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Association between the FAS rs1800682 Polymorphism and Thyroid Cancer Susceptibility

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ABSTRACT

Background and Objective: Thyroid carcinoma is the most frequently diagnosed malignancy of the endocrine system. Considerable attention has been directed toward the investigation of genetic polymorphisms within genes governing apoptotic pathways and their potential contribution to cancer susceptibility. FAS, a cell surface receptor, initiates the apoptotic signaling cascade upon engagement with its cognate ligand, FASL. The present study was designed to evaluate the association between the FAS-670A/G polymorphism (rs1800682) and thyroid cancer susceptibility in the northwestern Iranian population.

Methods: In this case-control study, 115 patients with thyroid cancer (confirmed by pathological examination of thyroid tissue) and 125 control individuals (healthy subjects with no personal or first-degree family history of any cancer) were enrolled. Peripheral blood samples (5 mL) were obtained from all participants. Genomic DNA was isolated using a proteinase K-based extraction protocol, and genotyping of the FAS (rs1800682) polymorphism was performed using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay with the MvaI restriction enzyme.

Findings: The genotype frequencies for AA, AG, and GG among the patient group were 41.74%, 30.43%, and 27.82%, respectively, compared to 43.2%, 33.6%, and 23.2% in the control group. The allelic frequencies for G and A were 43.04% and 56.96% in cases, versus 40% and 60% in controls. No statistically significant differences were observed between the patient and control groups under any of the inheritance models tested.

Conclusion: The results of the present study demonstrated that the FAS-670A/G (rs1800682) polymorphism cannot be considered as a predisposing factor for thyroid cancer in the studied population from the northwestern region of Iran.

Keywords: *Polymorphism, Gene, FAS, Cancer, Thyroid, rs1800682.*

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Introduction

Thyroid carcinoma is a heterogeneous malignancy that originates in the thyroid gland and ranks as the most frequently diagnosed endocrine neoplasm globally (1). The epidemiological distribution of thyroid cancer exhibits considerable international variation. Papillary thyroid carcinoma accounts for approximately 80% of all thyroid malignancies. Over the past four decades, a marked increase in thyroid cancer incidence has been observed worldwide, with a disproportionately higher burden among women and particularly pronounced in certain regions, such as South Korea. Estrogen receptors are abundantly expressed in neoplastic thyroid tissue, and evidence suggests that estrogen may play a contributory role in thyroid carcinogenesis, thereby underscoring the potential significance of hormonal factors in the etiology of thyroid cancer (2, 3).

Extensive research has been directed toward elucidating the molecular determinants underlying thyroid cancer pathogenesis. Key factors implicated in the development and progression of thyroid malignancy include dysregulated signaling pathways, molecular aberrations, lifestyle factors, and specific environmental exposures. At the core of these mechanisms are genetic and epigenetic alterations, including somatic mutations, single nucleotide polymorphisms, and aberrant gene methylation, which disrupt normal cellular processes (4-6). Emerging evidence indicates that impairment of programmed cell death, or apoptosis, constitutes a critical event in the pathogenesis of both autoimmune and proliferative thyroid disorders (7).

Apoptosis is a genetically orchestrated physiological mechanism essential for the regulation of cell proliferation, tissue homeostasis, and normal development in multicellular organisms, as well as for the elimination of damaged or potentially neoplastic cells (8). Disruption of apoptotic regulation can result in uncontrolled cellular growth and proliferation, ultimately culminating in tumorigenesis (9). The capacity to evade programmed cell death represents one of the fundamental hallmarks of cancer, frequently arising from genetic alterations affecting apoptosis-related genes, including FAS, FASL, TNF, TP53, Bcl-2, and others (10, 11). Accordingly, the identification and characterization of polymorphisms within these apoptosis-associated genes are of considerable importance for understanding thyroid cancer susceptibility.

FAS, also known as CD95 or APO-1, is a transmembrane cell surface receptor that belongs to the tumor necrosis factor (TNF) superfamily and serves as one of the principal molecular initiators of the extrinsic apoptotic pathway, a critical mechanism for eliminating damaged, infected, or superfluous cells (12). Upon specific binding of FAS to its physiological ligand, FASL (FAS ligand), a series of molecular events is set in motion: the adaptor protein FADD is recruited to the intracellular death domain of the receptor, leading to the assembly of the death-inducing signaling complex (DISC). This complex subsequently facilitates the proteolytic activation of caspase-8, which in turn activates downstream effector caspases (such as caspase-3, -6, and -7) that execute the apoptotic program (13).

