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TBXA2R rSNPs, Transcriptional Factor Binding Sites and Asthma in Asians

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Abstract

Four regulatory single nucleotide polymorphisms (rSNPs) (rs2238631, rs2238632, rs2238633 and rs2238634) in intron one, two rSNPs (rs1131882 and rs4523) in exon 3 and one rSNP (rs5756) in the 3'UTR of the thromboxane A2 receptor (TBXA2R) gene have been associated with childhood-onset asthma in Asians. These rSNP alleles alter the DNA landscape for potential transcriptional factors (TFs) to attach resulting in changes in transcriptional factor binding sites (TFBS). These TFBS changes are examined with respect to asthma which has been found to be significantly associated with the rSNPs.

Keywords

***TBXA2R*, rSNPs, TFBS, Asthma**

1. Introduction

Asthma is a chronic inflammatory condition of the airways characterized by recurrent episodes of reversible airway obstruction and increased bronchial hyper-responsiveness which results from the interactions between genes and environmental factors [1]-[3]. Asthma causes episodes of wheeze, cough, and shortness of breath [4]. Recent studies indicate that the genetic factors of childhood-onset asthma differ from those of adult-onset asthma [3] [5]. Childhood asthma is a major clinical and public health problem as it affects nearly one in eight children in the USA [6] and worldwide [7]. The disease is genetically heterogeneous and genome-wide association studies (GWAS) have identified a group of loci at chromosome 17q21 that are strongly associated with childhood-onset asthma in Caucasians [5] [8]. The genetic origins of asthma are diverse where some disease pathways are specific to wheezing syndromes while others are shared with atopy and bronchial hyper-responsiveness [5]. To that end another gene has recently surfaced in Asian populations that have been found to be associated with lung function childhood-onset asthma [9].

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The thromboxane A2 receptor (TBXA2R) gene which is located at chromosome 19p13.3 is a member of the seven-transmembrane G-protein-coupled receptor super family, which interacts with intracellular G proteins, regulates different downstream signaling cascades, and induces many cellular responses including the intracellular calcium influx, cell migration and proliferation, and apoptosis [10]. This gene is abundantly expressed in tissues at the mRNA and protein levels targeted by the TBXA2R ligand thromboxane A2 (TXA2) that include erythroleukaemia cells, vascular and bronchial smooth muscle, uterus and placental tissue, endothelium, epithelium, trophoblasts, thymus, liver and small intestine [11]. The activation of TBXA2R in bronchial smooth muscle cells by its ligand results in intercellular calcium mobilization with subsequent bronchoconstriction, which contributes to bronchial smooth muscle hyperplasia and airway remodeling, which occurs in response to chronic airway inflammation in asthma [12].

Four linked *TBXA2R* single nucleotide polymorphisms (SNPs, rs2238631, rs2238632, rs2238633 and rs2238634) which span a 431bp region of intron one have been found to be in linkage disequilibrium (LD) with two exon 3 SNPs [rs11318632, (c.795 T > C) and rs4523 (c.924 T > C)] [9], which are approximately 8.4 kb downstream from the intron one SNPs. The rs11318632 and rs4523 SNPs from exon 3 are synonymous and unlikely to influence the characteristics of the receptor protein. The exon 3 SNPs have been associated with asthma and its related phenotypes in Asian populations, where rs4523 SNP was found to be associated with adult asthma in a Japanese population [13] and childhood atopic asthma in a Chinese population [14], while the rs11318632 SNP was found to be associated with atopic asthma in a Korean population [15]. Two haplotypes (H2 & H4) involving the four linked *TBXA2R* SNPs from intron one where found to influence *TBXA2R* transcriptional activity and were also associated with asthma-related phenotypes [9]. This suggests that these SNPs may be part of a regulatory network for the *TBXA2R* gene in Asian populations. To follow up on this possibility these SNPs were examined for associations to potential transcription factor binding sites (TFBS).

Single nucleotide changes that affect gene expression by impacting gene regulatory sequences such as promoters, enhances, and silencers are known as regulatory SNPs (rSNPs) [16]-[19]. A rSNPs within a transcriptional factor binding site (TFBS) can change a transcriptional factor's (TF) ability to bind its TFBS [20]-[23] in which case the TF would be unable to effectively regulate its target gene [24]-[28]. This concept is examined for the above *TBXA2R* SNPs and their allelic association with TFBS. In this report, these SNP associations have been discussed with changes in potential TFBS and their possible relationship to childhood-onset asthma in Asians.

