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Identifying Changes in Punitive Transcriptional Factor Binding Sites Created by *PPARα/δ/γ* SNPs Associated with Disease

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Abstract

Single nucleotide polymorphisms (SNPs) located in the *PPARα/δ/γ* genes that have been previously found to be significantly associated with human disease or a condition were also found to alter the genes punitive transcriptional factor binding sites (TFBS). Two alleles (C/G) of the *PPARα* SNP (rs1800206) were found to generate 7 common and 8 unique punitive TFBS. One of the unique TFBS created by the minor G (0.02) allele is for the T-Box 4 (TBX4) transcription factor which is associated with heritable pulmonary arterial hypertension. Two alleles (A/G) of the *PPARδ* SNP (rs2016520) were found to generate 20 unique punitive TFBS while the two alleles (C/G) of the *PPARδ* SNP (rs9794) were found to generate 11 common and 11unique punitive TFBS. The alleles of the *PPARγ* SNPs (rs10865710, rs12629751, rs709158, rs1805192 and rs3856806) were found to generate 15, 12, 16, 2 and 21 common and 9, 4, 12, 4 and 7 unique punitive TFBS, respectively. These changes in TFBS are discussed with relation to alterations in gene expression that may result in disease or change in human condition.

Keywords

PPARα/δ/γ Gene Regulation, SNPs, TFBS, Human Disease

1. Introduction

The peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcriptional factors (TFs) that regulate many genes in cell differentiation and various metabolic processes including lipid and glucose homeostasis. They are nuclear hormone receptors belonging to a steroid receptor superfamily that include estrogen, thyroid hormone, vitamin D3 and glucocorticoid receptors [1] [2] [3]. The *PPAR* isotypes, *PPARα*, *PPARβ/δ* and *PPARγ* are derived from

three different genes found on chromosomes 22, 6 and 3, respectively. These isotypes modulate the expression of several genes which play a central role in regulating glucose, lipid and cholesterol metabolism [4]. *PPARα* is expressed in the liver, skeletal muscles, heart, intestinal mucosa, and brown adipose tissue while *PPARβ/δ* is expressed in liver, skeletal and cardiac muscle, adipose tissue and macrophages. *PPARγ* occurs as three isoforms $PPAR\gamma_1$, $PPAR\gamma_3$, which are expressed in the liver, intestine and spleen, and $PPAR\gamma_2$, which is expressed in brown and white adipose tissue [5]. There has been much published concerning the PPARs significant involvement in the progression of human disease [1] [3] [6] [7] [8].

There have been several *PPARα/δ/γ* single nucleotide polymorphisms (SNPs) significantly associated with various human diseases or conditions [9]-[17]. A SNP can alter a transcriptional factor motif sequence or a transcriptional factor binding site (TFBS) which in turn can affect the process of gene regulation [18] [19] [20]. A nucleotide change in a binding motif of a gene may increase or decrease the corresponding transcription factor's (TF) ability to bind the DNA and thereby affect gene expression [21] resulting in a disease or change in a human condition. In this study, eight *PPARα/δ/γ* SNPs that have been previously associated with a disease or condition were analyzed for producing alterations in punitive TFBS (**Table 1** & **Table 2**).

2. Materials and Methods

2.1. *PPARα/δ/γ* Genes and SNPs

The *PPARα/δ/γ* SNPs that have been shown to be significantly associated with disease or sickness [9]-[17] are listed in **Table 1** as well as the SNP alleles, frequencies and mutations. SNP information was collected using dbSNP, National Center for Biotechnology Information (NCBI), U.S. National Library of Medicine. The gene symbols of conserved (black) and unique (red)punitive TFBS between the two SNP alleles are found in the **Table 2**. The names of the punitive TFBS can be found in the Supplement.

2.2. Identifying TFBS

The JASPAR CORE database [22] [23] and Con Site [24] were used to identify the TFBS in previous studies [25]-[36]. 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 SNPs and TFBS within all genes listed in **Table 2**.

3. Results

The *PPARα* gene is mainly expressed in tissues with extensive fatty acid catabolism and its activation results in alterations in the transcription of several genes that regulate lipid and lipoprotein metabolism [6] [37]. One of its SNPs (rs18-

Table 1. *PPARα/δ/γ* genes whose SNPs have been shown to be associated with disease or sickness. Listed are the genes and NCBI reference sequence; their chromosome location as well as the SNP genome position and gene location; SNPs, their alleles and mutations; disease or condition associated with the SNP as well as the ethnic group. See references for information related to the disease/condition. MAF is minor allele frequency.

Gene	Chr	Position	SNP	Location	Alleles	Mutation	Disease/Condition	Ethnic Group	Reference
		(hg38)			(MAF)				
PPARα	22	46218377	rs1800206	exon 5	C	c.484C >G	Hypertriglyceridemia, Dyslipidemia,	Han Chinese	[10] [11] [16] [38] [39]
NM_005036.4					G (0.02)	p.Leu162Val	low-density lipoprotein-cholesterol		
PPARδ	6	35411001	rs2016520	5'UTR	A	c.-87A >G	Obesity risk, intracerebral hemorrhages	Han Chinese,	[9] [14] [17]
NM_006238.4					G (0.23)			male Han Chinese	
		35428018	rs9794	3'UTR	C	c.*1939C >G	Hypertriglyceridemia, obesity	Han Chinese	[10] [11] [17]
					G (0.27)				
PPARγ	3	12311699	rs10865710	promoter	C	c.-757C >G	Obesity risk, systemic sclerosis,	Han Chinese,	[9] [13] [16]
NM_138712.3					G (0.23)		low-density lipoprotein-cholesterol	Caucasian	
		12357908	rs12629751	intron 1	C	c.-2-21796C >T	Osteoarthritis	Southeast Chinese	[12]
					T (0.21)				
		12421677	rs709158	intron 2	A	c.1186 + 4523A >G	low-density lipoprotein-cholesterol	Han Chinese	[16]
					G (0.25)				
		12379739	rs1805192	exon 2	C	c.34C >G	Hypertriglyceridemia, Dyslipidemia,	Han Chinese	[10] [11] [16]
					G (0.26)	p.Pro12Ala	low-density lipoprotein-cholesterol		
		12434058	rs3856806	exon 7	C	c.1347C >T	Hypertriglyceridemia, Dyslipidemia,	Han Chinese	[10] [11] [16]
					T (0.23)	p.His449His	low-density lipoprotein-cholesterol		

