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Genetic Variants and Haplotype Structures in the *CASC* Gene Family to Predict Cancer Risk: A Bioinformatics Study

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ABSTRACT

Background and Aims: The cancer susceptibility (*CASC*) gene family of long noncoding RNAs (lncRNAs) plays an important role in cancer. The aim of this study was to identify genetic variants and haplotype structures of *CASC* genes associated with cancer risk.

Methods: Genome-wide association studies (GWAS) significant variants ($p \leq 5 \times 10^{-8}$) on *CASC* family genes were identified from the GWAS Catalog-EMBL-EBI, and then cancer-associated variants on *CASC* genes were extracted. These variants were functionally analyzed, including lncRNA:miRNA binding sites, Regulomedb scores, and eQTL. The 1000 Genome Project genotyping data Phase III were used to identify haplotypic blocks. Finally, the genes associated with them were examined for expression and gene-gene correlation analyses using OncoDB.

Results: There were six haplotypic blocks in four genes. The GC, TA, and AGAC haplotypes are located in the *CASC8* gene and increase the risk of prostate cancer, breast cancer, and colorectal cancer, respectively. The CA haplotype in the *CASC15* gene increases the risk of neuroblastoma, AA haplotype in the *CASC16* gene increases the risk of breast cancer, and ACGATG haplotype in the *CASC17* gene increases the risk of prostate cancer ($p \leq 5 \times 10^{-8}$). Their genes are interrelated and their expression is increased in these cancers. The rs2294214 is associated with skin cancer and has positive effects on five *CASC15*:miRNA binding sites. The rs3803662 is located in *CASC16*:miRNA binding sites, which has positive effects on hsa-miR-4475 and hsa-miR-7845-5p and negative effects on hsa-miR-4524a-3p and hsa-miR-4524b-3p.

Conclusion: These haplotypic structures and lncRNA:miRNA:SNP interactions on *CASC* family lncRNAs reveal novel genetic associations between *CASC* genes and various cancers.

1 | Introduction

Cancer is the second leading cause of death in the world, responsible for one in six deaths [1], and the number of cancer-related deaths worldwide almost doubled between 1990 and 2020 [2]. The global cancer rate has increased in recent decades and is expected to reach 28.4 million cases in 2040, representing a 47% increase compared to 2020 [3]. There are more than 200 types of cancer, of which breast cancer in women and lung cancer in men are the most common cancers, with incidence of 55.9% and 39%, respectively [3]. Although this disease is one of the deadliest complex diseases, many cases are curable with early diagnosis and effective treatment [2].

Cancer can start from any organ or tissue through uncontrolled cell growth and can metastasize to other organs in the body. Various factors such as genetics play a role in cancer susceptibility. Previous studies have investigated the role of variants, genes, and epigenetic factors on cancer risk, treatment, diagnosis, and prognosis [4–6]. Most cancer susceptibility (*CASC*) genes are a class of long noncoding RNA (lncRNA) [7], transcripts of more than 200 nucleotides (200 nt) that do not encode a protein and whose role in the pathogenesis of different types of diseases has been investigated in previous studies [8–10]. *CASC* genes are involved in important cellular processes, cancer susceptibility, cell proliferation, epithelial–mesenchymal transition (EMT), invasion, and migration [11]. For example, *CASC15* regulates EMT, proliferation, and migration of gastric cancer cells. This lncRNA is involved in tumorigenesis by modulating CDKN1A in the nucleus through interaction with WDR5 and EZH2, whereas knockdown of *CASC15* silences ZEB1 by acting as a competing endogenous RNA (ceRNA) that binds to miR-33a-5p [11]. Several genome-wide association studies (GWAS) have investigated the role of *CASC* family genetic variants in different cancers such as breast cancer, colorectal cancer, prostate cancer, bladder cancer, skin cancer, pancreatic cancer neuroblastoma, and leukemia [12–19]. For instance, the CASC16 rs3803662 (p-value 4×10^{-117}) and CASC8 rs6983267 (p-value 2×10^{-122}) variants were associated with the risk of breast and colorectal cancers, respectively [14, 17]. In addition, some variants exhibited pleiotropic effects [18]. These genes can have oncogenic or tumor suppressor effects and their expression is related to cancer development and progression by targeting different genes [11, 20] through various mechanisms such as being a competing endogenous RNA (ceRNA), acting as molecular sponges, competitively binding to miRNAs [11, 21], or suppressing miRNA levels [22].