2. Materials and Methods

Identifying TFBS

The JASPAR CORE database [29] [30] and ConSite [31] were used to identify the TFBS in this study. JASPAR is a collection of transcription factor DNA-binding preferences used for scanning genomic sequences where ConSite is a web-based tool for finding cis-regulatory elements in genomic sequences. The Vector NTI Advance 11 computer program (Invitrogen, Life Technologies) was used to locate the TFBS in the *TBXA2R* gene (NCBI Ref Seq NM_201636) from 9.4 kb upstream of the transcriptional start site to 1.4 kb past the 3'UTR which represents a total of 17.1 Kbp. The JASPAR CORE database was also used to compute each nucleotide occurrence (%) within the TFBS where upper case lettering indicate that the nucleotide occurs 90% or greater and lower case less than 90%. The occurrence of each SNP allele in the TFBS is also computed from the database (**Table & Supplement**).

3. Results

TBXA2RrSNPs and TFBS

The *TBXA2R* gene encodes a member of the G protein-coupled receptor family and the protein interacts with thromboxane A2 to induce platelet aggregation and regulate hemostasis. The activity of this receptor is mediated by a G-protein that activates a phosphatidylinositol-calcium second messenger system. The four *TBXA2R*rSNPs [rs2238631 (A/G), rs2238632 (C/T), rs2238633 (T/G) and rs2238634 (G/T)] in intron one have been found to be in moderate LD with the exon 3 SNP [rs1131882 (C/T), c.795T > C] while the other exon 3 SNP [rs4523 (C/T), c.924T > C] has been found to be in strong LD with a 3'UTR SNP (rs5756 (C/T) [9]. Since the exon 3 SNPs have been found to be associated with asthma in Asian populations [10]-[12] and certain haplotypes of the intron

one SNPs have an effect on the transcriptional activity of the *TBXA2R* gene [9], the potential TFBS for alleles of each of the seven SNPs were examined (**Table 1 & Supplement**).

The intron one rs2238631 SNP *TBXA2R*-A allele creates six unique TFBS for the ELK1 & 4, ETS1, GATA2, HAND1:TCFC2*α* and SPZ1 TFs which are involved in the mitogen-activate protein kinase signaling pathway, repression, controlling development, proliferation of hematopoietic and endocrine cell lineages, and initiation of B lymphopoiesis (**Table 1**). The intron one rs2238631 SNP *TBXA2R*-G allele creates two unique TFBS for the FOXC1 and TFAP2*α* TFs which are involved in cell viability and resistance to oxidative stress and activating transcription of some genes while inhibiting the transcription of other genes, respectively (**Table & Supplement**). Only one TFBS have been conserved between the two rs2238631 alleles which is for the EN1 TF which plays a role in development (**Table 1**).

Table 1. The TBXA2R SNPs that were examined in this study where the minor allele is in red. Also listed are the transcriptional factors (TF), their potential binding sites (TFBS) containing these SNPs and DNA strand orientation. TFs in red differ between the SNP alleles. Where upper case nucleotide designates the 90% conserved BS region and red is the SNP location of the alleles in the TFBS. Below the TFBS is the nucleotide occurrence (%) obtained from the Jaspar Core database. Also listed are the number (#) of binding sites in the gene for the given TF. Note: TFs can bind to more than one nucleotide sequence.

