that gal-3 boosts glioblastoma cell resistance to radiation and temozolomide (TMZ) chemotherapy, enhances proliferative capacity, and functions as a separate risk factor for OS. Additionally, the C allele of rs4652 and the A allele of rs4644 contributed to higher resistance to chemotherapy and radiation therapy. Furthermore, when compared to normal nervous tissue, the expression of gal-3 was significantly higher in glioblastoma tissues (3.10±0.12 vs. 1.36±0.19) and associated with the pathological grade of the tumor ($p<0.001$). Moreover, it was revealed from the univariant survival analysis that glioblastoma patients with low gal-3 expression score had a significantly longer OS and PFS than high score group (OS, 10 vs. 18 months, $p=0.001$; PFS, 7 vs. 15 months, $p<0.001$).

**SBC**

Chordoma is a rare type of cancer that originates from the remnants of the notochord, a structure that is present during early embryonic development and eventually develops into the spinal column. Chordomas typically occur in the bones of the skull base (SBC), spine, or sacrum (the triangular bone at the base of the spine), but they can also occur in other locations. A study evaluated the association of SNPs of gal-3 rs4644 and rs4652 with SBC in the Chinese population (13). The distribution of genotypes ($p=0.662$, 95% CI= 0.592–2.279) and allele frequencies ($p=0.638$) of rs4644 between the SBC group and the control group did not differ significantly from one another. The allelic distributions at rs4652 showed a significant difference between the SBC group and the control group ($p=0.016$), and allele A was linked to the development of SBC. In the additive model (CC vs. AC vs. AA, $p=0.083$), the genotype distribution at rs4652 did not differ between the patient groups with SBC and the control groups, however, it did in the recessive model (CC+AC vs. AA, $p=0.043$). Moreover, genotype AA of rs4652 was associated with shorter progression-free survival (PFS). The SBC features of patients with various genotypes for two *LGALS3* SNPs were analyzed. Age, sex, tumor diameter, intraoperative blood loss, tumor septa, tumor lobulation, tumor blood supply, and histological type did not differ between various genotype groups. The dominant model of *LGALS3* SNP genotype rs4652, diameter, period prior to in-patient care, treatment history, tumor septa, tumor blood supply, and resection grade were potential significant factors in the univariate analysis of tumor growth. The *LGALS3* SNP genotype at rs4652 and treatment history were independent predictors for tumor growth as per multivariate analysis. Additionally, the AA genotype group had a greater risk of advancement than the CC+AC genotype group (HR= 7.219, 95% CI, 2.347–22.204, $p=0.001$).

The studies conducted in the Chinese population revealed significant genetic associations in the context of gliomas, glioblastomas, and skull base chordomas. Allele A of rs4652 was found to be associated with increased risk in gliomas and SBC. In addition, rs4652 AA genotype was also associated with an increased risk of SBC. Moreover, in glioblastoma, the rs4644 AA genotype and rs4652 CC genotype were associated with an increased risk, providing valuable insights for risk assessment.

## Endocrine Cancers

There are two studies involving the assessment of genetic variants of *LGALS3* in the risk of development of thyroid cancer in the Italian and Portuguese populations. A study by Corrodo *et al.,* 2021(14) evaluated the potential involvement of polymorphism rs4644 as a risk factor for differentiated thyroid cancer (DTC) in the Italian population. Moreover, it assessed the impact on the transcriptome in a model of CRISPR/Cas9-engineered thyrocytes. Nthy-ori-3-1 human thyroid cell line was used for gene editing and *in vitro* tests. CRISPR/Cas9 gene editing