Given the importance of *CASC* genes in cancer, the lack of a comprehensive study on the role of *CASC* genetic variants as well as their candidate haplotypes in cancer, and the investigation of the potential role of their genetic variants in cancer by affecting lncRNA:miRNA interactions, this study aimed to investigate the novel genetic associations of CASC genes with cancer risk.

2 | Methods

2.1 | Study Pipeline

The study pipeline is illustrated in Figure 1. Significant GWAS variants were used in this study. First, significant GWAS variants in the *CASC* genes were identified, and then cancer-associated variants in the *CASC* genes were extracted. These variants were subjected to functional analysis, including lncRNA:miRNA binding sites, Regulomedb scores, and expression quantitative trait locus (eQTL). Their associated genes were analyzed for expression and gene-gene correlation analyses. Finally, the 1000 Genomes Project genotyping data were used to identify haplotype-significant GWAS variants associated with cancer. Ethics approval was not required as no animals or clinical samples were used in this study.

2.2 | Cancer-Associated Variants of *CASC* Genes and Haplotype Analysis

To identify significant cancer-associated variants ($p \leq 5 \times 10^{-8}$) on *CASC* genes, we used the GWAS Catalog-EMBL-EBI (gwas_catalog_v1.0.2-associations_e109_r2023-05-07) downloaded from (https://www.ebi.ac.uk/gwas/) [23]. The "disease/treat" and "mapped gene" sections of GWAS Catalog-EMBL-EBI were used to identify all *CASC* genes associated with different types of cancers. The R programming language (version 4.2.1, haven package and specific script) was used to remove duplicate results based on disease. To find linkage disequilibrium (LD) variants, HaploReg v4.2 (https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php) was used with; $r^2 \geq 0.8$ and $D' \geq 0.8$ [24]. To identify haplotypic blocks associated with *CASC* genes and cancer risk, 1000 genome Phase 3 genotyping data containing GWAS LD variants ($n = 2504$

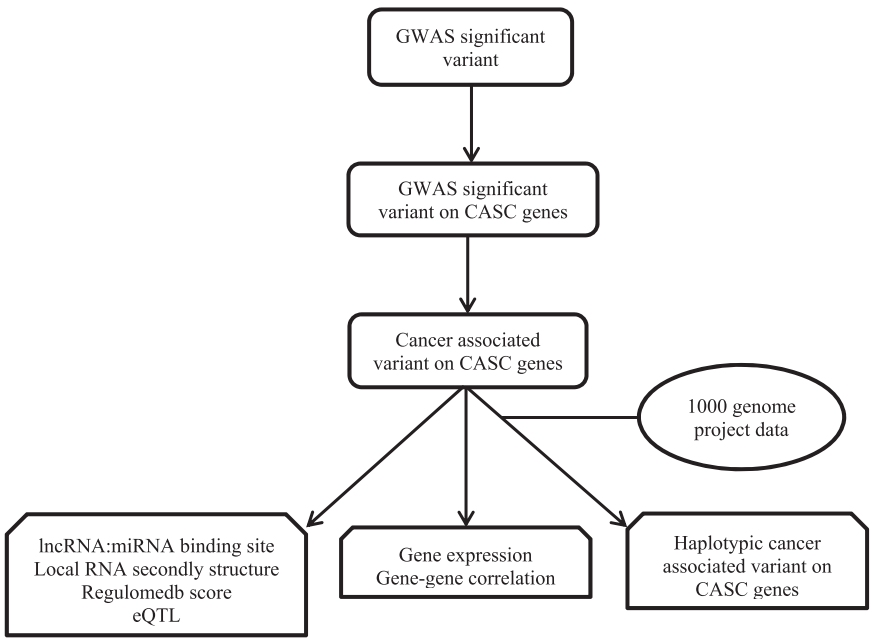

FIGURE 1 | Study pipeline. *CASC*, cancer susceptibility; eQTL, expression quantitative trait locus; GWAS, genome-wide association studies; lncRNA, long noncoding RNA; miRNA, microRNA.

samples) were downloaded from Ensembl Genome Browser 110 (https://asia.ensembl.org/index.html) [25]. LD plots and haplotypic blocks were created using HaploView V4.2. Finally, haplotypes associated with an increased cancer risk were identified based on their alleles. All variants in haplotypes were GWAS siginifcant variants, and the selected allele of each variant was reported to be associated with an increased risk of cancer in the original GWA study.