SNP	Allele	TFs	Protein name	# of Sites	TFBS	Strand
rs2238631	**A**	ELK1	ELK1, member of ETS oncogene family	1	aagccgGAta	minus
(A/G)					A = 96%	
Intron 1		ELK4	ELK4, ETS-domain protein	1	gCCGGAtac	minus
					A = 100%	
		EN1	Engrailed homeobox 1	1	acagggtatcc	plus
					t = 30%	
		ETS1	Protein C-ets-1	1	taTCCg	plus
					T = 98%	
		GATA2	GATA binding protein 2	10	gGATa	minus
					A = 98%	
		HAND1:TCFE2*α*	Heart- and neural crest derivatives-expressed protein 1: transcription factor E2A	1	tatCcGgctt	plus
					t = 83%	
		SPZ1	spermatogenicleucine zipper 1	1	aggGtatccgg	plus
					t = 34%	
	G	EN1	Engrailed homeobox 1	1	acagggtaccc	plus
					c = 30%	
		FOXC1	Forkhead box C1	1	gccggGTA	minus
					G = 100%	
		TFAP2*α*	Transcription factor AP-2 alpha (activating enhancer binding protein 2 alpha)	1	GCCgggtac	minus
					g = 49%	
rs2238632	**C**	MAFB	v-mafmusculoaponeuroticfibrosarcoma oncogene homolog B (avian)	1	Ggtgacgc	minus
(C/T)					c = 34%	
Intron 1		PAX2	Paired box gene 2	1	ggtgacgc	minus

Continued

					c = 35%	
	T	ARNT	aryl hydrocarbon receptor nuclear translocator	5	gACGTG	minus
					T = 100%	
		ARNT	aryl hydrocarbon receptor nuclear translocator	6	cACGTc	plus
					A = 95%	
		CREB1	cAMP responsive element binding protein 1	1	gcAcGtca	plus
					A = 100%	
		HIF1α:ARNT	Hypoxia-inducible factor 1:Aryl hydrocarbon receptor nuclear translocator	1	tgaCGTGc	minus
					T = 100%	
		MAFB	v-mafmusculoaponeuroticfibrosarcoma oncogene homolog B (avian)	1	Ggtgacgt	minus
					t = 20%	
		MAX	MYC associated factor X	1	gagCACGTca	plus
					A = 94%	
		PAX2	Paired box gene 2	1	ggtgacgt	minus
					t = 26%	
		USF1	Upstream transcription factor 1	3	CACGTca	plus
					A = 100%	
rs2238633	**G**	KLF4	Krueppel-like factor 4	1	aGGGtGgggt	minus
(T/G)					g = 90%	
Intron 1		MZF1_1-4	Myeloid zinc finger 1	21	tGGGGA	minus
					G = 95%	
		SP1	Specificity Protein 1	2	CcCcacCctg	plus
					c = 86%	
		ZNF354C	Zinc finger protein 354C	31	cccCAC	plus
					c = 38%	
	T	BRCA1	breast cancer 1, early onset	5	acAccac	plus
					A = 95%	
		EN1	Engrailed homeobox 1	1	gggtggtgtcg	minus
					t = 70%	
		KLF4	Krueppel-like factor 4	1	aGGGtGgtgt	minus
					t = 3%	
		ZNF354C	Zinc finger protein 354C	37	cacCAC	plus
					a = 44%	
rs2238634	**T**	HLTF	Helicase-like transcription factor	1	gagCtTagca	minus

Continued

(G/T)					T = 100%	
Intron 1		HNF4*α*	Hepatocyte nuclear factor 4, alpha	1	gGtgCtaAGctca	plus
					a = 79%	
		NR2F1	Nuclear receptor subfamily 2, group F, member 1	1	tGAgCttagcaccc	minus
					t = 85%	
		NR2E3	Nuclear receptor subfamily 2, group E, member 3	3	tgAGCTT	minus
					T = 100%	
		NR2E3	Nuclear receptor subfamily 2, group E, member 3	2	tAAGCTC	plus
					A = 100%	
		NR4A2	Nuclear receptor subfamily 4, group A, member 2	1	aAGctCAg	plus
					a = 57%	
		ZFX	Zinc finger X-chromosomal protein	1	taagctcaGGCCTc	plus
					a = 12%	
	G	ZFX	Zinc finger X-chromosomal protein	1	tcagctcaGGCCTc	plus
					c = 35%	
rs1131882	**C**	GATA2	GATA binding protein 2	10	cGATg	plus
(C/T)					G = 91%	
c.795T > C		GATA3	GATA binding protein 3	3	cGATga	plus
Exon 3					G = 98%	
		INSM1	Insulinoma-associated 1	1	tgtctGGGcgat	plus
					g = 67%	
		NFE2L1:MAFG	Nuclear factor erythroid 2-related factor 1 Transcription factor MafG	4	gaTGAa	plus
					g = 29%	
		NFIC	Nuclear factor 1 C-type	24	tgGGcg	plus
					g = 17%	
	T	MZF1_1-4	Myeloid zinc finger 1	14	tGGGcA	plus
					A = 90%	
		MZF1_5-13	Myeloid zinc finger 1	2	gtctGGGcaa	plus
					a = 63%	
		NFIC	Nuclear factor 1 C-type	14	tgGGca	plus
					a = 48%	
		NKX2-5	Natural killer 2 homeobox 5	2	ttcAttg	minus
					t = 65%	
		Nobox	NOBOX oogenesis homeobox	1	TcATtgcc	minus