technology was used to convert Nthy-Ori cells from their heterozygote genotype C/A to one of two homozygote genotypes (either A/A or C/C) in a single step. The population exhibited Hardy-Weinberg equilibrium (p=0.36), and because the control group was predominately made up of voluntary blood donors, it displayed a statistically significant older age than the patients (52.98% vs. 42.01%). Increased risk of DTC was linked to sex (females vs. males: OR= 2.93; 95%Cl=2.53-3.79; Py 10%) and smoking behavior (smokers vs. non-smokers: OR.4=1.34; 95%Cl=1.13-1.59; Pass=8.00x10"). Genotype AA was found to be associated with a decreased risk of DTC (OR=0.66, 95% CI=0.46-0.93, p=0.02). This study also revealed that CC-genotype was linked to higher expression of genes involved in the beginning and development of thyroid cancer (*DUSPS*), endometrial carcinoma (*ANOZ*), prostate/skin/kidney cancer (*HESI*), and pancreatic ductal adenocarcinoma (*HESI*). The tumor-suppressor genes (*CRYAB* and *IL1A*) or the enhanced expression of genes with anti-malignant effects in colorectal cancer (*GABBR1*) and thyroid cancer (*NOTCH3*) were linked to the tumor-protective AA-genotype. PLA study supported findings, showing increased TTF-1 and gal-3 interaction in ORI-AA as compared to ORI-CC cells. Furthermore, rs4644 genetic variation enhanced TCF4 transcription via nuclear beta-catenin accumulation, implicating TCF4 and gal-3 interaction.

In contrast, a study conducted in the Portuguese population identified SNPs, including rs4644 (Benign CA= 0.14, CC= 0.86, AA= 0.00 vs. Malignant CA= 0.00, CC= 0.875, AA= 0.125), rs10148371 (Benign GA= 0.09, GG= 0.82, AA= 0.00 vs. Malignant GA= 0.00, GG= 1.00, AA= 0.00), and rs11125 (Benign AT= 0.09, AA= 0 .91, TT=0.00 vs. Malignant AT=0.18, AA=0.73, TT=0.09) (15). In addition, analysis of rs4652 revealed that patients with papillary cancer had an AC genotype in 68%, AA in 20%, and CC in 12% of cases, whereas patients with multinodular goiter had an AC genotype in 67%, AA in 23%, and CC in 10% of cases. In the control population, 60% of the examined cases had the genotype AC, 24% had AA, and 16% had CC. However, no statistical difference in genotypic and allelic frequencies was observed between patients and controls ($p<0.05$). Moreover, no association was found between the rs4652 and different histological types of thyroid carcinoma.

In conclusion, these two studies provide divergent findings regarding the influence of *LGALS3* gene polymorphisms, particularly rs4644 and rs4652, on thyroid cancer risk and phenotype in different populations. The Italian study suggested that the rs4644 A-allele is protective against DTC and highlighted its impact on gene expression and transcriptional regulation. In contrast, the Portuguese study did not find any significant associations between *LGALS3* SNPs, including rs4652, and thyroid cancer susceptibility or histological subtype in the Portuguese population.

**Gal-3 and ligand interactions**

Above studies have shown a significant association between gal-3 gene variants and the risk of developing various cancers. These genetic variations appear to impact the structure and function of the gal-3 protein. *In-silico* analyses of different SNPs in the *LGALS3* were conducted, and the results indicated various potential effects (16). These effects predominantly encompassed modifications in methylation patterns, glycosylation, alterations in solvent accessibility, and changes in the secondary structure disorderliness of protein. Furthermore, experiments in zebrafish embryos demonstrated that rs201865041 (c.485G>A) led to the loss of function of the protein (17). Gal-3, in turn, plays a pivotal role in cancer development by interacting with both extracellular and intracellular ligands. It exerts influence over critical processes such as cell motility, migration, and apoptosis. These gene variants can disrupt the ability of gal-3 to effectively regulate these processes, shedding light on the complex relationship between genetic factors and cancer susceptibility, with implications for the development of therapeutic approaches. Following are the interactions of gal-3 with extracellular, cytoplasmic, and nuclear ligands in the context of cancer development.

**Extracellular Ligands**

Gal-3 is a multifunctional β-galactoside binding protein that exhibits extensive extracellular ligand interactions, including mucin-1 (MUC-1), lysosomal-membrane-associated glycoproteins-1 and -2 (LAMP-1 and LAMP-2), macrophage-1 antigen and macrophage-3 antigen (mac-1 and mac-3), CD-98, CD-45, CD-71, fibronectin, collagen IV, elastin, laminin, hensin, N-cadherin, desmoglein, αvβ3 integrin, vascular endothelial growth factor receptor-2 (VEGFR-2), neuron-glial antigen 2 (NG2), and α3β1-integrin (2,18). In the context of cancer biology, the interaction with extracellular ligands like MUC-1, integrins, N-cadherin, and NG2 are comprehensively studied (Figure 2 (a)). These interactions play crucial roles in mediating several facets of cancer progression, encompassing cell adhesion, motility, invasion and angiogenesis.