00206) has been associated with variation in lipid serum levels in Caucasian and Indian populations [38] [39], hypertriglyceridemia risk, dyslipidemia risk and low-density lipoprotein-cholesterol risk in Han Chinese [10] [11] [16]. The two alleles (C/G) of the SNP generates seven conserved punitive TFBS between the alleles while the common C allele generates an additional six unique TFBS and the minor G allele generates two unique TFBS (**Table 2**). Of the minor G allele TFBS, the TBX4 transcription factor is associated with the disease heritable pulmonary arterial hypertension [40] , which may in part be responsible for the variation in lipid serum levels and disease risks found to be significantly associated with the this SNP.

The *PPARδ* gene is expressed in high levels in liver, kidneys, cardiac and skeletal muscle, adipose tissue, brain, colon and vasculature [41]. One of its SNPs

Table 2. Location of *PPARα/δ/γ* gene SNPs contained in potential TFBS. (−/+) is the DNA strand location of the TFBS. TFBS in red are only present for the given allele.

Gene	*PPARα*	*PPARδ*	*PPARδ*	*PPARγ*	*PPARγ*	*PPARγ*	*PPARγ*	*PPARγ*	*PPARγ*	*PPARγ*
SNP	rs1800206	rs2016520	rs9794	rs10865710	rs12629751	rs12629751	rs709158	rs1805192	rs3856806	rs3856806
Common allele	C	A	C	C	C	C	A	C	C	C
	BHLHE40 (+)	ELF5 (+)	EGR1 (+)	EMX2 (-)	ALX3 (−/+)	LHX2 (−)	CEBPA (−/+)	ESR2 (−/+)	ARNT::HIF1A (−/+)	SNAI2 (−/+)
	CLOCK (+)	ERG (+)	GCM1 (−)	EN2 (−)	BARHL23 (+)	MEOX1 (−/+)	CEBPB (−/+)	NFIC (+)	BHLHE40 (−/+)	TBX4 (−)
	HEY1 (+)	ETS1 (+)	GCM2 (−)	FOXD2 (−)	EMX1 (+)	MIXL1 (−/+)	CEBPD (−/+)	NFIX (−/+)	BHLHE41 (+)	TCF3 (−/+)
	HEY2 (−)	ETV1 (+)	HIC2 (+)	FOXP2 (−)	EMX2 (−)	MNX1 (−/+)	CEBPE (−/+)	SP1 (+)	CLOCK (−/+)	TCF4 (−/+)
	HOXA5 (−)	ETV4 (+)	KLF5 (+)	FOXP3 (−)	EN2 (−)	NKX3−2 (+)	CEBPG (−)	THAP1 (+)	ELF5 (+)	TFE3 (−/+)
	ID4 (−)	ETV5 (+)	KLF16 (+)	LHX9 (−)	ESX1 (−/+)	NOTO (+)	CEBPG (+)	ZBTB7B (+)	FIGLA (−/+)	TFEB (−/+)
	MAX (+)	FEV (+)	MZF1 (−)	MAFG::NFE2L1 (−)	EVX1 (−/+)	NOTO (−/+)	DBP (−/+)	ZBTB7C (+)	HEY1 (−/+)	TFEC (+)
	MNT (+)	FLI1 (+)	NFIX (−)	MNX1 (−)	EVX2 (−/+)	POU2F2 (−)	FOXH1 (−)	ZNF354C (+)	HEY2 (−/+)	USF1 (−)
	NKX2−3 (−)	NEUROD2 (−)	SP1 (+)	NFAT5 (−)	FOXD2 (+)	POU6F1 (−/+)	HLF (−/+)		ID4 (−/+)	USF2 (−)
	NKX3−2 (−)	OLIG3 (−/+)	SP1 (+)	NFATC1 (−)	GBX1 (−)	RAX (−/+)	HOXA11 (−)		MAX (−/+)	
	SOX10 (+)	SPIB (+)	SP2 (+)	NFATC3 (−)	GBX1 (+)	RUNX1 (−)	HOXC10 (−)		MAX::MYC (+)	
	TCF3 (−)	YY1 (+)	SP2 (+)	NFIX (−)	GBX2 (−/+)	TBX4 (−)	HOXC11 (−)		MLX (−)	
	TCF4 (−)		SP3 (+)	NKX6−2 (−)	GSX1 (−/+)	TBX5 (−)	HOXC12 (−)		MLXIPL (−/+)	
			SP3 (+)	POU2F1 (+)	GSX2 (−/+)	TEAD1 (+)	HOXC13 (−)		MNT (−/+)	
			SP8 (+)	POU2F2 (−)	HOXA2 (−/+)	TEF (+)	HOXD12 (−)		NEUROD2 (+)	
			TBX5 (−)	POU3F1 (+)	HOXB2 (−/+)	TFEC (+)	NFAT5 (+)		NFATC1 (−)	
			TCF3 (+)	POU3F2 (+)	HOXB3 (−/+)		NFATC1 (+)		NFATC3 (−)	
			TCF4 (+)	POU5F1B (+)	ISL2 (+)		NFATC3 (+)		NRF1 (+)	
			TFAP2A (+)	RFX3 (−/+)			NFIC (+)		RHOXF1 (−)	
			TFAP2B (+)	RFX4 (−/+)			NFIX (−)			
			THAP1 (+)	SRY (−)			OTX1 (−/+)			
			ZBTB7C (+)	STAT1 (−/+)			PITX3 (−)			
			ZEB1 (+)	STAT3 (−/+)			REL (+)			
			ZNF354C (+)	STAT3 (+)			RHOXF1 (−)			
			ZNF740 (+)	STAT3 (+)			TEAD3 (−)			
			ZNF740 (+)	THAP1 (−)			TEAD4 (−)			
				VAX2 (−/+)			TFCP2 (−)			
							ZNF354C (−)			