2.3 | SNP Functional Analysis

Variant position, gene, and type of variant were determined using Ensembl Genome Browser 109 (https://asia.ensembl.org/index.html) [25] and dbSNP (https://www.ncbi.nlm.nih.gov/snp/) [26]. RegulomeDB (https://regulomedb.org/regulome-search/) [27] is used to score the regulatory functions of variants (ranging from 0 to 1) and determine the probability of a functional effect. LncRNA:miRNA target site SNPs identified with lncRNASNP v3 (https://gong_lab.hzau.edu.cn/lncRNASNP3/) [28]. The lncRNASNP v3 identifies lncRNA:miRNA binding sites using both TargetScan [29] and miRmap [30], and miRNA binding site conservation information is obtained using the UCSC LiftOver tool. The effect of miRNA binding site SNP on the lncRNA:miRNA interaction is examined by substituting the alternative allele in place of the wild-type allele and investigation of lncRNA:miRNA binding sites based on miRmap and TargetScan. If a lncRNA:miRNA interaction is detected only in the alternative transcript, it is termed an interaction gain, whereas an interaction only in the wild-type transcript is defined as an interaction loss [28]. The eQTL variants were identified using Genotype-Tissue Expression (GTEx) portal (https://gtexportal.org/home/). The local RNA secondary structure of LncRNA:miRNA target site SNPs was examined using RNAsnp (https://rth.dk/resources/rnasnp/) [31].

2.4 | Gene Expression and Correlation Analyses

OncoDB (https://oncodb.org/) [32] was used to perform gene expression and correlation analyses. The cancer cases were from cancer patients from the TCGA data and the controls were from normal tissue from the GTEx study. Both the expression profile and expression correlation modules were used for these analyses.

3 | Results

In the GWA studies, six genes *CASC8, CASC11, CASC15, CASC16, CASC17*, and *CASC19* were significantly associated with cancer. *CASC8* was the most importantcancer-related *CASC* gene with 25 GWAS significant variants. The results are shown in Table 1 and the full results including eQTL and

TABLE 1 | Significant GWAS variants ($p \leq 5 \times 10^{-8}$) on *CASC* genes for different types of cancers.

Gene	Disease	Variant
CASC8	**Breast cancer**	rs13281615, rs1562430, rs10096351, rs2392780
	Colorectal cancer	rs6983267, rs4871022, rs10505477, rs7014346
	hormone-sensitive cancer	rs1447295, rs10505477
	Prostate cancer	rs1447295, rs4871798, rs1447293, rs4871790, rs6983267, rs445114, rs16902094, rs4506170, rs10505477
	Cancer	rs6983267
	Cancer (pleiotropy)	rs56868629, rs78449170, rs28451337, rs6983267, rs144898130, rs146836668, rs116846195, rs62516012
CASC11	**Bladder cancer**	rs9642880, rs10094872
	Pancreatic cancer	rs10094872
	Cancer (pleiotropy)	rs10094872
CASC15	**Bladder cancer**	rs76088467
	Breast cancer	rs7760611
	Neuroblastoma	rs4712653, rs9295536, rs6939340
	Prostate cancer	rs12665509
	Skin cancer	rs55775505, rs2294214
CASC16	**Breast cancer**	rs4784227, rs3803662, rs3112612, rs12922061, rs3803661
	Cancer	rs4784227
	Cancer (pleiotropy)	rs2335
CASC17	Prostate cancer	rs1859962, rs4793529, rs17765344, rs7217073, rs8071558, rs6501436
	Cancer (pleiotropy)	rs9911515
CASC19	Chronic lymphocytic leukemia	rs2466035, rs2466029
	Prostate cancer	rs138042437

Abbreviations: *CASC*, cancer susceptibility; GWAS, genome-wide association studies.

regulomedb scores are presented in Supporting Information: Results 1.