The FAS gene is subject to transcriptional regulation, and a common single nucleotide polymorphism (SNP) located in its promoter region has been identified as a potential modulator of gene expression. This polymorphism, designated FAS-670A/G (rs1800682), is positioned within the enhancer region of the gene, specifically at a site that corresponds to a binding motif for the transcription factor STAT1. Although the precise functional consequences of this variant and the direct role of STAT1 in regulating FAS expression remain incompletely characterized, it has been hypothesized that the G allele may alter the affinity of STAT1 binding to the promoter, thereby disrupting the fine-tuned regulation of FAS transcription. As a result, this sequence variation could lead to aberrant FAS expression levels, dysregulation of apoptotic signaling, and

consequently an altered capacity for cells to undergo programmed cell death. Such perturbations in the apoptotic machinery are thought to increase cellular susceptibility to oncogenic transformation and may thus contribute to interindividual differences in the risk of developing various cancers, including thyroid carcinoma (14). In addition, several studies have been undertaken to evaluate the role of this polymorphism in thyroid cancer predisposition across diverse ethnic populations. For example, investigations conducted in Turkish (15) and Chinese (16) cohorts have reported no statistically significant association between the FAS rs1800682 polymorphism and susceptibility to breast cancer, thyroid cancer, or adult acute myeloid leukemia. In contrast, research performed in a Korean population (17) has documented a significant association between FAS gene polymorphisms—specifically rs1800682, rs1571013, and rs1468063—and papillary thyroid carcinoma. These discrepant findings suggest that the contribution of genetic polymorphisms to carcinogenesis may vary across populations, likely reflecting underlying genetic heterogeneity (18). Given that no study to date has examined the association between this specific polymorphism and thyroid cancer risk in the northwestern region of Iran, the present study was designed to investigate the relationship between the FAS-670A/G promoter polymorphism and susceptibility to thyroid tumors in the population of East Azerbaijan Province, Iran.

Methods

This case-control investigation was carried out at the Radiobiology Laboratory of the University of Tabriz. The patient cohort consisted of 115 individuals diagnosed with thyroid tumors (86 females and 29 males) who had undergone thyroidectomy at either Imam Reza Hospital or Noor-e Nejat Hospital in Tabriz. The control group comprised 125 healthy subjects (93 females and 32 males) with no documented family history of malignancy among first- or second-degree relatives. Exclusion criteria for the patient group included hospitalized individuals with thyroid tumors who did not undergo surgical resection, as well as those with benign thyroid conditions that did not require surgical intervention. Demographic and clinical data were collected for all participants following the acquisition of written informed consent. The study protocol, involving the use of human biological samples, received ethical approval from the Research Ethics Committee of Azarbaijan Shahid Madani University (approval code: IR.AZARUNIV.REC.1405.017).

Genomic DNA extraction: Peripheral venous blood samples were obtained from each study participant via standard phlebotomy procedures; specifically, 5 cc of whole blood was drawn and immediately transferred into sterile Falcon tubes that had been pre-filled with EDTA, a potent anticoagulant agent, to prevent coagulation. DNA extraction was subsequently carried out using a standard salting-out precipitation protocol. This procedure involved the removal of erythrocytes by the addition of lysis buffer followed by centrifugation, and the subsequent digestion of leukocytes using proteinase K (Sialon, Iran). The integrity and concentration of the extracted DNA were evaluated by agarose gel electrophoresis and spectrophotometric analysis, respectively.

Polymerase Chain Reaction and Enzymatic Digestion: Extracted DNA samples were amplified using the polymerase chain reaction (PCR). Amplification of fragments was performed using forward and reverse primers (19) with sequences 5'-ATAGCTGGGGCTATGCGATT-3' and 5'-CATTTGACTGGGCTGTCCAT-3', respectively, in a thermal cycler (SensoQuest, GmbH, Germany). PCR was carried out in a final volume of 25 µL containing 2.5 µL of 10× PCR buffer, 0.76 µL of 100 mM $MgCl_2$, 0.5 µL of 10 mM dNTPs (SinaClon, Iran), 0.9 µL of each forward and reverse primer (10 pmol), 0.18 µL of Taq polymerase (SinaClon, Iran) equivalent to 1 unit of enzyme, 1 µL of DNA (approximately 200 ng), and 18.26 µL of double-distilled deionized water. The optimal PCR cycling conditions consisted of an initial denaturation step at 94°C for 2 minutes, followed by 35 cycles of 30 seconds at 94°C, 30 seconds at 63°C,