Continued

Minor allele	G	G	G	G	T	T	G	G	T	T
	CLOCK (+)	GLI2 (−)	EGR1 (+)	EN2 (−)	ALX3 (−/+)	HOXA2 (−/+)	CEBPA (−/+)	FOSL2 (−)	ARNT::HIF1A (+)	NFATC1 (−)
	HOXA5 (−)	NFKB1 (−)	HIC2 (+)	FOXD2 (−)	BHLHE23 (+)	HOXB2 (−/+)	CEBPB (−/+)	MEF2C (−)	BHLHE22 (+)	NFATC3 (−)
	ID4 (−)	NFKB2 (−)	KLF5 (+)	HOXA2 (−)	CDX1 (+)	HOXB3 (−/+)	CEBPD (−/+)	NFIX (−/+)	BHLHE40 (+)	NRF1 (+)
	NKX2−3 (−)	REL (+)	MZF1 (−)	HOXB2 (−)	EMX1 (+)	HOXC10 (−)	CEBPE (−/+)	RHOXF1 (+)	CLOCK (−/+)	OLIG1 (+)
	NKX3−2 (−)	ZBTB7A (−)	NFIX (−)	HOXB3 (−)	EMX2 (−)	LHX2 (−)	CEBPG (−)	THAP1 (−)	ELF5 (+)	OLIG2 (+)
	TBX4 (+)	ZBTB7B (−)	SP1 (+)	LHX9 (−)	ESX1 (−/+)	MEF2C (+)	DBP (−/+)	YY1 (−)	FIGLA (−)	OLIG3 (−/+)
	TCF3 (−)	ZBTB7C (−)	SP1 (+)	MAFG::NFE2L1 (−)	EVX1 (−/+)	MEOX1 (−/+)	HLF (−/+)		HIC2 (−)	RHOXF1 (−)
	TCF4 (−)	ZNF354C (−)	SP2 (+)	MEIS1 (+)	EVX2 (−/+)	MIXL1 (−/+)	HOXC10 (−)		HLTF (−/+)	SNAI2 (−/+)
	ZEB1 (−)		SP2 (+)	MIXL1 (−)	GBX1 (−)	MNX1 (−/+)	HOXC12 (−)		HOXA5 (−)	TCF3 (−/+)
			SP2 (+)	NFAT5 (−)	GBX2 (−/+)	NOTO (−)	HOXC13 (−)		ID4 (−)	TCF4 (−/+)
			SP3 (+)	NFATC1 (−)	GSX1 (−/+)	POU2F2 (−)	HOXD11 (−)		MAX (−/+)	TFE3 (−/+)
			TFAP2A (+)	NFATC3 (−)	GSX2 (−/+)	RAX (−/+)	HOXD12 (−)		MLXIPL (−)	TFEB (−/+)
			TFAP2B (+)	NFIX (−)	HLTF (+)		NFAT5 (+)		MNT (−/+)	USF1 (−)
			THAP1 (+)	NKX6−1 (−)			NFATC3 (+)		NEUROD2 (−/+)	ZBTB18 (−)
				NKX6−2 (−)			PITX3 (−)			
				POU2F1 (+)			REL (+)			
				POU3F1 (+)			RHOXF1 (−)			
				POU3F2 (+)			RHOXF1 (−)			
				POU5F1B (+)						
				SRY (−)						
				STAT3 (+)						
				STAT3 (+)						
				THAP1 (−)						
TFBS										
Conserved	7	0	11	16	21		16	2	20	
Major unique	6	12	11	9	12		12	6	8	
Minor unique	2	8	0	6	4		1	4	8	

(rs2016520) has been associated with obesity risk and intracerebral hemorrhages while a second SNP (rs9794) has been found to be associated with hypertriglyceridemia and obesity in Han Chinese [9] [14] [17]. The two alleles (A/G) of the rs2016520 SNP does not generate any conserved punitive TFBS between the alleles while the common A allele generates twelve punitive unique TFBS and the minor G alleles generates eight punitive unique TFBS (**Table 2**). Of the common A allele TFBS, the NEUROD2 transcriptional regulator is implicated in neuronal determination and the OLIG3 TF which promotes formation and maturation of oligodendrocytes, especially within the brain could in part be associated with obesity risk and intracerebral hemorrhages (Supplement). The second SNPs

(rs9794) has been associated with hypertriglyceridemia and obesity risk in Han Chinese [10] [11] [17]. The two alleles (C/G) of the rs9794 SNP generates eleven conserved punitive TFBS between the alleles while the common C allele generates eleven unique punitive TFBS and the minor G allele generates no unique TFBS (**Table 2**). Of the common C allele TFBS, the GCM1 and 2 TFs bind to the trophoblast specific element 2 (TSE2) of the aromatase gene enhancer and act as a master regulator of parathyroid development, respectively (Supplement). The deletion of these TFBS caused by the minor G allele for these two TFs could in part be associated with hypertriglyceridemia and obesity risk in Han Chinese [10] [17].

The *PPARγ* gene is expressed at high levels in adipose tissue, lipid storage, glucose metabolism as well as the transcriptional regulation of genes involved in these metabolic processes [42]. One of its SNPs (rs10865710) has been associated with obesity risk, systemic sclerosis and low-density lipoprotein-cholesterol in Han Chinese [9] [13] [16]. The two alleles (C/G) of this SNP generates sixteen conserved punitive TFBS between the alleles while the common C allele generates nine unique punitive TFBS and the minor G allele generates six unique TFBS (**Table 2**). Of the common C allele unique punitive TFBS, the POU2F2 TFBS is found in immunoglobulin gene promoters and its absence from the minor G allele TFBS may in part be responsible for the association of this SNP with systemic sclerosis (Supplement). The presence of the MNX1 and RXF3 TFBS with the common C allele and the NKX6-1 TFBS with the minor G allele which are involve with pancreas development and function as well as insulin gene regulation, respectively, may in part be responsible for association of this SNP with obesity risk and low-density lipoprotein-cholesterol (Supplement).