The *CASC15* rs2294214 variant is associated with skin cancer and *CASC16* rs3803662 variant is associated with breast cancer, which are located in the lncRNA:miRNA binding site. The effects of these variants on the local RNA secondary structure were not significant (Supporting Information: Results 2). The rs2294214 variant had a gain effect on *CASC15* interactions with five miRNAs. The rs3803662 variant exhibited a gain effect on *CASC15* interactions with hsa-miR-6873-5p, whereas it had loss effects on *CASC15* interactions with other miRNAs. The complete results are shown in Table 2 and Supporting Information: Results 3.

Interestingly, significant GWAS variants had different LD blocks. The results showed that *CASC17* and CASC8 have one LD block for prostate cancer. *CASC8* and *CASC16* have one LD

TABLE 2 | lncRNA:miRNA:SNP interactions for GWAS significant variants.

lncRNA:miRNA:SNP	Target site interaction	Effect on interaction
CASC15: hsa-miR-362-3p: rs2294214	lncRNA:5′ UGGGAAGAAGAGAGCCAGCCAGGUGUGUUCGAUGCCUUC 3′ |||||||. miRNA:3′ ACUUAGGAACUUAUCCACACAA 5′	Gain
CASC15:hsa-miR-329-3p: rs2294214	lncRNA:5′ UGGGAAGAAGAGAGCCAGCCAGGUGUGUUCGAUGCCUUC 3′ |||||||. miRNA:3′ UUUCUCCAAUUGGUCCACACAA 5′	Gain
CASC15: hsa-miR-603: rs2294214	lncRNA:5′ UGGGAAGAAGAGAGCCAGCCAGGUGUGUUCGAUGCCUUC 3′ ||||||. miRNA:3′ CGUUUUCAUUAACGUCACACAC 5′	Gain
CASC15: hsa-miR-1228-3p: rs2294214	lncRNA:5′ UGGGAAGAAGAGAGCCAGCCAGGUGUGUUCGAUGCCUU 3′ ||||||. miRNA:3′ CCCCCCGCUCCGUCCACACU 5′	Gain
CASC15: hsa-miR−8485: rs2294214	lncRNA:5′ UGGGAAGAAGAGAGCCAGCCAGGUGUGUUCGAUGCCUUC 3′ ||||||. miRNA:3′ UAUGCACACACACACACACAC 5′	Gain
CSAC16:hsa-miR-4475:rs3803662	lncRNA:5′ UGGGUACAUGGAACUGUAAGCUGUCCCUUAGCGAAGAAUA 3′ |||||||. miRNA:3′ UAUUACUUACGAACCAGGGAAC 5′	Gain
CSAC16: hsa-miR-7845-5p:rs3803662	lncRNA:5′ UGGGUACAUGGAACUGUAAGCUGUCCCUUAGCGAAGAAU 3′ |||||||. miRNA:3′ GGUGCUGGGAGGGACAGGGAA 5′	Gain
CSAC16:hsa-miR-4524a-3p:rs3803662	lncRNA:5′ UGGGUACAUGGAACUGUAAGCUGUCUCUUAGCGAAGAA 3′ |||||||. miRNA:3′ UAUCGUCGUAUUCGGACAGAGU 5′	Loss
CSAC16:hsa-miR-4524b-3p:rs3803662	lncRNA:5′ UGGGUACAUGGAACUGUAAGCUGUCUCUUAGCGAAGA 3′ ||||||. miRNA:3′ AUCGUCGUACUUGGACAGAG 5′	Loss

Abbreviations: *CASC*, cancer susceptibility; GWAS, genome-wide association studies; lncRNA, long noncoding RNA; miRNA, microRNA; SNP, single nucleotide polymorphism.

block for breast cancer, and *CASC8* has two LD blocks associated with colorectal cancer. Haplotypes of significant variants are shown in Figure 2. Additional results are presented in Supporting Information: Results 4 and 5.