and 45 seconds at 72°C, with a final extension step at 72°C for 7 minutes. PCR products were loaded onto a 2% agarose gel to verify the size of the resulting fragments, and the gel was visualized using ethidium bromide staining (SinaClon, Iran) and a UV transilluminator. Correct amplification of the target fragment yielded a product of 193 base pairs. Digestion with the MvaI restriction enzyme allowed genotyping of the FAS polymorphism at the relevant site, such that in the presence of the G allele, the enzyme digested the fragment into two products of 136 and 57 base pairs. The restriction digestion reaction was performed in a final volume of 20 µL containing 1.2 µL of 10× enzyme-specific buffer, 0.88 µL of MvaI enzyme (1 unit), 6.36 µL of PCR product, and 11.56 µL of double-distilled water. The tubes were then incubated at 40°C for 7 hours.

Following PCR amplification, the expected 193-bp amplicon was visualized on a 2% agarose gel (Figure 1). Restriction enzyme digestion with MvaI revealed distinct banding patterns corresponding to the different genotypes. In the presence of the G allele, the enzyme cleaved the 193-bp product into two fragments of 136 bp and 57 bp, whereas the A allele remained uncut, preserving the intact 193-bp fragment. Consequently, the AA genotype displayed a single band at 193 bp, the GG genotype exhibited two bands at 136 bp and 57 bp, and the heterozygous AG genotype showed all three bands (193, 136, and 57 bp) on the agarose gel (Figure 2). To confirm the accuracy of the RFLP results, two samples from each genotype pattern were subjected to direct sequencing; the sequencing chromatograms are presented in Figure 3. As illustrated, the AA genotype is characterized by a single large green peak, the GG genotype by a single large black peak, and the heterozygous AG genotype by two distinct peaks in green and black.

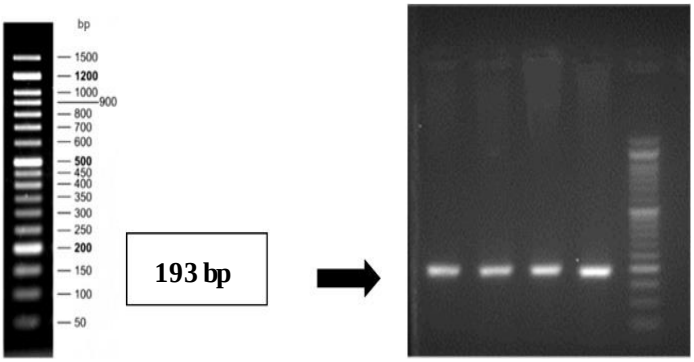

Figure 1. Electrophoresis on 2% agarose gel for a selection of PCR products from patients and a 50-bp DNA ladder. (The molecular size marker is shown in the figure)

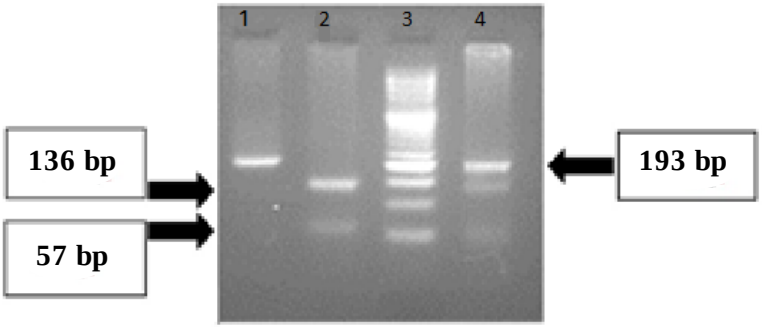

Figure 2. Electrophoresis on 2% agarose gel for the enzyme-digested products. Lane 1: AA genotype, Lane 2: GG genotype, Lane 3: 50-bp DNA ladder, Lane 4: AG genotype

