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Research Article

SNP (rs1570360) in Transcriptional Factor Binding Sites of the VEGFA Promoter is Associated with Hypertensive Nephropathy and Diabetic Retinopathy

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Abstract

The Vascular Endothelial Growth Factor A (VEGFA) gene SNP (rs1570360) (G/A) alters the potential TFBS in the promoter which may be associated with the hypertensive nephropathy and diabetic retinopathy reported in humans. The SNP VEGFA-G allele creates four unique TFBS for the EGR1, KLF4, MZF1-5-13 and SP2 TFs while the A-allele creates six unique TFBS for the EGR2, EHF, FOXH1, MAFK, SPIB and THAP1 TFs. These TFBS changes created by the SNP are discussed with regard to possible causes of the two diseases.

Abbreviations

SNP: Single Nucleotide Polymorphism; VEGFA: Vascular Endothelial Growth Factor A; TFs: transcriptional factors; TFBS: Transcription Factor Binding Sites; HD: Human disease

Introduction

The human vascular endothelial growth factor (VEGF)-A gene is encoded at chromosome 6p21.1 and the transcribed protein is usually expressed as a disulfide-linked homodimer, but can also be expressed as a heterodimer with placental growth factor (PGF). VEGFA is a signaling protein involved in the regulation of angiogenesis, vasculogenesis and endothelial cell growth. It induces endothelial cell proliferation, promotes cell migration, inhibits apoptosis and induces permeabilization of blood vessels. The single nucleotide polymorphism (SNP) rs1570360 (A/G) in the promoter region located at -1154bp from the transcriptional start site (TSS) of the VEGFA gene has been associated with many disease conditions in humans [1-9]. A SNP in a gene's regulatory region involving a TFBS can change a TFs ability to bind DNA [10-13] in which case TFs would be unable to effectively regulate their target genes [14-18]. This concept is examined for the rs1570360 SNP in the VEGFA promoter [6,19,20] and its implications are discussed with relation to the human diseases Hypertensive Nephropathy (HN) and Diabetic Retinopathy (DR). HN is a common cause of end-stage renal disease or hypertensive kidney disease in the United States [21]. The pathological features of the disease are vascular wall thickening with arteriolar hyaline deposits, intimal fibrosis and glomerular ischemic changes [22]. In a recent study it was shown that the G-to-A allele mutation of the VEGFA rs1570360 SNP (A/G) was associated with a significant increased risk of HN in a Hispanic population [1]. DR is a prominent pathologic vascular complication in diabetes. Proliferative Diabetic Retinopathy (PDR) an advanced stage is reached when abnormal growth of retinal vessels leads to neovascularization with the retina and vitreous gel which is often accompanied by extensive hemorrhage and fibrosis [9]. VEGF is up-regulated in DR patients and promotes neovascularization and migration as well as vascular permeability and leakage [9]. It has been reported that the AA genotype of the VEGFA rs1570360 SNP (A/G) is significantly associated with PDR [9]. In this report the presence of the rs1570360 SNP A-allele in TFBS of the VEGFA promoter are discussed in association with these diseases.

Materials and Method

Identifying TFBS

Potential TFBS were identified for the rs1570360 VEGFA SNP using the Jaspar Core [23,24] and the ConSite databases [25]. JASPAR is a collection of transcription factor DNA-binding motifs used for scanning genomic sequences and ConSite is a web-based tool for finding cis-regulatory elements in genomic sequences. The TFBS motifs and allele locations are listed in (Table 1). The Vector NTI Advance 11 computer program (Invitrogen, Life Technologies) was used to locate the TFBS in the VEGFA gene (NCBI Ref Seq NM_001171626) which represents a scan from 2.2 kb upstream of exon one to 1.7 Kb past the 3'UTR involving a total of 19.6 Kbp.