Continued

					t = 84%	
		PAX2	Paired box gene 2	1	cttCattg	minus
					t = 32%	
		SOX17	SRY (sex determining region Y)-box 17	1	ttcaTTGcc	minus
					T = 100%	
rs4523	**C**	AR	Androgen receptor	1	gggtGtACatcctGttCcgccg	minus
(C/T)					C = 100%	
c.924T > C		ELF5	E74-like factor 5	1	tacaTCCtg	minus
Exon 3					c = 45%	
		ELK1	ELK1, member of ETS oncogene family	1	gaacagGAtg	plus
					g = 50%	
		ELK4	ELK4, ETS-domain protein	1	aCaGGAtgt	plus
					g = 75%	
		ETS1	Protein C-ets-1	15	caTCCt	minus
					c = 40%	
		FEV	ETS oncogene family	1	caGGAtgt	plus
					g = 46%	
		FOXC1	Forkhead box C1	2	aggatGTA	plus
					G = 100%	
		GATA2	GATA binding protein 2	32	gGATg	plus
					g = 28%	
		NR3C1	Nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)	1	gtgtacAtcctGTtCcgc	minus
					c = 67%	
		SPI1	Spleen focus forming virus (SFFV) proviral integration oncogene spi1	3	aGGATgt	plus
					g = 79%	
	T	ELF5	E74-like factor 5	1	tataTCCtg	minus
					t = 45%	
		ELK1	ELK1, member of ETS oncogene family	1	gaacagGAta	plus
					a = 50%	
		ETS1	Protein C-ets-1	3	taTCCt	minus
					t = 14%	
		FEV	ETS oncogene family	1	caGGAtat	plus
					a = 54%	
		FOXL1	Forkhead box L1	1	aggatATA	plus
					A = 91%	

Continued

		GATA2	GATA binding protein 2	10	gGATa a = 28%	plus
		GATA3	GATA binding protein 3	2	gGATat a = 62%	plus
		KLF4	Krueppel-like factor 4	1	tGGGtGtata t = 7%	minus
		ZNF354C	Zinc finger protein 354C	4	ataCAC a = 44%	plus
rs5756 (C/T) 3'UTR	**C**	ARNT:AHR	aryl hydrocarbon receptor nuclear translocator aryl hydrocarbon receptor	28	gGCGTG G = 96%	plus
		BRCA1	breast cancer 1, early onset	22	ccAccac c = 51%	minus
		EN1	Engrailed homeobox 1	5	gcgtggtggcg g = 70%	plus
		HIF1α:ARNT	Hypoxia-inducible factor 1: Aryl hydrocarbon receptor nuclear translocator	10	gggCGTGg G = 100%	plus
		KLF4	Krueppel-like factor 4	4	cGGGcGtggt G = 98%	plus
		PAX2	Paired box gene 2	9	cacCacgc c = 55%	minus
		TFAP2A	Transcription factor AP-2 alpha (activating enhancer binding protein 2 alpha)	8	GCCaccacg c = 9%	minus
		TFAP2A	Transcription factor AP-2 alpha (activating enhancer binding protein 2 alpha)	5	GCCgggcgt g = 74%	plus
		ZNF354C	Zinc finger protein 354C	37	caCCAC C = 94%	minus
	T	NFIC	Nuclear factor 1 C-type	18	cgGGca a = 48%	plus
		NFE2L1:MAFG	Nuclear factor erythroid 2-related factor 1 Transcription factor MafG	20	caTGcc T = 100%	minus
		TFAP2A	Transcription factor AP-2 alpha (activating enhancer binding protein 2 alpha)	8	GCCaccatg t = 7%	minus
		ZEB1	Zinc finger E-box binding homeobox 1	22	cACCat t = 34%	minus
		YY1	YY1 transcription factor	22	aCCATg T = 100%	minus