**MUC-1**

Gal-3 is a carbohydrate-binding protein that can recognize and bind to specific carbohydrate structures, particularly those containing N-acetylglucosamine residues. MUC-1 is a heavily glycosylated protein, and gal-3 can interact with the glycosylated region of MUC-1 in the extracellular domain. The binding of gal-3 to the T carbohydrate, a major tumor-associated antigen on MUC-1, mediates the interactions primarily (19). The binding of gal-3 to MUC-1 can modulate various biological processes. It can contribute to cell adhesion, promote cancer cell migration and invasion, and influence signalling pathways involved in cell growth and survival. Gal-3 has been shown to interact with MUC-1, clustering MUC-1 on the cell surface and exposing smaller cell surface adhesion molecules like E-cadherin. Such aggregation improved the survival of the cells by preventing cellular anoikis, a particular kind of apoptotic process that is brought on by the loss of cell adhesion or a deficiency in cell-matrix interactions. Additionally, it has been noted that aggregated cells outlive single cells in circulation by a significant margin. As a result, prolonged survival of disseminated tumor cells in circulation brought on by interactions between gal-3 and MUC-1 may have significant repercussions on the ability of cancer cells to metastasize. The physical entrapment of circulating cancer cells in the microvasculature at target tissues is also expected to increase as a result of mucin-galectin interactions, which also accelerates metastasis (20). Gal-3 is expressed more often in the blood of many cancer patients, which activates numerous critical processes in the metastatic cascade. There is a study showing that the activation of the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K)/ serine or threonine kinase (Akt) signaling pathways by binding of gal-3 to the T antigen on MUC-1 led to increased cell proliferation and motility (21). The dysregulated expression of MUC-1 was revealed as a pivotal factor in the progression of cancer, invasion, and metastasis. This aberrant upregulation was observed to be associated with various epithelial cancer types, such as lung, liver, pancreatic, and breast cancer (22). Additionally, MUC-1 is consistently found to exhibit positive expression in cervical, thyroid, gall bladder, and colorectal cancers.

**Mgat5-modified glycans and Integrin**

Gal-3 has been found to interact with modified glycans produced by the enzyme N-acetylglucosaminyltransferase V (MGAT-5). In Mgat5-/- mammary epithelial tumor cells, fibronectin fibrillogenesis and fibronectin-dependent cell spreading have been found to be deficient (23). Gal-3 binding to branched N-glycan ligands stimulates focal adhesion remodelling, focal adhesion kinase (FAK), and PI3K activation, local F-actin instability, and translocation to fibrillar adhesions, which has been shown to control fibronectin polymerization and tumor cell motility. Moreover, the Mgat5-dependent gal-3 lattice facilitates EGF signal transduction, triggering gal-3-dependent integrin activation, and subsequently leading to Src-dependent phosphorylation of caveolin-1 (Cav1) and activation of the RhoA/ Rho-associated

protein kinases (ROCK) signalling pathway (24). In addition, a study on thyroid cancer established synergistic link between gal-3 and Cav-1 (25). Furthermore, Gal-3 promotes angiogenesis by binding to the αvβ3 integrins on endothelial cells, which induces integrin clustering and activates signalling pathways that affect the angiogenic activity of vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), as well as promoting FAK phosphorylation (26).

**N-cadherin**

Gal-3 can bind to N-cadherin and interfere with its activity, which reduces cell-cell adhesion and increases invasiveness. It has been experimentally verified in murine mammary cancer cell lines. It has been demonstrated that extracellular gal-3 can bind to N-cadherin, contributing to the destabilization of cell-cell junctions and may facilitate cell migration (27).