A second *PPARγ* gene SNP (rs12629751) has been associated with osteoarthritis in southeast Chinese [12]. The two alleles (C/T) of this SNP generates twenty-one common punitive TFBS between the alleles while the common C allele generates twelve unique punitive TFBS and the minor T allele generates four unique TFBS (**Table 2**). Of the common C allele unique TFBS, the NKX3-2 TFBS occurs whose TF is a repressor that acts as a negative regulator of chondrocyte maturation which may in part be responsible for the association of this SNP with osteoarthritis (Supplement).

A third *PPARγ* gene SNP (rs709158) has been associated with low-density lipoprotein-cholesterol in Han Chinese [16]. The two alleles (A/G) of this SNP generates sixteen common punitive TFBS between the alleles while the common A allele generates twelve unique punitive TFBS and the minor A allele generates one unique TFBS (**Table 2**). Of the common A allele unique TFBS, the HOXC11 TFBS whose TF also binds to a promoter element of the lactase-phlorizin hydrolase gene which may in part be associated with low-density lipoprotein-cholesterol in Han Chinese [43] (Supplement).

A fourth *PPARγ* gene SNP (rs1805192) has been associated with hypertriglyceridemia, dyslipidemia and low-density lipoprotein-cholesterol in Han Chinese [10] [11] [16]. The two alleles (C/G) of this SNP generates two common punitive

TFBS between the alleles while the common C allele generates six unique punitive TFBS and the minor G allele generates four unique TFBS (Table 2). Of the common C allele unique TFBS, the ERS2 TFBS whose TF is expressed in many tissues including pulmonary epithelial cells and the MEF2C TFBS generated by the minor G allele whose transcriptional activator controls cardiac morphogenesis and myogenesis, and is also involved in vascular development are in part responsible for hypertriglyceridemia, dyslipidemia, low-density lipoprotein-cholesterol in Han Chinese (Supplement).

A fifth *PPARγ* gene SNP (rs3856806) has also been associated with hypertriglyceridemia, dyslipidemia and low-density lipoprotein-cholesterol in Han Chinese [10] [11] [16]. The two alleles (C/T) of this SNP generates twenty common punitive TFBS between the alleles while the common C allele generates eight unique punitive TFBS and the minor T allele generates eight unique TFBS (Table 2). An examination of Table 2 would indicate that there are no apparent unique TFBS by either allele that would contribute to this SNPs' association with hypertriglyceridemia, dyslipidemia and low-density lipoprotein-cholesterol in Han Chinese (Table 1). However, the TF database used in this study (Materials and Methods) represent a small portion of the nuclear TFs that interact in nucleus.

4. Discussion

The *PPARα/δ/γ* genes have several SNPs that have been associated with human disease or conditions [9]-[17] (Table 1). SNPs in TFBS that alter the binding ability of the respective TF and cause changes in gene expression levels are considered regulatory (r) SNPs [44]. There have been many reports on the possible outcome of such alterations by identifying punitive TFBS based on the two alleles of the SNP associated with a disease or sickness [25]-[36]. The eight SNPs among the three genes studied in this report again provide several punitive TFBS changes per SNP allele (Table 1 & Table 2).

As an example, the *PPARα* gene has an exon five SNP (rs1800206) that has been associated with hypertriglyceridemia risk, dyslipidemia risk and low-density lipoprotein-cholesterol risk in Han Chinese (Table 1). The minor G allele of the SNP generates a punitive TBX4 (T-Box 4) TFBS not present with the common C allele (Table 2, Supplement). The TBX4 TF has been associated with the disease heritable pulmonary arterial hypertension [40] which may in part be responsible for the disease/condition found in Han Chinese. The occurrence of the minor G allele in the Han Chinese population is 0.02. A frequency that might be expected among heritable diseases. This SNP has also been associated with changes in triglyceridemia, total cholesterol, low-density lipoprotein-cholesterol (LDL-c), high-density lipoprotein-cholesterol(HDL-c) and apolipoprotein A1 (APOA1) plasma concentrations in populations of African-Americans, Caucasians and Indians [38] [39] [45] [46].

Another example is the *PPARδ* gene which has a 5'UTR SNP (rs2016520) that has been associated with obesity risk and intracerebral hemorrhages in Han

Chinese (Table 1). The major A allele of the SNP generates a punitiveNEU-ROD2 TFBS not present with the minor G allele (Table 2, Supplement). The NEU-ROD2 TF is a regulator implicated in neuronal determination and is a critical factor essential for the repression of the genetic program for neuronal differentiation. The presence of this TFBS created by one SNP allele and not the other may in part be the reason for its association with intracerebral hemorrhages in Han Chinese [14]. *PPARδ* promotes inflammation and tumor growth [47] and an increase in HDL-c concentration in cardiovascular disease [48]. The SNPs major A allele generates a punitive ERG TFBS not present with the minor G allele whose TF is associated with inflammation (Table 2, Supplement) while the minor G allele generates the punitive NFKB1 & 2 and REL TFBS not found with the common A allele whose TFs are associated with inflammation and tumorigenesis (Table 2, Supplement).