The intron one rs2238632 SNP *TBXA2R*-C allele creates no unique TFBS while the *TBXA2R* -T allele creates five unique TFBS which are for the ARNT, CREB1, HIF1*α*:ARNT, MAX and USF1 TFs which are involved with xenobiotic metabolism, circadian rhythmicity, cellular and systemic responses to hypoxia, transcriptional regulator and a cellular TF, respectively (**Table & Supplement**). Two TFBS have been conserved between the two alleles which are the MAFB and PAX2 TFs that are involved with the transcription of erythroid-specific genes in myeloid cells and plays a role in kidney cell development, respectively (**Table 1**).

The intron one rs2238633 SNP *TBXA2R*-G allele creates two unique TFBS for the MZF1_1-4 and SP1 TFs which are involved in transcriptional regulation and the regulation of genes involved in cell growth, apaoptosis, differentiation and immune responses, respectively (**Table & Supplement**). The intron one rs2238633 SNP *TBXA2R*-T allele also creates two unique TFBS for the BRCA1 and SP1 TFs which are involved in maintaining genomic stability and controlling development, respectively (**Table & Supplement**). Two TFBS have been conserved between the two alleles which are the KLF4 and ZNF354C TFs that are involved with the regulation of key transcription factors during embryonic development, activation and repression, respectively (**Table & Supplement**).

The intron one rs2238634 SNP *TBXA2R*-T allele creates five unique TFBS for the HLTF, HNF4*α*, NR2F1, NR2E3 and NR4A2 TFs which are involved with altering chromatin structure, regulates the expression of hepatic genes, initiation of transcription, signaling pathways and transcription regulation, respectively (**Table & Supplement**). The intron one rs2238634 SNP *TBXA2R*-G allele creates no unique TFBS. One TFBS has been conserved between the two alleles which is the ZFX TF which is a probable transcription activator.

The exon 3 rs1131882 SNP *TBXA2R*-C allele creates four unique TFBS for the GATA2, GATA3, INSM1 and NFE2L.1: MAFG TFs which are involved with regulation of genes for development and proliferation of hematopoietic and endocrine cell lineages, endothelial cell biology, neuroendocrine differentiation of human lung tumors, and up-regulation of cytoprotective genes via the antioxidant response element, respectively (**Table & Supplement**). The exon 3 rs1131882 SNP *TBXA2R*-T allele creates six unique TFBS for the MZF1_1-4, MZF1_5-13, NKX2-5, Nobox, PAX2 and SOX17 TFs which are involved with transcription regulation, negative regulator of chondrocyte maturation, oogenesis and kidney cell differentiation (**Table & Supplement**). One TFBS has been conserved between the two alleles which is the NFIC TF which is involved with activating transcription and replication.

The exon 3 rs4523 SNP *TBXA2R*-C allele creates five unique TFBS for the AR, ELK4, FOXC1, NR3C1 and SPI1 TFs which are involved with the regulation of eukaryotic gene expression, transcriptional activation and repression, viability and resistance to oxidative stress, regulation of carbohydrate, protein and fat metabolism as well as activating gene expression during myeloid and B-lymphoid cell development, respectively (**Table & Supplement**). The exon 3 rs4523 SNP *TBXA2R*-T allele creates four unique TFBS for the FOXL1, GATA3, KLF4 and ZNF354C TFs which are involved with the regulation of multiple processes including metabolism, cell proliferation and gene expression during ontogenesis, endothelial cell biology, embryonic development and transcription repression, respectively (**Table & Supplement**). Five TFBS have been conserved between the two alleles which are the ELF5, ELK1, ETS1, FEV and GATA2 TFs that are involved with regulation epithelium-specific genes, the mitogen-activate protein kinase signaling pathway, the TTRAP, UBE2I and Death associated protein, transcriptional repression and genes for development and proliferation of hematopoietic and endocrine cell lineages (**Table & Supplement**).