**Neuron-glial antigen 2**

Neuron-glial antigen 2 (NG2) is a transmembrane chondroitin sulfate proteoglycan. It has been proposed that it stimulates angiogenesis and cell motility by forming the NG2-gal-3-α3β1 integrin complex at the pericyte-endothelial cell interface (28).

**Cytoplasmic Ligands**

There are various cytoplasmic ligands of gal-3, including B-cell lymphoma-2 (Bcl-2), Kirsten Rat Sarcoma viral oncogene homolog (K-Ras), ALG-2-interacting protein X or ALG-2 interacting protein-1 (Alix/AIP-1), cytokeratin, carbohydrate-binding protein 70 (CBP70), and, cysteine and histidine-rich protein (Chrp) (2,29). It was found that gal-3 interacts with these ligands through protein-protein interactions (Figure 2(b)). Most of the ligands play a role in the process of apoptosis.

**Bcl-2**

The specific molecular mechanism by which Bcl-2 interacts with gal-3 to contribute to cancer is not yet fully understood. Bcl-2 is known for its anti-apoptotic properties. It prevents cells from undergoing programmed cell death, allowing them to survive and potentially accumulate genetic mutations that can lead to cancer. Gal-3 is unique among galectin proteins because it contains a specific motif known as NWGR (Asn-Trp-Gly-Arg) within its CRD. The Bcl-2 homology 1 (BH1) domain is a part of the Bcl-2 protein family and is involved in the anti-apoptotic function of these proteins. This NWGR motif in Gal-3 has structural similarities to the BH1 domain of certain Bcl-2 family members, particularly in terms of amino acid sequence (30). Furthermore, a study in thyroid carcinoma cells demonstrated that gal-3 interacts with pro-apoptotic Bax, a member of Bcl-2 family, leading to inhibition of apoptosis (31).

**K-Ras**

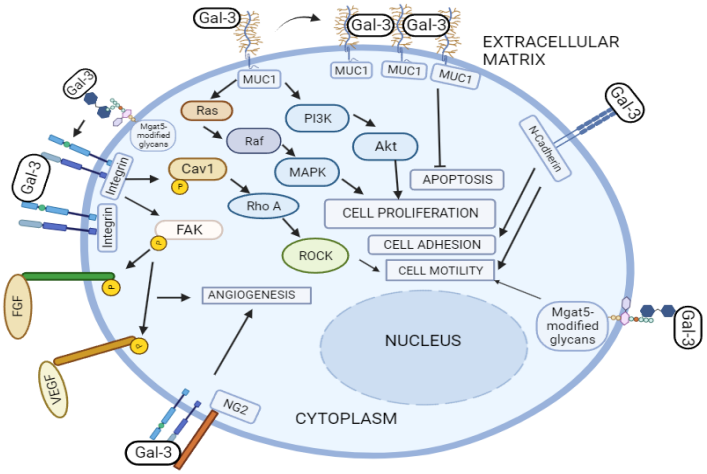
Gal-3 selectively binds to activated K-Ras, facilitating strong activation of both Raf-1 and PI3K and attenuation of Extracellular signal-regulated kinase (ERK), that are members of MAPK and PI3K/Akt pathway (32). The constitutive activation of K-Ras results in aberrant signalling that contributes to cancer initiation and progression, leading to persistent activation of downstream signalling pathways involved in cell growth and survival. It was demonstrated in human breast cancer cells (BT-549/Gal-3), upregulation of gal-3 was accompanied by a notable rise in wild-type K-Ras-GTP. According to the investigation, only the wild-type gal-3 protein showed the ability to bind and activate K-Ras, impacting the BT-549 human breast cancer cells' several oncogenic functions (33).