A third example is the *PPARγ* gene which has an intron one SNP (rs1269751) that has been associated with osteoarthritis (OA) in southeast Chinese (Table 1). The major C allele of the SNP generates a punitive NKX3-2 TFBS not present with the minor T allele (Table 2, Supplement). The NKX3-2 TF is a repressor that acts as a negative regulator of chondrocyte maturation. The presence of the NKX3-2 TFBS created by one SNP allele and not the other may in part be the reason for its association with osteoarthritis in southeast Chinese. Nkx3-2 has been found to induce chondrocyte precursor cells, maintained early-stage chondrocytes and down-regulated terminal-stage chondrocytes [49]. One of the strongest environmental risk factors for knee OA is obesity [50] and is also considered to be a moderate risk factor for hip OA [51]. The *PPARγ* gene has a SNP (rs10865710) in its promotor that is associated with obesity risk [9]. The minor G allele of this SNP generates a punitive NKX6-1 TFBS not found with the major C allele (Table 2). The NKX6-1 TF is involved in transcriptional regulation of islet beta cells. This TF binds to the insulin promoter and is involved in the regulation of the insulin gene (Supplement). The lack of this BS with the major C allele could have a profound effect on obesity in humans. Other examples involving the presence or absence of unique SNP allele TFBS can be found in Table 2 and potential human health issues can be made.

The *PPARα/δ/γ* SNPs that provide changes in punitive TFBS are not only found in the promoter but in the introns, exons and the UTRs of these genes (Table 2). The nucleus of the cell is where epigenetic alterations and TFs operate to convert chromosomes into single stranded DNA for mRNA transcription while it is the cytoplasm where mRNA is processed by separating exons and introns for protein translation. Consequently, it doesn't matter where TFs bind the DNA in the nucleus because it is only there that TFs function. There are three SNPs in the coding regions (exons) of two genes which are *PPARα* (rs1800206), *PPARγ* (rs-1805192 and rs3856806). These SNPs result in missense mutations in which p.L162V and p.P12A are non synonymous changes and p.H449H is a synonymous change in the amino acids of the proteins (Table 1). In this study, the same SNPs result in multiple punitive TFBS changes in the DNA. This raises

the question: are the significant associations of these SNPs with disease or change in condition the result of nucleotide or amino acid substitutions? (Table 1). All three amino acid substitutions are considered to be clinical benign changes to human health [52] while there are reports indicating these substitution are significant associations to disease or condition [10] [11] [15] [16]. This might suggest that the nucleotide and not the amino acid substitutions are responsible for the significant associations that have been reported.

In conclusion, the alterations in punitive TFBS created by SNPs as identified in this study provides a nuclear solution as to why significant associations have been found between some SNPs and human disease or sickness. Alterations in TFBS would affect the TFs ability to regulate a gene which could result in human disease or sickness.

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Supplement

Transcriptional factors (TF), protein name and their description or function.

TF	Protein name	TF description/function
ALX3	ALX Homeobox 3	This gene encodes a nuclear protein with a homeobox DNA-binding domain that functions as a transcriptional regulator involved in cell-type differentiation and development.
ARNT::HIF1A	Aryl hydrocarbon receptor nuclear translocator:: Hypoxia-inducible factor 1	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.
BHLHE22	Basic Helix-Loop-Helix Family Member E22	Inhibits DNA binding of TCF3/E47 homodimers and TCF3 (E47)/NEUROD1 heterodimers and acts as a strong repressor of Neurod1 and Myod-responsive genes, probably by heterodimerization with class a basic helix-loop-helix factors.
BHLHE23	Basic Helix-Loop-Helix Family Member E23	May function as transcriptional repressor.
BHLHE40	Basic Helix-Loop-Helix Family Member E40	Transcriptional repressor involved in the regulation of the circadian rhythm by negatively regulating the activity of the clock genes and clock-controlled genes.
BHLHE41	Basic Helix-Loop-Helix Family Member E41	Transcriptional repressor involved in the regulation of the circadian rhythm by negatively regulating the activity of the clock genes and clock-controlled genes.
CDX1	Caudal type homeo box 1	This gene is a member of the caudal-related homeobox transcription factor gene family. The encoded protein is a major regulator of intestine-specific genes involved in cell growth an differentiation.
CEBPA	CCAAT/enhancer binding protein (C/EBP), alpha	C/EBP is a DNA-binding protein that recognizes two different motifs: the CCAAT homology common to many promoters and the enhanced core homology common to many enhancers
CEBPB	CCAAT/enhancer binding protein (C/EBP), beta	Important transcriptional activator regulating the expression of genes involved in immune and inflammatory responses. Regulates the transcriptional induction of peroxisome proliferator-activated receptor gamma (*PPAR*G)
CEBPD	CCAAT/enhancer binding protein (C/EBP), delta	The protein encoded by this intronless gene is a bZIP transcription factor which can bind as a homodimer to certain DNA regulatory regions. It can also form heterodimers with the related protein CEBP-alpha. The encoded protein is important in the regulation of genes involved in immune and inflammatory responses, and may be involved in the regulation of genes associated with activation and/or differentiation of macrophages.
CEBPE	CCAAT/enhancer binding protein (C/EBP), epsilon	The protein encoded by this gene is a bZIP transcription factor which can bind as a homodimer to certain DNA regulatory regions. It can also form heterodimers with the related protein CEBP-delta.
CEBPG	CCAAT/enhancer binding protein (C/EBP), gamma	The C/EBP family of transcription factors regulates viral and cellular CCAAT/enhancer element-mediated transcription. C/EBP proteins contain the bZIP region, which is characterized by two motifs in the C-terminal half of the protein: a basic region involved in DNA binding and a leucine zipper motif involved in dimerization.
CLOCK	Clock Circadian Regulator	Transcriptional activator which forms a core component of the circadian clock.circadian rhythms in gene expression, which are translated into rhythms in metabolism and behavior. The circadian clock, an internal time-keeping system, regulates various physiological processes through the generation of approximately 24 hour in gene expression, which are translated into rhythms in metabolism and behavior. The circadian clock, an internal time-keeping system.
DBP	D-Box Binding PAR BZIP Transcription Factor	The protein encoded by this gene is a member of the PAR bZIP transcription factor family and binds to specific sequences in the promoters of several genes. The encoded protein can bind DNA as a homo-or heterodimer and is involved in the regulation of some circadian rhythm genes.
EGR1	Early growth response 1	The protein encoded by this gene belongs to the EGR family of C2H2-type zinc-finger proteins. It is a nuclear protein and functions as a transcriptional regulator. The products of target genes it activates are required for differentitation and mitogenesis.
ELF5	E74-like factor 5	A member of an epithelium-specific subclass of the Etstranscritpion factor family.