Since *CASC8* and *CASC16* gene variants are associated with breast cancer susceptibility, the gene-gene correlation of these lncRNAs has been investigated in breast cancer patients. The results showed that *CASC16* has a negative correlation with *CASC8* ($p = 1.9 \times 10^{-9}$). These results were from 1135 TCGA breast cancer patients and show that when the expression (transcript per million) of CASC8 is increased, it is accompanied by decreased expression of CASC16 in the same patient. Since *CASC8, CASC17*, and *CASC19* gene variants are associated with prostate cancer susceptibility, the gene-gene correlation of these lncRNAs has been investigated in prostate cancer patients. The results for gene–gene correlation showed that *CASC8* has a positive correlation with *CASC17* ($p = 2.3 \times 10^{-6}$) and *CASC19* ($p = 9 \times 10^{-13}$). In addition, *CASC17* and *CASC19* ($p = 8.5 \times 10^{-44}$) are also positively correlated. These results were related to 505 TCGA prostate cancer cases and showed that increased expression of *CASC8* was accompanied by increased expression of *CASC17* and *CASC19* in the same patient. The identified correlations (positive or negative) show the balance of biological systems, functional relationships, and important biological mechanisms between these breast/prostate cancer genes, and their coregulation suggests that these genes may share a common biological process. Gene expression correlations provide a robust method for predicting gene function. The complete results are shown in Figure 3.

The expression of normal and prostate cancer tissues was significantly different for *CASC8* and *CASC19* genes ($p \leq 1 \times 10^{-3}$). The complete results are shown in Figure 4.

4 | Discussion

This study identified several LD blocks in *CASC* genes and lncRNA:miRNA interactions associated with cancer. There were six haplotypic blocks in four genes. The GC haplotype increases the risk of prostate cancer, the TA haplotype increases the risk of breast cancer, and the AGAC haplotype increases the risk of colorectal cancer. These haplotypes are located in the *CASC8* gene. The ACGATG haplotype in the *CASC17* gene increases the risk of prostate cancer. The CA haplotype in the *CASC15* gene increases the risk of neuroblastoma, whereas the AA haplotype in the *CASC16* gene increases the risk of breast cancer. LD blocks for prostate cancer were located in *CASC8* and *CASC17* genes. The significant role of variants on these blocks was identified in previous GWAS [18, 19, 33–41]. Further analysis showed that these genes are positively correlated with each other and their expression is increased in prostate cancer. The genes in the two LD blocks *CASC8* and *CASC16* showed a negative correlation for breast cancer, and their expression were increased in breast cancer. The important roles of variants in these blocks were identified in previous GWAS [42–46]. Two LD blocks in *CASC8* gene were identified for colorectal cancer, and *CASC8* gene expression was increased in colon and rectal cancers. In this regard, variants in these LD blocks play an important role in cancer based on previous GWA studies [47–50].

The rs2294214 variant is associated with skin cancer. This variant is located in the binding site of *CASC15* with hsa-miR-362-3p, hsa-miR-603, hsa-miR-1228-3p, hsa-miR-329-3p, and hsa-miR-8485, which positively affects these interactions. The role of *CASC15* in proliferation, migration, and invasion of skin cancer was identified [51]. Although these interactions have not