Results

The rs1570360 SNP and TFBS

This SNP is located in the promoter region of the VEGFA gene at -614 base pairs (bps) from the beginning of exon 1 [19] or -1154 bps from the TSS in exon 1 [26,27]. The major G- allele frequency of the SNP (A/G) ranges from 0.61 in Northern Han Chinese [28] to 0.94 in a black ethnic group [27]. The G-allele creates four unique potential TFBS for the EGR1, KLF4, MZF1-5-13 and SP2 TFs (Table 1, Supplement) while the A-allele creates six unique potential TFBS for the EGR2, EHF, FOXH1, MAFK, SPIB and THAP1 TFs. The two alleles create five common potential TFBS for the KLF5, SP1, SREBF1, TFAP2C and ZNF354C TFs (Table 1, Supplement). The G-allele [G (+ strand) or C (- strand)] located in the potential EGR1, KLF4, MZF1_5-13, and SP2 TFBS have a 97%, 98% 69% and 71% occurrence, respectively and consequently have been reasonably well conserved in human evolution (Table 1, Figure 1). As can be seen from (Table 1), each of these potential TFBS occur only once in the gene except for the KLF4 TFBS which also appears in intron six, and consequently, this SNP would probably have a great impact on these four TFs regulating the gene. The A-allele [A (+ strand) or

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Table 1: The VEGFA rs1570360 SNP (G/A) alleles. Listed are the transcriptional factors (TFs), protein name, the TFBS containing the SNP allele, DNA strand orientation and number of times the TFBS occurs in the gene. TFs in bold only occur with the given allele. Upper case nucleotides are conserved (>90%) in the TFBS region and bold is the SNP location of each allele. Below the TFBS is the nucleotide occurrence (%) obtained from the Jaspar core database.

Allele	TFs	Protein Name	TFBS	Strand	# of Sites
G	**EGR1**	Early growth response 1	gcctCagCcc**C**tcc	minus	1
			C=97%		
	KLF4	Kruppel-like factor 4	gtGGa**G**gGGc	plus	2
			G=98%		
	KLF5	Kruppel-like factor 5	gCCc**C**tCCac	minus	1
			C=100%		
	MZF1_5-13	Myeloid zinc finger 1	ggA**g**GGGctg	plus	1
			g=69%		
	SP1	Specificity Protein 1	CCC**c**TCCACA	minus	1
			c=77%		
	SP2	Specificity Protein 2	cctCagCCc**c**tccac	minus	1
			c=71%		
	SREBF1	Sterol regulatory element binding transcription factor 1	cTCAgccc**c**t	minus	1
			c=1%		
	TFAP2C	Transcription factor AP-2 γ	gcgagCctcAGccc**c**	minus	1
			c=18%		
	ZNF354C	Zinc finger protein 354C	**c**tCCAC	minus	27
			c=38%		
A	**EGR2**	Early growth response 2	agccC**t**tCCaCacgc	minus	1
			t=16%		
	EHF	Ets homologous factor	cC**T**TCCAc	minus	3
			T=100%		
	FOXH1	Forkhead box H1	gccc**t**TccACa	minus	1
			t=5%		
	KLF5	Kruppel-like factor 5	cCtcagCCC**t**	minus	1
			t=30%		
	MAFK	v-maf avian musculoaponeurotic fibrosarcoma oncogene homolog K	gagccTCAGCcc**t**tc	minus	1
			t=47%		
	SP1	Specificity Protein 1	cctCagCCc**t**t	minus	1
			t=15%		
	SPIB	Transcription factor Spi-B	tgtGGA**A**	plus	1
			A=96%		`
	SREBF1	Sterol regulatory element binding transcription factor 1	cTCAgccc**T**t	minus	1
			T=99%		
	TFAP2C	Transcription factor AP-2 γ	gcgagCctcAGccc**t**	minus	1
			t=20%		
	THAP1	THAP domain containing, apoptosis associated protein 1	cagCCc**t**tc	minus	3
			t=29%		
	ZNF354C	Zinc finger protein 354C	**t**tCCAC	minus	9
			t=6%		

T (- strand)] located in the potential EGR2, EHF, FOXH1, MAFK, SPIB and THAP1 TFBS have 16%, 100%, 5%, 47%, 96% and 29% occurrence, respectively and have not been well conserved in human evolution except for the EHF and SPIB TFBS (Table 1). The EHF TFBS occurs two other times in the gene (introns 5 & 6) while the SPIB site occurs only the one time and consequently, the SNP should