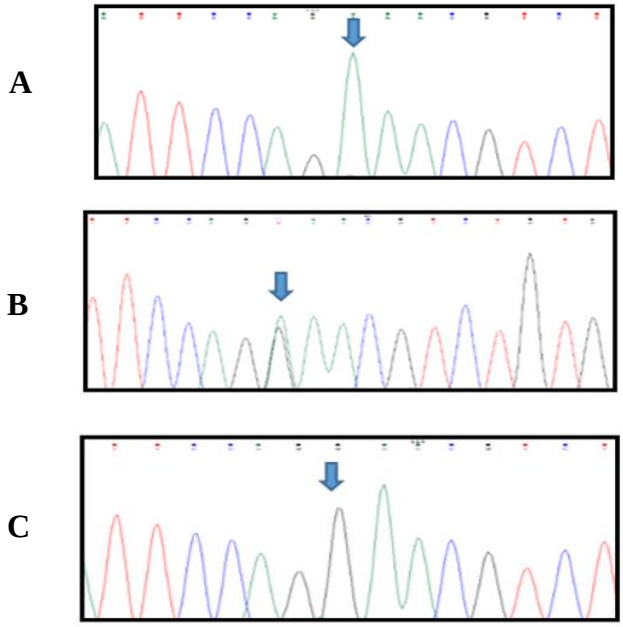

Figure 3. Sequencing results for AA (A), AG (B), and GG (C) genotypes

To validate the genotyping results obtained via PCR-RFLP (Polymerase Chain Reaction–Restriction Fragment Length Polymorphism), PCR products from a subset of samples were submitted to Pishgam Company (Tehran, Iran) for direct sequencing, and the resulting chromatograms were analyzed using Chromas software. All statistical analyses were conducted using SPSS version 26. Associations between the FAS-670A/G polymorphism and thyroid cancer susceptibility, as well as clinicopathological parameters, were evaluated using chi-square or Fisher's exact tests, as appropriate. Odds ratios (OR) were calculated using binary logistic regression. Comparisons of continuous variables between the case and control groups were performed using independent samples t-tests. The normality of data distribution was assessed using the Kolmogorov–Smirnov or Shapiro–Wilk tests, and homogeneity of variances was examined using Levene's test. A p-value of less than 0.05 was considered statistically significant in all analyses.

In Silico Analysis: The analysis of single nucleotide polymorphisms (SNPs) using computational tools is referred to as in silico analysis. To study non-synonymous single nucleotide polymorphisms in coding and non-coding regions, various bioinformatics tools are employed. Specifically, the rs1800682 polymorphism in the FAS gene is located in a non-coding region. For this analysis, online software including AliBaba, SpliceAid, and HaploReg were used. AliBaba version 1.2 (www.gene-regulation.com) was utilized to analyze the presence of transcription factor binding sites in the promoter regions of the gene. The SpliceAid website (http://193.206.120.249/splicing_tissue.html) was used for online analysis and visualization of the splicing process involving pre-mRNA sequences. Finally, HaploReg (www.pubs.broadinstitute.org), a software tool for examining non-coding regions of the genome with a focus on regulatory SNPs associated with diseases, was used to assess the binding affinity of transcription factors and proteins to the rs1800682 polymorphism of the FAS gene.

Results

The genotype frequency distribution for the rs1800682 polymorphism in the FAS gene in both patient and healthy control populations was in accordance with Hardy–Weinberg equilibrium. This polymorphism

was genotyped in 115 patients with thyroid cancer, with a mean age of 38.44±10.32 years, and 125 healthy individuals, with a mean age of 42.5±7.2 years, serving as the control group. Following genotyping, all patients and healthy individuals were classified into three genotype groups: AA, GG, and AG. The frequency distribution of rs1800682 genotypes in thyroid cancer patients and the control group is presented in Table 1.

Table 1. Genotype and allele frequency distribution in patient and control samples for the rs1800682A>G (FAS -670A/G) polymorphism under different inheritance models

Models	Genotypes	p-value	OR	95% CI for OR	
				Lower	Upper
	GG vs AA	0.505	1.241	0.658	2.343
	GA vs AA	0.831	0.937	0.518	1.697
Recessive	GG vs AA+AG	0.411	1.276	0.713	2.284
Dominant	GG+AG vs AA	0.819	1.062	0.636	1.772
Codominant	AG vs AA+GG	0.600	0.865	0.502	0.489
Allelic	G vs A	0.499	1.134	0.788	1.631

No significant association was observed between genotype frequency distribution and disease status in any of the genotypes. The G allele of the FAS-670A>G polymorphism was detected in 43.04% of patients and 40% of healthy individuals. The A allele was observed in 56.96% of patients and 60% of healthy individuals. No significant difference was found in the frequency of the A and G alleles between patients and the control group.