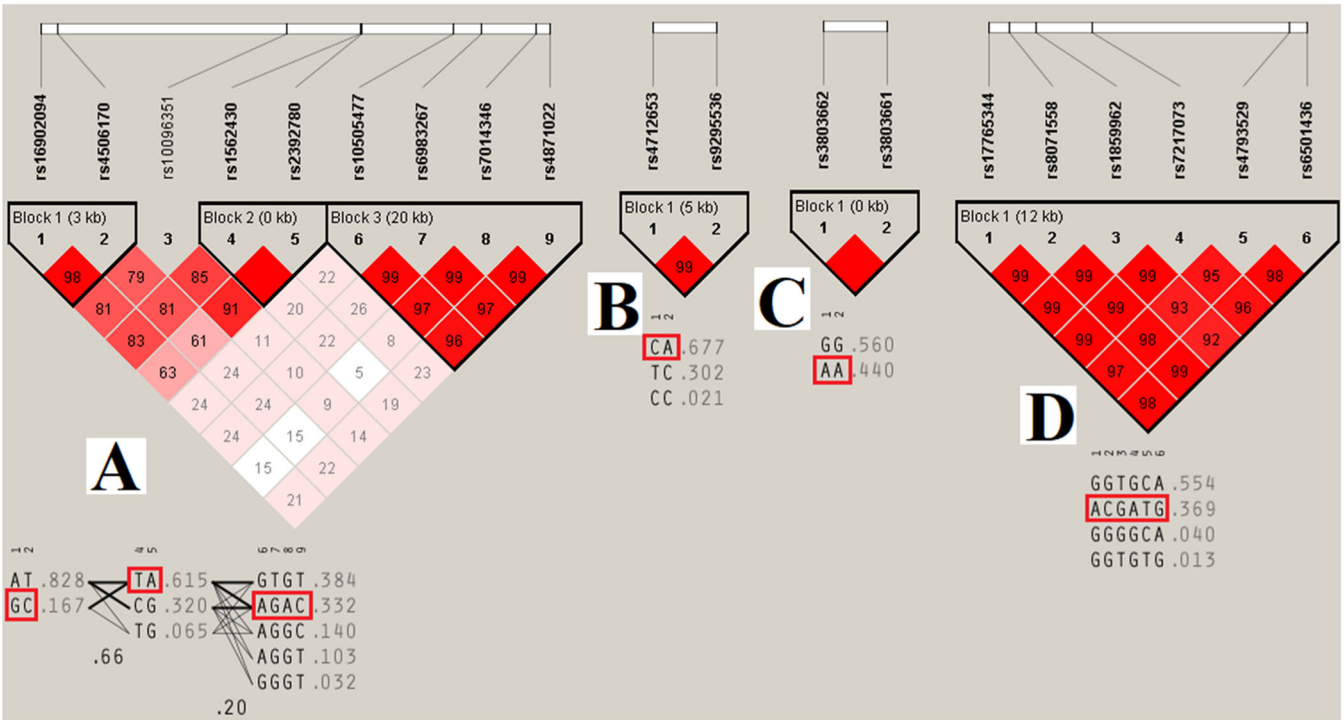

FIGURE 2 | LD plots and haplotypic blocks associated with *CASC* genes. A for *CASC8*; B, for *CASC15*; C, for *CASC16*; D, for *CASC17*. *CASC*, cancer susceptibility; LD, linkage disequilibrium.