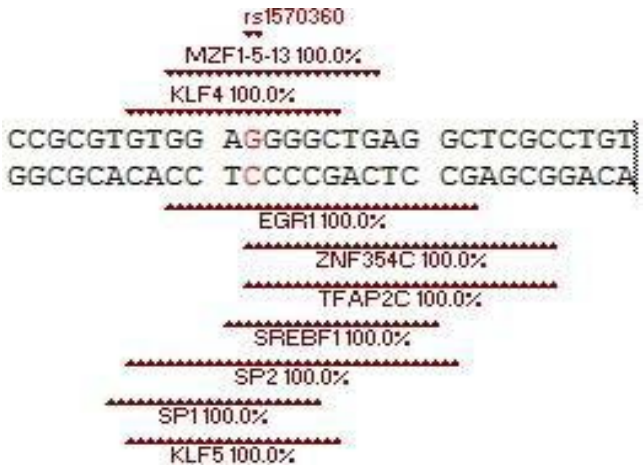

Figure 1: Double stranded DNA from the *VEGFA* promoter showing the potential TFBS for nine different TFs which can bind their respective DNA sequence either above (+) or below (-) the duplex (cf. Table1). The rs1570360 common *VEGFA*-G allele is found in each of these TFBS. As shown, this rSNP is located -1154bp from the TSS in the promoter of the *VEGFA* gene. Also included with the potential TFBS is their 100% sequence homology to the duplex.

have an impact on regulating the SPIB site.

The rs1570360 SNP and disease associations

Presently there are two human diseases of interest that have been associated with this SNP (Table 2). They are hypertensive nephropathy in a Hispanic population [1] and diabetic retinopathy in a Caucasian population [9]. For the hypertensive nephropathy disease the G-allele frequency changes from 0.76 in the control group to 0.58 in the affected group while for the diabetic retinopathy disease the G-allele frequency changes from 0.62 in the control group to 0.26 in the affected group. In both studies, the A-allele frequency increased significantly [1,9] in the affected group at the expense of the G-allele (Table 2).

Discussion

The rs1570360 SNP VEGFA-G allele which generates the potential early growth response-1 (EGR1) TFBS has been found to be associated with hypertensive nephropathy [29] and proliferative diabetic retinopathy [30]. In addition, the VEGFA-G allele which also generates the Kruppel-like factor-4 (KLF4) TFBS has been found to be associated with nephropathy [31,32]. Consequently the loss of those TFBS in the VEGFA promoter created by the alternate VEGFA-A allele should have an impact on the regulation of the gene by the EGR1 and KLF4 TFs (Table 1, Figure 1). EGR1 belongs to a family of four zinc finger DNA-binding proteins which is induced by many stimuli, including hypoxia, shear stress, injury, growth factors and cytokines [32,33]. EGR1 plays a key role in orchestrating tissue response to acute injury by activating the transcription of many proliferation-associated genes such as VEGFA [33]. From (Table 1), it can be seen that the VEGFA-G allele [C (- strand)] in the potential EGR1 TFBS has been extremely well conserved in human evolution with a 97% occurrence which means that individuals carrying the VEGFA-G allele would have an EGR1 TFBS 97% of the time. This becomes especially important since this binding site only occurs only in the VEGFA promoter. From the Table, it can also be seen that the EGR homologue EGR2 TFBS is created by the VEGFA-A allele [T (- strand)] and the T-nucleotide in this motif has not been well conserved in human evolution with a 16% occurrence which means that individuals carrying the A-allele would have a EGR2 TFBS 16% of the time. The EGR2 TFBS also only occurs once at this location in the VEGFA gene. Consequently, if the EGR TF is required to active the VEGFA gene, then individuals carrying the VEGFA-A allele might be at a disadvantage. Similar logic can be used to evaluate the other TFBS in (Table 1). EGR1 is up-regulated in the kidney in response to renal artery occlusion [34]. The Transcription Factor (TF) Stimulating Protein-1 (SP1) is involved with the transcription regulation of the Kruppel-like factor-4 (KLF4) gene which encodes a zinc finger- containing TF. The two proteins are part of a (SP/KLF) family of TFs that are involved with diverse cellular processes, such as vascular smooth muscle cell (VSMC) proliferation, cell differentiation, apoptosis, oncogenesis [35,36], pluripotent stem cells [37] and gene transcription [38-41]. There have been 20 KLFs identified in mammals that participate in one of the above biological functions [40] in addition to blood vessel, hematopoiesis and epidermal development [42]. KLF4 plays a key role in pathological vascular processes and acts as a molecular switch in regulating VSMC function [40]. KLF4 and SP1 physically interact in a co-operative manner when occupying the angiotensin II type 1 receptor (AT1R) promoter inducing transcription in VSMCs under basal conditions [43]. KLF4 and SP1 also have TFBSs in VEGFA promoter and the SP1 TF has been shown to bind its TFBS and regulate the gene [44]. The KLF4 TF is expressed in kidney podocytes [45] and acts as a tumor suppressor in renal cell carcinoma [31]. From (Figure 1) and (Table 1), it can be seen for the rs1570360 SNP that the KLF4 TF binds the duplex DNA on the plus strand while SP1 binds the DNA on the minus strand suggesting that these two TFs may be involved in duplex strand separation at this location [46,47] during transcription. Since KLF4/SP1 bind the DNA at the same location, a nucleotide change in their TFBS could affect the regulation of the VEGFA gene. With a 98% and 77% nucleotide occurrence of the G-allele in vertebrates, respectively, in the KLF4 and SP1 TFBS (Table 1), individuals with the rs1570360 A-allele may not experience effective SP1/KLF4 regulation of the VEGFA gene. As an example, a significantly higher incidence of the VEGFA rs1570360 A-allele has been found in HN [1] and PDR [9] patients compared to their respective control groups (Table 2). In fact, the AA-genotypes change from 6.5% in the control group to 18.6% in the HN patients while the AG-genotypes change from 34.2% to 47.7%, respectively. This indicates that even individuals with an AG heterozygous genotype succumb to the disease at a higher incidence than their control. Evidently, individuals with the VEGFA rs1570360