The 3'UTR rs5756 SNP *TBXA2R*-C allele creates seven unique TFBS for the ARNT:AHR, BRCA1, EN1, HIF1*α*:ARNT, KLF4, PAX2 and ZNF354C TFs which are involved with xenobiotic metabolism, genomic stability, controlling development, hypoxia, embryonic development, kidney cell differentiation and repression, respectively (**Table & Supplement**). The 3'UTR rs5756 SNP *TBXA2R*-T allele creates four unique TFBS for the NFIC, NFE2L1:MAFG, ZEB1 and YY1 TFs which are involved with activating transcription and replication, up-regulation of cytoprotective genes, transcription repression and control of transcription, respectively (**Table & Supplement**). Only one TFBS has been conserved between the two alleles which is the TFAP2*α* that is involved with controlling transcription.

4. Discussion

GWAS over the last decade have identified nearly 6500 disease or trait-predisposing SNPs where only 7% of these are located in protein-coding regions of the genome [32] [33] and the remaining 93% are located within

non-coding areas [34] [35] such as regulatory or intergenic regions. SNPs which occur in the putative regulatory region of a gene where a single base change in the DNA sequence of a potential TFBS may affect the process of gene expression are drawing more attention [16] [18] [36]. A SNP in a TFBS can have multiple consequences. Often the SNP does not change the TFBS interaction nor does it alter gene expression since a transcriptional factor (TF) will usually recognize a number of different binding sites in the gene. In some cases the SNP may increase or decrease the TF binding which results in allele-specific gene expression. In rare cases, a SNP may eliminate the natural binding site or generate a new binding site. In which cases the gene is no longer regulated by the original TF. Therefore, functional rSNPs in TFBS may result in differences in gene expression, phenotypes and susceptibility to environmental exposure [36]. Examples of rSNPs associated with disease susceptibility are numerous and several reviews have been published [36]-[39].

GWAS have also identified many potential rSNPs and candidate genes associated with the asthma [5] [8] [40] [41], which indicates that the genetic origins of the disease are extremely diverse [5]. The EVE consortium conducted a meta-analysis of North American GWAS including individuals of European American, African American or African Caribbean and Latino ancestry. The study revealed that previously identified loci on chromosome 17q21 (encoding *ORMDL*3 and *GSDMB*) [8] and the nearby *IL*1*RL*1, *TSLP* and *IL*33 genes were robust to ethnic differences and had significant associations in all three ethnic groups [42]. The same study also identified another asthma susceptibility locus at *PYHIN*1, with the association being specific to individuals of African descent. The associated SNPs in *PYHIN*1 occur with a minor allele frequencies of 0.26 - 0.29 in African-Americans and African-Caribbean controls, less than 0.05 in the Latino populations and not polymorphic in European Americans [42]. Yet another asthma susceptibility locus at *TBXA*2*R* has been associated with childhood-onset in Asians [9] which has been the focus of this report.

In this study the intron one rs2238631 *TBXA*2*R*-A minor allele [T (+ strand) or A (-strand)] located in the ELK1, ELK4, ETS1 and HAND1:TCFE2*α* TFBS has a 96%, 100%, 98% and 83% occurrence, respectively, in humans. These BS occurs only once in the gene and therefore a change in these TFBS created by this rSNP would probably have any impact on the regulation of the gene (**Table & Supplement**). In contrast, the intron one rs2238631 TBXA2R-A allele located in the SPZ1 TFBS has a 34% occurrence and also only occurs once in the gene which might not have much of an impact on the regulation of the gene since other nucleotides can be substituted at this position. Also, the intron one rs2238631 TBXA2R-A allele located in the GATA2 TFBS has a 98% occurrence but occurs nine other times in the gene; therefore, it might not have much of an impact on gene regulation. The rs2238631 *TBXA*2*R*-G common allele [C (+ strand) or G (-strand)] located in the FOXC1 and TFAP2*α* TFBS has a 100% and 49% occurrence in humans and these BS occur only once in the gene and therefore a change in these TFBS created by this rSNP would probably have any impact on the regulation of the gene for the FOXC1 TF but not much impact for the TFAP2*α* TF (**Table & Supplement**). The arrangement of these TFBS within various haplotypes might explain the LD found between these *TBXA*2*R* rSNPs [9].