**Alix/AIP1**

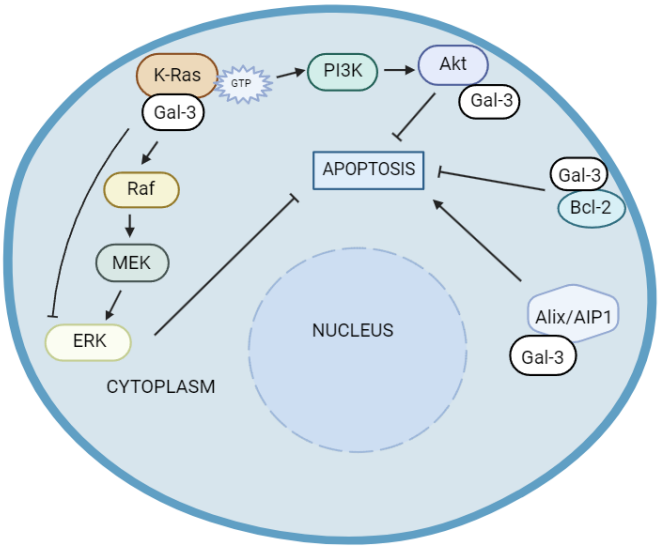
The yeast two-hybrid technique was used to identify Alix/AIP1 protein as a gal-3-binding cytoplasmic protein from a Jurkat cell cDNA library (34). Alix/AIP1 was documented to prevent paraptosis, a type of programmed cell death, but not apoptosis (35). Moreover, it has been established that Alix controls the expression of two proteins in breast cancer, the immune

checkpoint protein programmed cell death ligand 1 (PD-L1) and the cell survival epidermal growth factor receptor (EGFR) (36).

(a)




(b)



(c)

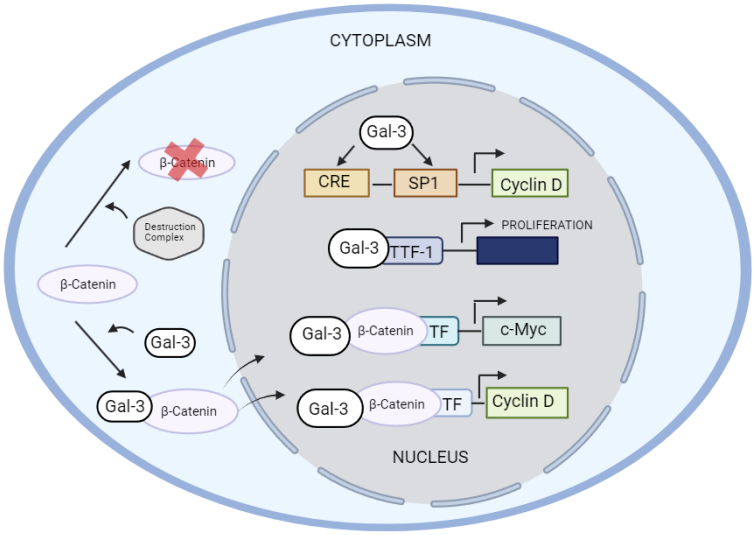



**Figure 2**: Interactions of gal-3 with (a) extracellular ligands (b) cytoplasmic ligands (c) nuclear ligands in cancer development.

## Nuclear Ligands

Galectin -3 binds to nuclear ligands like β-Catenin, thyroid transcription factor-1 (TTF-1), gemin-4, specificity protein 1 (SP1), and cAMP response element (CRE) binding sites, (29,37). Gemin-4 is a component of the complex, containing 15 polypeptides that are involved in processes like pre-mRNA splicing. The other ligands are involved in cancer biology (Figure 2(c)).

### β-Catenin

Gal-3 has the ability to bind to the β-catenin, which is the component of the Wnt signalling pathway, frequently dysregulated in cancer. By interacting with β-catenin, gal-3 can enhance the nuclear translocation of β-catenin, allowing it to interact with transcription factors and activate target genes like cellular myelocytomatosis (c-Myc) and Cyclin-D, involved in cell proliferation, survival, and invasion (38). This aberrant activation of Wnt signalling can contribute to uncontrolled cell growth and the acquisition of malignant properties. Gal-3 binding to β-catenin leads to its stabilization. In the absence of Wnt signalling, β-catenin is usually targeted for degradation by a protein complex known as the destruction complex, which includes proteins like glycogen synthase kinase-3 (GSK-3β) (39). However, gal-3 binding to β-catenin can protect it from degradation, resulting in its accumulation and increased transcriptional activity. This enhanced stability and nuclear localization of β-catenin can drive the expression of target genes involved in cell proliferation and survival, promoting cancer development. In a large-scale investigation involving Hepatocellular carcinoma (HCC) patients from various sets, gal-3 was shown to be closely correlated with vascular invasion and poor mortality (40). In HCC cells, gal-3 plays a key role in various metastasis-related processes, such as angiogenesis and the epithelial-to-mesenchymal transition (EMT). The PI3K-Akt-GSK-3-βcatenin signalling cascade was mechanistically activated by gal-3. The β-catenin/ transcription factor 4 (TCF4) transcriptional complex directly targeted insulin-like growth factor binding protein (IGFBP3) and vimentin to control angiogenesis and EMT, respectively.