Statistical evaluations performed under multiple inheritance models revealed no significant associations between the FAS rs1800682 polymorphism and thyroid cancer risk, as neither genotype frequencies (AA, AG, GG) nor allele frequencies (A and G) differed significantly between the patient and control groups (p=0.05). The AA genotype was the most frequent, accounting for 41.74% (n=48) of patients and 43.2% (n=54) of controls. The heterozygous AG genotype was observed in 30.43% (n=35) of patients and 33.6% (n=42) of controls, whereas the GG genotype exhibited the lowest prevalence, detected in 27.82% (n=32) of patients and 23.2% (n=29) of controls. Clinicopathological parameters, including tumor grade, patient age, tumor size, and lymph node involvement, were also evaluated, and the findings are summarized in Table 2. Of particular interest, a statistically significant association was identified between tumor size and the FAS-670A/G polymorphism (p=0.0077, p<0.05), suggesting that genotype at this locus may influence tumor size in patients with thyroid carcinoma.

In silico analysis using AliBaba software predicted that the wild-type A allele facilitates binding of the transcription factor NF-1, whereas the mutant G allele is associated with binding of the transcription factor TEC1. SpliceAid bioinformatics analysis further indicated that the A-to-G nucleotide substitution enables binding of the SRp55 splicing regulatory protein to the pre-mRNA sequence, with a positive score of 5. Additionally, HaploReg analysis revealed that the substitution of the wild-type allele with the mutant allele results in the acquisition of binding sites for several regulatory proteins, including CFOS, GATA2, CEBPB, TBP, POL2, and STAT3, while concurrently altering the binding motifs for the transcription factors Hsf, STAT, and ZBRK1. The results obtained from the HaploReg software are presented in Figure 4.

Table 2. Correlation between clinicopathological characteristics and FAS-670A/G genotypes in patients with thyroid carcinoma

Clinical features of patients	AA Number(%)	AG Number(%)	GG Number(%)	p-value
Tumor size (cm)				
≤2.5	21(29.6)	17(23.9)	9(12.7)	0.0077
>2.5	10(14.1)	2(2.8)	12(16.9)	
Lymph node involvement				
Positive	11(17.2)	8(12.5)	12(18.8)	0.1867
Negative	15(23.4)	12(18.8)	6(9.4)	
Pathology				
Medullary carcinoma	0(0)	0(0)	1(1.3)	0.6415
Hürthle cell carcinoma	1(1.3)	1(1.3)	1(1.3)	
Follicular carcinoma	2(2.7)	2(2.7)	0(0)	
Papillary carcinoma	27(36)	19(25.3)	21(28)	
Tumor grade				
1	23(32.4)	22(31)	14(19.7)	0.1362
2	2(2.8)	0(0)	3(4.2)	
3	2(2.8)	1(1.4)	4(5.6)	
Age				
>35	27(24.3)	15(13.5)	16(14.4)	0.5698
≤35	20(18)	18(16.2)	15(13.5)	