Similar logic can be used to evaluate the potential TFBS within the other *TBXA*2*R* rSNPs found in the table. It should be noted that the minor alleles in the intron 1 rSNPs create more unique TFBS than do the common alleles by a ratio of 18 to 4, respectively (**Table 1**) while the same ratio for the exon 3 and 3'UTR rSNPs is 13 to 17. Unique TFBSs that would be expected to have an impact on asthma are ELK1 and SPZ1 created by the minor allele of rs2238631, HIF1*α*:ARNT created by the minor allele of rs2238632, INSM1 created by the minor allele of rs1131882 and FOXC1 created by the minor allele of rs4523. Other unique TFBS that would be expected to have an impact on asthma which are created by the rSNP common alleles would be FOXC1 (rs2238631) and HIF1*α*:ARNT (rs5756). The two haplotypes (H2 & H4) involving the four linked *TBXA*2*R* SNPs from intron one found to influence *TBXA*2*R* transcriptional activity and were also associated with asthma-related phenotypes [9] involving the minor alleles of rs2238631 and rs2238632 which create the unique TFBS for the ELK1, SPZ1 and HIF1*α*:ARNT, respectively. Also that worth mentioning would be the minor allele of rs2238634 which creates the NR2E3 TFBS whose TF is involved with signaling pathways (**Table & Supplement**).

The changes in biological and physiological conditions that have been associated with these rSNPs of the *TBXA*2*R* gene are shown in the table and supplement along with rSNP allele-specific TFBS. What a change in the rSNP alleles can do is to alter the DNA landscape around the SNP for potential TFs to attach and regulate a gene. This change in the DNA landscape can alter gene regulation which in turn can result in a change of a biological process or signaling pathway resulting in disease or illness. In this report, the seven rSNPs of the *TBXA*2*R* gene which have been examined illustrate that a change in rSNP alleles can provide different TFBS

which in turn could also be associated with asthma.

Conflict of Interest

Author declares that there is no conflict of interests.

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Supplement

Table 1. Transcriptional factor (TF) descriptions.

TFs	TF description
AR	Steroid hormone receptors are ligand-activated transcription factors that regulate eukaryotic gene expression and affect cellular proliferation and differentiation in target tissues.
ARNT	Involved in the induction of several enzymes that participate in xenobiotic metabolism.
ARNT:AHR	The dimer alters transcription of target genes. Involved in the induction of several enzymes that participate in xenobiotic metabolism.
BRCA1	This gene encodes a nuclear phosphoprotein that plays a role in maintaining genomic stability, and it also acts as a tumor suppressor.
CREB1	This gene encodes a transcription factor that is a member of the leucine zipper family of DNA binding proteins
ELF5	A member of an epithelium-specific subclass of the Ets transcritpion factor family.
ELK1	The protein encoded by this gene is a nuclear target for the ras-raf-MAPK signaling cascade.
ELK4	Involved in both transcriptional activation and repression.
EN1	Homeobox-containing genes are thought to have a role in controlling development.
ETS1	The protein encoded by this gene belongs to the ETS family of transcription factors and has been shown to interact with TTRAP, UBE2I and Death associated protein.
FEV	It functions as a transcriptional repressor.
FOXC1	This gene belongs to the forkhead family of transcription factors which is characterized by a distinct DNA-binding forkhead domain. An important regulator of cell viability and resistance to oxidative stress.
FOXL1	FOX transcription factors are characterized by a distinct DNA-binding forkhead domain and play critical roles in the regulation of multiple processes including metabolism, cell proliferation and gene expression during ontogenesis.
GATA2	A member of the GATA family of zinc-finger transcription factors that are named for the consensus nucleotide sequence they bind in the promoter regions of target genes and play an essential role in regulating transcription of genes involved in the development and proliferation of hematopoietic and endocrine cell lineages.
GATA3	Plays an important role in endothelial cell biology.
HAND1:TCFE2α	Hand1 belongs to the basic helix-loop-helix family of transcription factors. The Tcfe2a gene encodes the transcription factor E2A, a member of the “class I” a family of basic helix-loop-helix (bHLH) transcription factors (also known simply as “E-proteins”). The transcription factor E2A controls the initiation of B lymphopoiesis.
HIF1α:ARNT	HIF1 is a homodimeric basic helix-loop-helix structure composed of HIF1a, the alpha subunit, and the aryl hydrocarbon receptor nuclear translocator (Arnt), the beta subunit. The protein encoded by HIF1 is a Per-Arnt-Sim (PAS) transcription factor found in mammalian cells growing at low oxygen concentrations. It plays an essential role in cellular and systemic responses to hypoxia.
HLTF	This gene encodes a member of the SWI/SNF family. Members of this family have helicase and ATPase activities and are thought to regulate transcription of certain genes by altering the chromatin structure around those genes.
HNF4α	The encoded protein controls the expression of several genes, including hepatocyte nuclear factor 1 alpha, a transcription factor which regulates the expression of several hepatic genes
INSM1	This gene is a sensitive marker for neuroendocrine differentiation of human lung tumors.
KLF4	Transcription factor that can act both as activator and as repressor. Regulates the expression of key transcription factors during embryonic development.
MAFB	The encoded nuclear protein represses ETS1-mediated transcription of erythroid-specific genes in myeloid cells.
MAX	The protein encoded by this gene is a member of the basic helix-loop-helix leucine zipper (bHLHZ) family of transcription factors
MZF1_1-4	Binds to target promoter DNA and functions as trancription regulator. May be one regulator of transcriptional events during hemopoietic development. Isoforms of this protein have been shown to exist at protein level.
MZF1_1-5-13	Binds to target promoter DNA and functions as trancription regulator. May be one regulator of transcriptional events during hemopoietic development. Isoforms of this protein have been shown to exist at protein level.
NFE2L1:MafG	Nuclear factor erythroid 2-related factor (Nrf2) coordinates the up-regulation of cytoprotective genes via the antioxidant response element (ARE). MafG is a ubiquitously expressed small maf protein that is involved in cell differentiation of erythrocytes. It dimerizes with P45 NF-E2 protein and activates expression of a and b-globin.