Gal-3 was also suggested to be associated with increased tumorigenesis and metastasis of HCC cells in animal models by enhancing β-catenin signalling (40).

**TTF-1**

Gal-3 binds with TTF-1, and this binding complex enhances the transcriptional activity of TTF-1, promoting the growth of thyroid cells (41). It was established that gal-3 is necessary for sustaining the highly proliferating altered phenotype of papillary thyroid cancer, utilizing an antisense method (42).

**SPI and CRE sites**

The nuclear protein-DNA complex at the SP1 and CRE sites of the cyclin D1 promoter, one of the cell-cycle regulators, is also stabilized by gal-3 (37). A study revealed that gal-3 increases cyclin D1 promoter activity in human breast epithelial cells through cis-elements, including the SP1 and CRE sites (43).

## Critical Comments

- Genetic polymorphisms play a significant role in understanding cancer susceptibility and progression. Among these, two well-known single nucleotide polymorphisms of gal-3, rs4644 and rs4652, have been extensively investigated in numerous cancer types, shedding light on their potential roles in oncogenesis. However, the polymorphism rs11125 is less explored in the broader context of cancer. Given the positive results observed in cervical cancer (5), it is crucial that further investigations should be undertaken to explore the potential involvement of *LGALS3* variants, including rs11125 in a wider spectrum of cancers. This will help in gaining a comprehensive understanding of the impact of polymorphism on cancer in addition to presenting an opportunity for therapeutic interventions and personalized medicine strategies across various malignancies. Furthermore, it is crucial to conduct studies with a more extensive sample size for each variant, which not only increases the statistical power but also reduces biasness.
- SNPs within exonic regions have been extensively studied. However, intronic SNPs have remained underexamined despite their critical roles in genetic regulation. More studies are required to investigate intronic SNPs, which is essential for a comprehensive understanding of genetic diversity, disease susceptibility, and therapeutic strategies.
- The *LGALS3* SNPs research has primarily focused on the Asian and Caucasian populations, with a notable gap in studies involving African populations. Within the Asian demographic, particular emphasis has been placed on the East Asian populations, primarily Chinese and Japanese cohorts. There is a lack of published research on the South Asian cohort, which constitutes a significant proportion of the world's population. More inclusive studies encompassing African, South Asian, and other underrepresented populations should be conducted. These will help to develop healthcare strategies that can effectively benefit the majority of the population.
- *In-silico* analysis has provided valuable insights into the potential implications of non-synonymous substitutions within the *LGALS3* in relation to cancer development. Notably, when assessing the common SNP rs4644, software tools such as SIFT and Polyphen have highlighted its association with deleterious and damaging effects (16). However, for the most common SNP, such as rs4652, studies including *in-silico* analysis are currently unavailable. More comprehensive bioinformatics analysis can help to highlight some putative functional and clinically relevant variants, which can be tested further in multiple ethnic cohorts.
- While *in-silico* analysis provides valuable initial assessments, experimental studies are required to understand the underlying molecular mechanisms and the biological impact of

these genetic variations. In breast cancer, it was revealed that rs4644, the substitution of the proline by histidine, makes the protein more susceptible to MMPs cleavage (4). The cleaved gal-3 was found to be bound with more affinity to the endothelial cells of the microvessels, promoting cellular processes like migration and angiogenesis. For gastric cancer, the substitution of A>C at SNP rs4652 increases the affinity of gal-3 with fibroblast receptor proteins, activating fibroblasts (myofibroblasts), which promotes the angiogenesis and growth of gastric cancer cells (8). In another study, it was indicated that genetic alterations distort protein structure, affecting the cellular pathways in which they are involved, including the Wnt /B-catenin pathway (9,10). While it is evident that genetic variation in *LGALS3* can influence the structure and function of gal-3, a multifunctional protein known to interact with various ligands and modulate diverse biological processes, the precise mechanisms underlying the impact of these genetic variants on the development of various cancers remain unclear and require further experimental studies.