Continued

EMX1	Empty Spiracles Homeobox 1	Transcription factor, which in cooperation with EMX2, acts to generate the boundary between the roof andarchipallium in the developing brain.
EMX2	Empty Spiracles Homeobox 2	Transcription factor, which in cooperation with EMX1, acts to generate the boundary between the roof andarchipallium in the developing brain.
EN2	Engrailed homeo box 2	The human engrailed homologs 1 and 2 encode homeodomain-containing proteins and have been implicated in the control of pattern formation during development of the central nervous system.
ERG	v-ets avian erythroblastosis virus E26 oncogene homolog	This gene encodes a member of the erythroblast transformation-specific (ETS) family of transcriptions factors. All members of this family are key regulators of embryonic development, cell proliferation, differentiation, angiogenesis, inflammation, and apoptosis.
ESR2	Estrogen receptor beta	Estrogen receptor β is a member of the family of estrogen receptors and the superfamily of nuclear receptor transcription factors and is expressed by many tissues including blood monocytes and tissue macrophages, colonic and pulmonary epithelial cells.
ESX1	ESX Homeobox 1	This gene likely plays a role in placental development and spermatogenesis.
ETS1	Protein C-ets-1	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.
ETV1	ETS Variant 1	This gene encodes a member of the ETS (E twenty-six) family of transcription factors. differentiation. The ETS proteins regulate many target genes that modulate biological processes like cell growth, angiogenesis, migration, proliferation and differentiation.
ETV4	ETS Variant 4	GO annotations related to this gene include transcription factor activity, sequence-specific DNA binding is ETV1 and RNA polymerase II core promoter proximal region sequence-specific DNA binding. An important paralog of this gene ETV1.
ETV5	ETS Variant 5	GO annotations related to this gene include transcription factor activity, sequence-specific DNA binding is ETV1 and RNA polymerase II core promoter proximal region sequence-specific DNA binding. An important paralog of this gene ETV1.
EVX1	Even-Skipped Homeobox 1	The encoded protein may play an important role as a transcriptional repressor during embryogenesis.
EVX2	Even-Skipped Homeobox 2	The encoded protein is a homeobox transcription factor that is related to the protein encoded by the
FEV	ETS oncogene family	Drosophila even-skipped (eve) gene, a member of the pair-rule class of segmentation genes. It functions as a transcriptional repressor.
FIGLA	Folliculogenesis Specific BHLH Transcription Factor	Germline specific transcription factor implicated in postnatal oocyte-specific gene expression.
FLI1	Fli-1 Proto-Oncogene, ETS Transcription Factor	This gene encodes a transcription factor containing an ETS DNA-binding domain.
FOSL1 & 2	FOS-like antigen 1 & 2	The Fos gene family consists of 4 members: FOS, FOSB, FOSL1, and FOSL2. These genes encode leucine zipper proteins that can dimerize with proteins of the JUN family, thereby forming the transcription factor complex AP-1. The FOS proteins have been implicated as regulators of cell proliferation, differentiation, and transformation.
FOXD2	Forkhead box D2	Transcription factor required for formation of positional identity in the developing retina, regionalization of the optic chiasm and morphogenesis of the kidney.
FOXH1	Forkhead box H1	Transcriptional activator
FOXP2	Forkhead box P2	This gene belongs to subfamily P of the forkhead box (FOX) transcription factor family. Forkhead box transcription factors play important roles in the regulation of tissue- and cell type-specific gene transcription during both development and adulthood. Transcriptional repressor. It plays an important role in the specification and differentiation of lung epithelium.
FOXP3	Forkhead box P3	Transcriptional regulator which is crucial for the development and inhibitory function of regulatory T-cells (Treg). Plays an essential role in maintaining homeostasis of the immune system by allowing the acquisition of full suppressive function and stability of the Treg lineage and by directly modulating the expansion and function of conventional T-cells.