Continued

NFIC	Recognizes and binds the palindromic sequence 5'-TTGGCNNNNNGCCAA-3' present in viral and cellular promoters and in the origin of replication of adenovirus type 2. These proteins are individually capable of activating transcription and replication.
NKX2-5	This gene encodes a member of the NK family of homeobox-containing proteins. Transcriptional repressor that acts as a negative regulator of chondrocyte maturation.
NOBOX	This homeobox gene encodes a transcription factor that is thought to play a role in oogenesis.
NR2E3	This protein is part of a large family of nuclear receptor transcription factors involved in signaling pathways.
NR2F1	Coup (chicken ovalbumin upstream promoter) transcription factor binds to the ovalbumin promoter and, in conjunction with another protein (S300-II) stimulates initiation of transcription.
NR3C1	Glucocorticoids regulate carbohydrate, protein and fat metabolism, modulate immune responses through suppression of chemokine and cytokine production and have critical roles in constitutive activity of the CNS, digestive, hematopoietic, renal and reproductive systems.
NR4A2	Transcriptional regulator which is important for the differentiation and maintenance of meso-diencephalic dopaminergic (mdDA) neurons during development.
PAX2	Probable transcription factor that may have a role in kidney cell differentiation.
SOX17	Acts as transcription regulator that binds target promoter DNA and bends the DNA.
SP1	Can activate or repress transcription in response to physiological and pathological stimuli. Regulates the expression of a large number of genes involved in a variety of processes such as cell growth, apoptosis, differentiation and immune responses.
SPI1	This gene encodes an ETS-domain transcription factor that activates gene expression during myeloid and B-lymphoid cell development.
SPZ1	This gene encodes a bHLH-zip transcription factor which functions in the mitogen-activate protein kinase (MAPK) signaling pathway.
TFAP2A	The protein encoded by this gene is a transcription factor that binds the consensus sequence 5'-GCCNNNGGC-3' and activates the transcription of some genes while inhibiting the transcription of others.
USF1	This gene encodes a member of the basic helix-loop-helix leucine zipper family, and can function as a cellular. transcription factor.
YY1	Multifunctional transcription factor that exhibits positive and negative control on a large number of cellular and viral genes by binding to sites overlapping the transcription start site
ZEB1	This gene encodes a zinc finger transcription factor. Acts as a transcriptional repressor.
ZFX	A member of the krueppel C2H2-type zinc-finger protein family and probable transcriptional activator.
ZNF354C	May function as a transcription repressor.