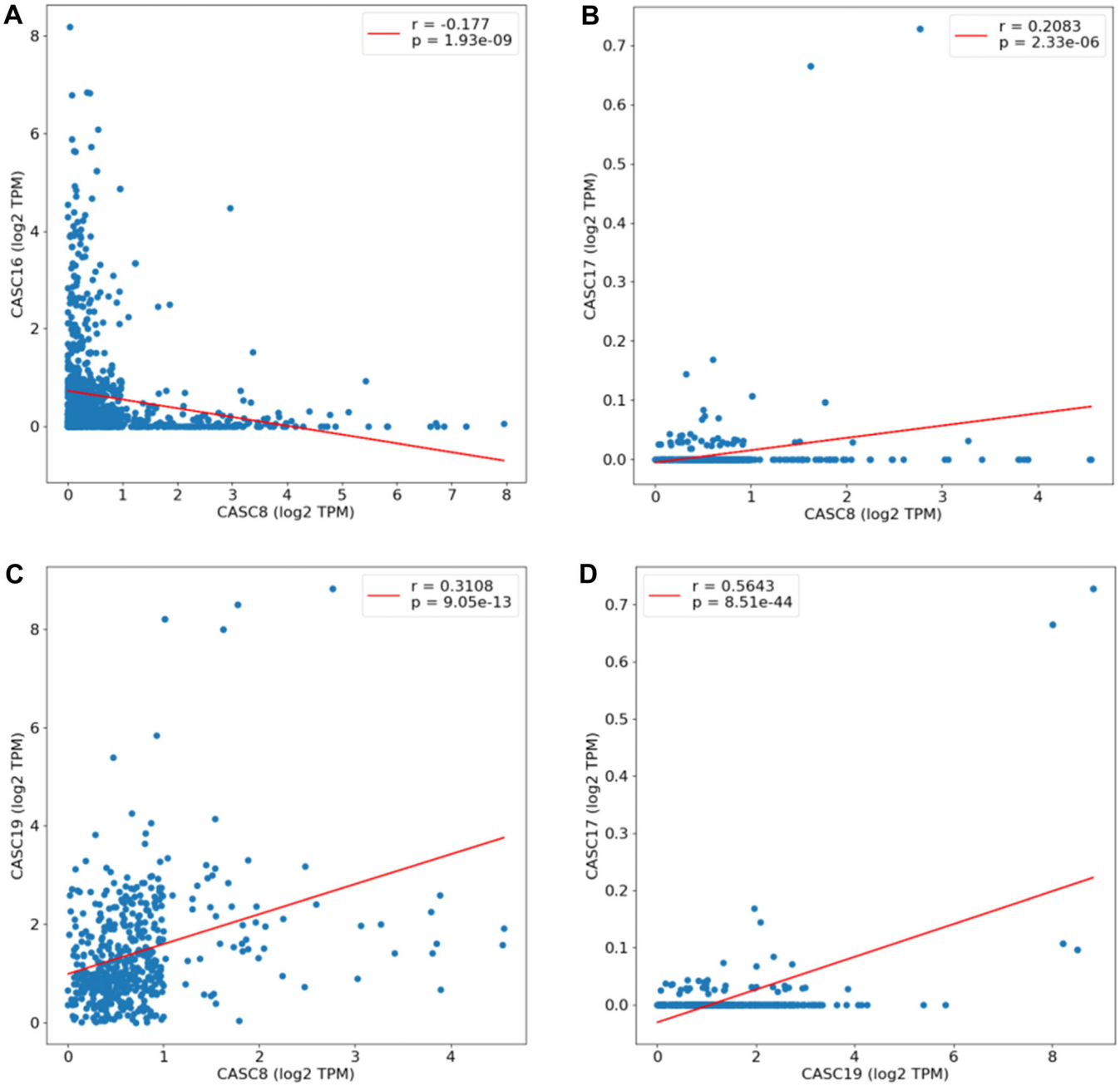

FIGURE 3 | *CASC* lncRNAs gene–gene correlations. A is related to breast cancer. B, C, and D are related to prostate cancer. *CASC*, cancer susceptibility; lncRNA, long noncoding RNA.

been investigated in previous studies, the association of hsa-miR-362-3p, hsa-miR-603, hsa-miR-1228-3p miRNAs, and rs2294214 with skin cancer has been investigated in previous studies [52–55]. rs3803662 is located in *CASC16* binding sites, which has positive effects on hsa-miR-4475 and hsa-miR-7845-5p and negative effects on hsa-miR-4524a-3p and hsa-miR-4524b-3p binding sites. The role of rs3803662 and several other *CASC16* variants identified in breast cancer [56, 57], and the role of these miRNAs in cancer is under investigation [58, 59].

According to the results of the present study, further studies in the following subjects are recommended. First, as Figure 4 shows, the expression of CASC16 in breast cancer tissues is significantly increased compared to normal tissues, while the expression of CASC8 is slightly decreased in the mentioned tissues. These results are consistent with the results of Figure 3, which show that increased expression of CASC16 is accompanied by reduced expression of CASC8 in breast cancer patients. In addition, according to Figure 4, the expression of CASC8 and CASC19 in prostate cancer tissues is significantly increased compared to normal tissues, and the expression of CASC17 in this tissue is increased insignificantly and is consistent with the results of Figure 3, which states that the increased expressions of CASC8, CASC17, and CASC19 in breast cancer patients are related to each other. However, based on the lack of previous studies on the association and correlation of these genes, the functional consequences or mechanisms behind the identified gene-gene correlation