Continued

GBX1	Gastrulation Brain Homeobox 1	GO annotations related to this gene include sequence-specific DNA binding. An important paralog of this gene is GBX2.
GBX2	Gastrulation Brain Homeobox 2	May act as a transcription factor for cell pluripotency and differentiation in the embryo
GCM1	Glial Cells Missing Homolog 1	Transcription factor that is necessary for placental development. Binds to the trophoblast-specific element 2 (TSE2) of the aromatase gene enhancer.
GCM2	Glial Cells Missing Homolog 2	The protein is a transcription factor that acts as a master regulator of parathyroid development.
GLI2	GLI Family Zinc Finger 2	This gene encodes a protein which belongs to the C2H2-type zinc finger protein subclass of the Gli family. Members of this subclass are characterized as transcription factors which bind DNA through zinc finger motifs. Gli family zinc finger proteins are mediators of Sonic hedgehog (Shh) signaling and they are implicated as potent oncogenes in the embryonal carcinoma cell.
GSX1	GS Homeobox 1	Activates the transcription of the GHRH gene. Plays an important role in pituitary development.
GSX2	GS Homeobox 2	During telencephalic development, causes ventralization of pallial progenitors and, depending on the developmental stage, specifies different neuronal fates.
HEY1	Hes Related Family BHLH Transcription Factor With YRPW Motif 1	This gene encodes a nuclear protein belonging to the hairy and enhancer of split-related (HESR) family of basic helix-loop-helix (bHLH)-type transcriptional repressors. Expression of this gene is induced by the Notch and c-Jun signal transduction pathways.
HEY2	Hes Related Family BHLH Transcription Factor With YRPW Motif 2	This gene encodes a nuclear protein belonging to the hairy and enhancer of split-related (HESR) family of basic helix-loop-helix (bHLH)-type transcriptional repressors. The encoded protein forms homo-or hetero-dimers that localize to the nucleus and interact with a histone deacetylase complex to repress transcription.
HIC2	HIC ZBTB Transcriptional Repressor 2	Transcriptional repressor.
HLF	Hepatic leukemia factor	This gene encodes a member of the proline and acidic-rich (PAR) protein family, a subset of the bZIP transcription factors. The encoded protein forms homodimers or heterodimers with other PAR family members and binds sequence-specific promoter elements to activate transcription.
HLTF	Helicase-like transcription factor	Member of the SWI/SNF (SWItch/Sucrose Non Fermen table) family which have helicase and ATPase activities and are thought to regulate transcription of certain genes by altering the chromatin.
HOXA1	Homeobox protein Hox-A1	The genes encoding the class of transcription factors called homeobox genes are found in clusters named A, B, C, and D on four separate chromosomes. This gene is part of the A cluster on chromosome 7 and encodes a DNA-binding transcription factor which may regulate gene expression, morphogenesis, and differentiation. Sequence-specific transcription factor which is part of a developmental regulatory system that provides cells with specific positional identities on the anterior-posterior axis. Seems to act in the maintenance and/or generation of hindbrain segments.
HOXA2	Homeobox protein Hox-A2	Sequence-specific transcription factor which is part of a developmental regulatory system that provides cells with specific positional identities on the anterior-posterior axis.
HOXA5	Homeobox protein Hox-A5	DNA-binding transcription factor which may regulate gene expression, morphogenesis, and differentiation.
HOXB2	Homeobox protein Hox-B2	This gene is a member of the Antphomeobox family and encodes a nuclear protein with a homeobox DNA-binding domain. The encoded protein functions as a sequence-specific transcription factor that is involved in development.
HOXB3	Homeobox protein Hox-B3	This gene is a member of the Antphomeobox family and encodes a nuclear protein with a homeobox DNA-binding domain. The encoded protein functions as a sequence-specific transcription factor that is involved in development.
HOXA11	Homeobox protein Hox-A11	Sequence-specific transcription factor which is part of a developmental regulatory system that provides cells with specific positional identities on the anterior-posterior axis.

Continued

HOXC10	Homeobox protein Hox-C10	The protein level is controlled during cell differentiation and proliferation, which may indicate this protein has a role in origin activation
HOXC11	Homeobox protein Hox-C11	The product of this gene binds to a promoter element of the lactase-phlorizin hydrolase. It also may play a role in early intestinal development.
HOXC12	Homeobox protein Hox-C12	This gene is one of several homeobox HOXC genes located in a cluster on chromosome 12.
HOXC13	Homeobox protein Hox-C13	The product of this gene may play a role in the development of hair, nail, and filiform papilla.
HOXD11	Homeobox protein Hox-D11	Deletions that remove the entire HOXD gene cluster or the 5' end of this cluster have been associated with severe limb and genital abnormalities.
HOXD12	Homeobox protein Hox-D12	This gene is one of several homeobox HOXD genes located in a cluster on chromosome 2
ID4	Inhibitor Of DNA Binding 4, HLH Protein	Transcriptional regulator (lacking a basic DNA binding domain) which negatively regulates the basic helix-loop-helix (bHLH) transcription factors by forming heterodimers and inhibiting their DNA binding and transcriptional activity. Implicated in regulating a variety of cellular processes, including cellular growth, senescence, differentiation, apoptosis, angiogenesis, and neoplastic transformation.
ISL2	ISL LIM Homeobox 2	Transcriptional factor that defines subclasses of motoneurons that segregate into columns in the spinal cord and select distinct axon pathways.
KLF5	Krueppel-like factor 5	This gene encodes a member of the Kruppel-like factor subfamily of zinc finger proteins. The encoded protein is a transcriptional activator that binds directly to a specific recognition motif in the promoters of target genes. This protein acts downstream of multiple different signaling pathways and is regulated by post-translationalm modification. It may participate in both promoting and suppressing cell proliferation. Expression of this gene may be changed in a variety of different cancers and in cardiovascular disease. Alternative splicing results in multiple transcript variants.
KLF16	Krueppel-like factor 16	Transcription factor that binds GC and GT boxes and displaces Sp1 and Sp3 from these sequences. Modulates dopaminergic transmission in the brain.
LHX2	LIM Homeobox 2	Acts as a transcriptional activator. Stimulates the promoter of the alpha-glycoprotein gene. Transcriptional regulatory protein involved in the control of cell differentiation in developing lymphoid and neural cell types
LHX9	LIM Homeobox 9	Involved in gonadal development.
MAF::NFE2L1	Nuclear factor erythroid 2-related factor 1 Transcription factor 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.
MAX	MYC Associated Factor X	Transcription regulator. Forms a sequence-specific DNA-binding protein complex with MYC or MAD which recognizes the core sequence 5-CAC[GA]TG-3.
MAX::MYC	v-*myc* avian myelocytomatosis viral oncogene homolog *MYC* associated factor X	The protein encoded by this gene is a multifunctional, nuclear phosphoprotein that plays a role in cell cycle progression, apoptosis and cellular transformation. It functions as a transcription factor that regulates transcription of specific target genes. The MYC:MAX complex is a transcriptional activator.
MEF2C	Myocyte enhancer factor 2C	Transcription activator which binds specifically to the MEF2 element present in the regulatory regions of many muscle-specific genes. Controls cardiac morphogenesis and myogenesis, and is also involved in vascular development.
MEIS1	MeisHomeobox 1	Homeobox genes, of which the most well-characterized category is represented by the HOX genes, play a crucial role in normal development.
MEOX1	Mesenchyme Homeobox 1	Mesodermal transcription factor that plays a key role in somitogenesis and is specifically required for sclerotome development. Required for maintenance of the sclerotome polarity and formation of the cranio-cervical joints. Binds specifically to the promoter of target genes and regulates their expression. Activates expression of NKX3-2 in the sclerotome. Activates expression of CDKN1A and CDKN2A in endothelial cells, acting as a regulator of vascular cell proliferation.