## 4.CONCLUSION

The association of specific SNPs with a range of cancer types across different populations signifies the impact of genetic variants on cancer susceptibility and development. The SNP rs4644 has been reported with the risk of various cancers in different populations, including breast cancer in Asian and Caucasian populations, prostrate, thyroid cancer and glioblastoma in German, Italian and Chinese cohorts. Similarly, rs4652 was linked with cervical, gastric, gliomas, glioblastomas, SBC and NSCLC in Chinese population. rs11125 was observed to be associated with cervical cancer in Chinese cohort. Furthermore, the differences in genotypic frequencies of rs4644 and rs4652 in Turkish colorectal cancer patients compared to controls highlights the relevance of Gal-3 genetic variants in cancer. The genetic variants, including SNPs exert a strong influence on integral biological processes through protein-ligand interactions. These findings emphasize on the critical importance of SNP research in cancer, indicating the necessity for further comprehensive investigations. In addition, further studies are required to elucidate the intricate mechanisms through which genetic variations in *LGALS3* impact the structure and function of Gal-3, subsequently influencing the downstream signalling leading to cancer development. Addressing this research gap will contribute to the development of targeted therapeutic strategies and ultimately improving cancer management and outcomes across different populations.

## 5.LIST OF ABBREVIATIONS

Akt: Serine or threonine kinase
Alix/AIP-1: ALG-2-interacting protein X or ALG-2 interacting protein-1
Bcl-2: B-cell lymphoma-2
BH1: Bcl-2 homology 1
Cav-1: Caveolin-1
CBP70: Carbohydrate-binding protein 70
Chrp: Cysteine and histidine-rich protein
c-Myc: Cellular myelocytomatosis
CRE: cAMP response element
DTC: Differentiated thyroid cancer
EGFR: Epidermal growth factor receptor
EMT: Epithelial-to-mesenchymal transition
ERK: Extracellular signal-regulated kinase
FAK: Focal adhesion kinase
FGF: Fibroblast growth factor

Gal-3: Galectin-3
GSK-3β: Glycogen synthase kinase-3
HCC: Hepatocellular carcinoma
IGFBP3: Insulin-like growth factor binding protein
K-Ras: Kristen Rat Sarcoma viral oncogene homolog
LSCC: Laryngeal squamous cell carcinoma
MALDI-TOF MS: Matrix-assisted laser desorption/ionization time-of flight mass spectrometry
MAPK: Mitogen-activated protein kinase
MGAT-5: N-acetylglucosaminyltransferase V
MMP: Matrix metalloproteinases
NG-2: Neuron-glial antigen 2
NSCLC: Non-small cell lung cancer
PCR-RFLP : Polymerase chain reaction-restriction fragment length polymorphism
PCR-SSCP: Polymerase chain reaction-single-strand conformation polymorphism
PD-L1: Programmed cell death ligand 1
PFS: Progression-free survival
Pgp: P-glycoprotein 1
PRISMA: Preferred reporting items for systematic reviews and meta-analysis
qPCR: Quantitative polymerase chain reaction
ROCK: Rho-associated protein kinases
SBC: Skull base chordoma
SCLC: Small cell lung cancer
SNP: Single nucleotide polymorphism
SP1: Specificity protein 1
TCF4: Transcription factor 4
TMZ: Temozolomide
TTF-1: Thyroid transcription factor-1
UTR: Untranslated region
VEGF: Vascular endothelial growth factor

**ETHICS APPROVAL AND CONSENT TO PARTICIPATE**

Not applicable.

**HUMAN AND ANIMAL RIGHTS**

No Animals/Humans were used for studies that are base of this research.

**CONSENT FOR PUBLICATION**

Not applicable.

**FUNDING**

None.

**CONFLICT OF INTEREST**

There is no conflict of interest exists.

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