Query SNP: rs1800682 and variants with r^2 >= 0.8

chr	pos (hg38)	LD (r^2)	LD (D')	variant	Ref	Alt	AFR freq	AMR freq	ASN freq	EUR freq	SiPhy cons	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	NHGRI/EBI GWAS hits	GRASP QTL hits	Selected eQTL hits	GENCODE genes	dbSNP func annot
10	88981858	0.98	0.99	rs7082101	C	A	0.82	0.53	0.44	0.42		GI	7 tissues	OVRY		4 altered motifs			37 hits	ACTA2	intronic
10	88982198	0.98	0.99	rs7069841	T	C	0.82	0.53	0.44	0.42		GI	5 tissues			4 altered motifs			37 hits	ACTA2	intronic
10	88982292	0.98	0.99	rs7082720	C	T	0.82	0.53	0.44	0.42			5 tissues			Isl2			37 hits	ACTA2	intronic
10	88983440	0.98	0.99	rs7910660	G	A	0.82	0.53	0.44	0.42		VAS, GI	7 tissues	14 tissues	PU1,GATA2	HNF1,Pax-1			38 hits	ACTA2	intronic
10	88983584	0.98	0.99	rs7910825	G	A	0.82	0.53	0.44	0.42		VAS	6 tissues	GI		5 altered motifs		4 hits	42 hits	ACTA2	intronic
10	88986603	0.99	1	rs1926201	G	C	0.82	0.53	0.44	0.42		VAS	8 tissues	7 tissues	SIN3AK20,PU1				37 hits	ACTA2	intronic
10	88986776	0.99	1	rs1926200	G	A	0.82	0.53	0.44	0.42		VAS	11 tissues	7 tissues	EGR1,PU1,SIN3AK20	EWSR1-FLI1,Ets,GATA			37 hits	ACTA2	intronic
10	88986903	0.99	1	rs1926199	G	T	0.82	0.53	0.44	0.42		VAS	7 tissues	7 tissues		9 altered motifs			37 hits	ACTA2	intronic
10	88987690	0.99	0.99	rs7914490	A	G	0.80	0.53	0.44	0.43		BLD	9 tissues	BLD,BLD,BLD		4 altered motifs			35 hits	ACTA2	intronic
10	88988869	0.99	1	rs1926197	A	G	0.82	0.53	0.44	0.42		FAT	11 tissues	LNG					38 hits	ACTA2	intronic
10	88990206	1	1	rs1800682	A	G	0.77	0.53	0.44	0.43		22 tissues	8 tissues	37 tissues	6 bound proteins	Hsf,STAT,ZBRK1	1 hit	4 hits	41 hits	ACTA2	intronic
10	88991759	0.84	0.98	rs1324551	C	T	0.82	0.56	0.44	0.46		24 tissues		50 tissues	7 bound proteins	CFOS,GATA2,CEBPB,TBP,POL2,STAT3			45 hits	FAS	intronic
10	88992261	0.85	0.99	rs6586163	A	C	0.82	0.56	0.44	0.46		21 tissues	4 tissues	7 tissues					44 hits	FAS	intronic
10	88992274	0.85	0.99	rs6586164	T	A	0.82	0.56	0.44	0.46		21 tissues	4 tissues	7 tissues		Elf5,PU.1			44 hits	FAS	intronic
10	88992859	0.85	0.99	rs3824729	A	G	0.82	0.56	0.44	0.46		19 tissues	8 tissues	8 tissues		4 altered motifs			40 hits	FAS	intronic
10	88993281	0.85	0.99	rs10887877	A	G	0.82	0.56	0.44	0.46				13 tissues	NFKB,POL24H8	7 altered motifs			44 hits	FAS	intronic
10	88993503	0.85	0.99	rs7097572	T	C	0.82	0.56	0.44	0.46		18 tissues	10 tissues	11 tissues	NFKB,POL2,POL24H8	7 altered motifs		4 hits	44 hits	FAS	intronic
10	88993991	0.85	0.99	rs1926196	T	C	0.82	0.57	0.44	0.46		13 tissues	12 tissues	8 tissues	POL24H8	NF-I,RREB-1		15 hits	45 hits	FAS	intronic
10	88994001	0.85	0.99	rs1926195	G	A	0.82	0.56	0.45	0.46		13 tissues	12 tissues	9 tissues	POL24H8	Cdx,Myc,Pou2f2			44 hits	FAS	intronic
10	88994850	0.82	0.99	rs7897395	T	C	0.82	0.57	0.44	0.47		BLD	5 tissues			10 altered motifs			40 hits	FAS	intronic
10	88995152	0.84	0.99	rs7069061	A	G	0.82	0.56	0.44	0.47		BLD	6 tissues		POL2,TBP	6 altered motifs			39 hits	FAS	intronic
10	88995196	0.84	0.99	rs7072828	T	A,G	0.82	0.56	0.44	0.47		BLD	6 tissues	BLD	POL2,TBP				40 hits	FAS	intronic
10	88995299	0.85	0.99	rs6586165	T	A	0.82	0.56	0.44	0.46		6 tissues	9 tissues	6 tissues	POL2,TBP	Cdx			44 hits	FAS	intronic
10	88996308	0.85	0.99	rs6586166	C	T	0.83	0.56	0.44	0.46		BLD	6 tissues						40 hits	FAS	intronic
10	88996389	0.85	0.99	rs6586167	T	G	0.83	0.56	0.44	0.46		BLD	6 tissues	BLD,OVRY		BDP1,E2F			44 hits	FAS	intronic