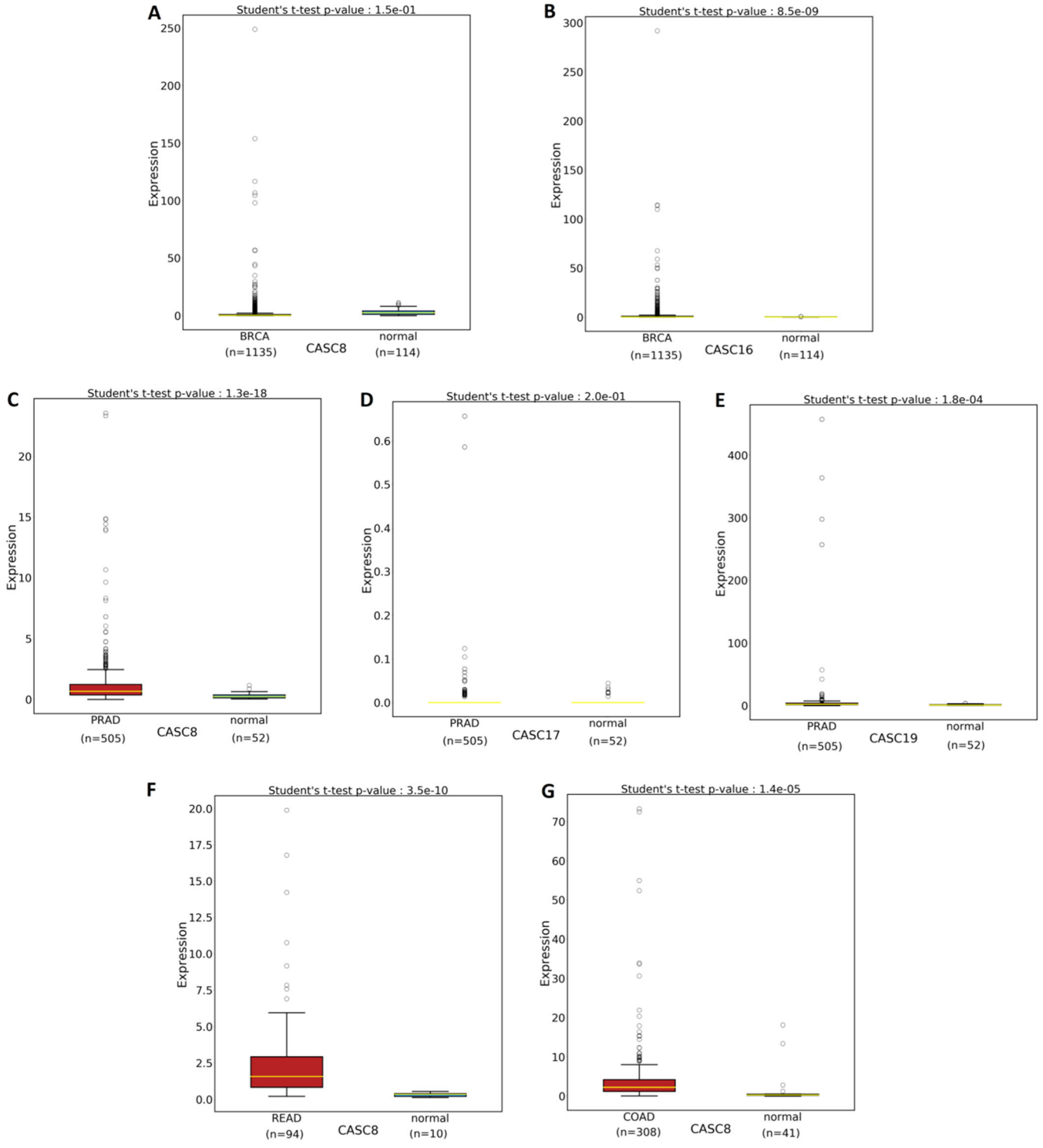

FIGURE 4 | Gene expression based on the cancer type. A and B for breast cancer. C, D, E for prostate cancer. F and G for rectum and colon cancer.

should be considered in future studies. Secondly, this study only focused on the GWAS significant variants and all risk variants retrieved by the GWAS catalog, while we found that GWAS variants had different LD blocks, maybe because some GWAS may report the lead variant with the smallest p-value to represent the locus. Therefore, this study may miss some LD blocks mapped by non-lead GWAS variants, which should be considered in future studies.

In summary, this study identified novel haplotypic structures in *CASC8* (associated with increased risk of breast cancer, colorectal cancer, and prostate cancer), *CASC15* (associated with increased risk of neuroblastoma and skin cancer), *CASC16* (associated with increased risk of breast cancer), and *CASC17* (associated with increased risk of prostate cancer), as well as lncRNA:miRNA:SNP interactions in *CASC15* and *CASC16*. These interactions were not investigated in previous studies.

These results reveal novel genetic associations between *CASC* genes and various cancers. Future studies are needed to confirm these findings based on case-control studies.

Author Contributions

Morteza Gholami: conceptualization, investigation, writing–original draft, methodology, writing–review and editing, software, supervision, data curation, formal analysis. **Mohsen Asouri:** conceptualization, writing–original draft, methodology, writing–review and editing, software. **Ali Asghar Ahmadi:** conceptualization, writing–original draft, writing–review and editing, methodology, formal analysis.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that supports the findings of this study are available in Supporting Information of this article.

Transparency Statement

The lead author Morteza Gholami affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.