Table 2: The rs1570360 SNP (G/A) genotype and allele frequencies for hypertensive nephropathy (HN) and proliferative diabetic retinopathy (PDR) patients and controls from two studies. Also listed is the sample size of each ethnic group.

Sample size	Genotypes Percent			Allele Frequencies		Ethnic group	Patients	Reference
N	AA	AG	GG	A	G			
86	18.6	47.7	33.7	0.42	0.58	Hispanic	HN	1
155	6.5	34.2	47.7	0.24	0.76	Hispanic	Control	
45	57.8	33.3	8.9	0.74	0.26	Caucasian	PDR	9
61	34.4	47.5	18	0.38	0.62	Caucasian	Control	

A-allele may be at risk for HP in the Hispanic population. Among PDR patients, the AA-genotypes change from 34.4% in the control group to 57.8% in disease patients while the AG-genotypes change from 47.5% to 33.3%, respectively. This indicates that Caucasians with an AG heterozygous genotype may be somewhat protected from the disease when carrying a VEGFA rs1570360 G-allele which is contrary to what was observed with HN patients. This may be due to the nature of each disease, the TFs regulating the VEGFA gene and the ethnic group studied. As an example, in a Brazilian study it has been reported that in a systemic hypertension group of patients compared to a control group, the rs1570360 SNP VEGFA-A allele reduces the VEGFA promoter activity by 25% compared to the VEGFA-G allele; however, there was no significant difference between the alleles or genotypes of the disease patients and the control group in this report [48]. Single nucleotide changes in TF motifs have the ability to alter gene regulation and thereby result in disease. There are many reports appearing in the literature describing human disease and the association with SNPs [49], however, few of these reports are examining the SNP location for accompanying changes in potential TFBS that would affect gene regulation [50]. The present report illustrates how a SNP in the regulatory region can change the DNA landscape and alter the potential TFBS for the TFs to regulate a gene; however, further binding assays and gene activation studies are required for verification.

Conclusion

A single nucleotide substitution in the promoter of the VEGFA gene created by the rs1570360 SNP (A/G) results a change in TFs binding motifs which are associated with the human diseases hypertensive nephropathy and proliferative diabetic retinopathy. The VEGFA-G allele creates four unique potential TFBS for the EGR1, KLF4, MZF1_5-13, and SP2 TFs while the VEGFA-A allele creates six unique potential TFBS for the EGR2, EHF, FOXH1, MAFK, SPIB and THAP1 TFs. The EGR1 TF is involved with renal artery occlusion while the KLF4TF is involved with pathological vascular processes making the VEGFA-G allele favorable over the A allele in avoiding these human diseases. Therefore, SNP related changes in TFBS for TFs that regulate genes can lead to human disease or sickness.

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