Figure 4. Results obtained from the HaploReg software. **As a result of the A-to-G nucleotide change at the FAS -670A/G polymorphism, the proteins CFOS, GATA2, CEBPB, TBP, POL2, and STAT3 are predicted to bind to the corresponding region.**

Discussion

The findings of the present investigation revealed no statistically significant association between the FAS-670A/G genotypes or alleles and overall susceptibility to thyroid cancer. However, a notable exception was observed in the subgroup analysis, wherein the G allele demonstrated a significant correlation with increased tumor size among affected patients. These results are consistent with previous reports from Turkish (15) and Chinese (16) populations, which similarly failed to establish a link between this polymorphism and thyroid cancer risk. In contrast, a study conducted in a Korean population (17) reported significant associations between FAS gene polymorphisms, including rs1800682, rs1571013, and rs1468063, and papillary thyroid carcinoma. Taken together with the cumulative evidence from the literature, the current findings suggest that the FAS-670A/G polymorphism is unlikely to serve as a major genetic determinant of thyroid cancer susceptibility.

In addition, the In Silico analyses conducted in the present study revealed marked alterations in the binding patterns of multiple transcription and splicing regulatory factors resulting from the substitution of the wild-type allele with the mutant variant. Notably, SRp55—a widely expressed splicing factor—acquires binding affinity following the allelic change and, under conditions of DNA damage, may be upregulated even in the absence of functional p53. Previous evidence indicates that reduced SRp55 activity may confer cellular resistance to DNA damage. In this context, Pecce et al., employing RNA immunoprecipitation assays, demonstrated that the synonymous p.Cys630 mutation in the RET gene creates a novel splicing motif that facilitates SRp55 binding; the subsequent binding of SRp55 to this motif enhances the levels of RET receptor-encoding mRNA, thereby contributing to cancer progression (20). The findings of the present investigation are consistent with these observations, as SpliceAid-based In Silico analysis predicted that SRp55 binds to the RNA transcript harboring the FAS rs1800682 polymorphism with a positive score of 5.

A substantial body of research has been dedicated to investigating the association between FAS gene polymorphisms and susceptibility to various malignancies across geographically diverse populations. In a study conducted by Tahmasebi Fard in Tehran, both the FAS-670A/G polymorphism and other polymorphisms within the FAS and FASL genes were found to be significantly associated with an increased risk of breast cancer (21). Conversely, Chen et al. reported no significant role for the FAS-670A/G polymorphism in disease susceptibility (22). In the context of thyroid malignancy, Erdogan et al. examined the association between the FAS-670A/G polymorphism and papillary thyroid carcinoma and concluded that this variant does not appear to contribute to disease development (15). In contrast, Eun et al. reported a significant association between the FAS single nucleotide polymorphisms rs1800682, rs1571013, and rs1468063 and papillary thyroid carcinoma (17).

In a study conducted in China, Huang et al. examined the association between the FAS-670A/G polymorphism and susceptibility to adult acute myeloid leukemia and reported no significant relationship between this variant and disease risk (16). Dastmalchi et al. investigated the role of FAS gene polymorphisms in breast cancer and, through In Silico analyses, demonstrated that promoter region variants, including FAS-670A/G, affect the protein binding profile at the promoter, specifically reducing the binding affinity of the STAT1 transcription factor in the presence of the G allele (19). This altered transcription factor binding may, in turn, modulate FAS gene transcription and subsequent translation. With the exception of two of the aforementioned studies, the majority of investigations have not reported significant associations between various diseases and different polymorphisms of the FAS and FASL genes. In alignment with this prevailing trend, the present study found no significant association between the FAS-670A/G polymorphism and thyroid cancer risk. However, a noteworthy finding was the significant correlation between the G allele and tumor size among affected patients. The observed

inconsistencies across studies may be attributable to differences in the genetic architecture of the populations examined, variations in cancer type, racial heterogeneity, and environmental exposures—including geographical location and associated dietary patterns—all of which may modulate the effects of genetic variants (18).

The findings of the present study indicate that the FAS rs1800682 polymorphism does not contribute to thyroid cancer susceptibility in the northwestern Iranian population. In light of these results, further investigations are warranted to examine the association between this polymorphism and thyroid cancer risk in larger cohorts comprising both patients and healthy controls, as well as in diverse geographical regions across Iran and other countries.

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