Continued

MIXL1	Mix Paired-Like Homeobox	Homeodomain proteins, such as MIXL1, are transcription factors that regulate cell fate during development
MLX	MLX, MAX Dimerization Protein	Transcription regulator. Forms a sequence-specific DNA-binding protein complex with MAD1, MAD4, MNT, WBSCR14 and MLXIP which recognizes the core sequence 5-CACGTG-3. Plays a role in transcriptional activation of glycolytic target genes. Involved in glucose-responsive gene regulation.
MLXIPL	MLX Interacting Protein Like	This protein forms a heterodimeric complex and binds and activates, in a glucose-dependent manner, carbohydrate response element (ChoRE) motifs in the promoters of triglyceride synthesis genes.
MNT	MAX Network Transcriptional Repressor	Binds DNA as a heterodimer with MAX and represses transcription. Binds to the canonical E box sequence 5-CACGTG-3 and, with higher affinity, to 5-CACGCG-3.
MNX1	Motor Neuron And Pancreas Homeobox 1	Putative transcription factor involved in pancreas development and function.
MZF1	Myeloid Zinc Finger 1	Binds to target promoter DNA and functions as transcription regulator. May be one regulator of transcriptional events during hemopoietic development.
NEUROD2	Neuronal Differentiation 2	Transcriptional regulator implicated in neuronal determination. Mediates calcium-dependent transcription activation by binding to E box-containing promoter. Critical factor essential for the repression of the genetic program for neuronal differentiation; prevents the formation of synaptic vesicle clustering at active zone to the presynaptic membrane in postmitotic neurons.
NFAT5	Nuclear Factor Of Activated T-Cells 5	The product of this gene is a member of the nuclear factors of activated T cells family of transcription factors. Proteins belonging to this family play a central role in inducible gene transcription during the immune response. This protein regulates gene expression induced by osmotic stress in mammalian cells.
NFATC1	Nuclear Factor Of Activated T-Cells 1	The product of this gene is a component of the nuclear factor of activated T cells DNA-binding transcription complex. This complex consists of at least two components: a preexisting cytosolic component that translocates to the nucleus upon T cell receptor (TCR) stimulation, and an inducible nuclear component. Proteins belonging to this family of transcription factors play a central role in inducible gene transcription during immune response.
NFATC3	Nuclear Factor Of Activated T-Cells 3	Acts as a regulator of transcriptional activation. Plays a role in the inducible expression of cytokine genes in T-cells, especially in the induction of the IL-2.
NFIC	Nuclear factor 1 C-type	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.
NFIX	Nuclear Factor I X	Recognizes and binds the palindromic sequence 5-TTGGCNNNNNGCCAA-3 present in viral and cellular transcription and replication promoters and in the origin of replication of adenovirus type 2. These proteins are individually capable of activating transcription and replication.
NFKB1	Nuclear factor of kappa light polypeptide oncogene homolog gene enhancer in B-cells 1	NF-kappa-B is a pleiotropic transcription factor present in almost all cell types and is the endpoint of a series of signal transduction events that are initiated by a vast array of stimuli related to many biological processes such as inflammation, immunity, differentiation, cell growth, tumorigenesis and apoptosis.
NFKB2	Nuclear factor of kappa light polypeptide oncogene homolog gene enhancer in B-cells 2	This gene encodes a subunit of the transcription factor complex nuclear factor-kappa-B (NFkB). The NFkB complex is expressed in numerous cell types and functions as a central activator of genes involved in inflammation and immune function. The protein encoded by this gene can function as both a transcriptional activator or repressor depending on its dimerization partner.
NKX2-3	NK2 Homeobox 3	This gene encodes a homeodomain-containing transcription factor. The encoded protein is a member of the NKX family of homeodomain transcription factors.
NKX3-2	Natural killer 3 homeobox 2	This gene encodes a member of the NK family of homeobox-containing proteins. Transcriptional repressor that acts as a negative regulator of chondrocyte maturation.
NKX6-1	NK6 Homeobox 1	Transcription factor which binds to specific A/T-rich DNA sequences in the promoter regions of a number of genes. Involved in transcriptional regulation in islet beta cells. Binds to the insulin promoter and is involved in regulation of the insulin gene.
NKX6-2	NK6 Homeobox 2	An important paralog of this gene is NKX6-1.

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NOTO	Notochord Homeobox	Transcription regulator acting downstream of both FOXA2 and T during notochord development. Required for node morphogenesis
NRF1	Nuclear respiratory factor 1	This gene encodes a protein that homodimerizes and functions as a transcription factor which activates the expression of some key metabolic genes regulating cellular growth and nuclear genes required for respiration, heme biosynthesis, and mitochondrial DNA transcription and replication.
OLIG1	Oligodendrocyte Transcription Factor 1	Promotes formation and maturation of oligodendrocytes, especially within the brain. Cooperates with OLIG2 to establish the pMN domain of the embryonic neural tube.
OLIG2	Oligodendrocyte Transcription Factor 1	Required for oligodendrocyte and motor neuron specification in the spinal cord, as well as for the development of somatic motor neurons in the hindbrain. Cooperates with OLIG1 to establish the pMN domain of the embryonic neural tube.
OLIG3	Oligodendrocyte Transcription Factor 1	May determine the distinct specification program of class A neurons in the dorsal part of the spinal cord and suppress specification of class B neurons.
OTX1	Orthodenticle Homeobox 1	This gene encodes a member of the bicoid sub-family of homeodomain-containing transcription factors. The encoded protein acts as a transcription factor and may play a role in brain and sensory organ development.
PITX3	Paired Like Homeodomain 3	Transcriptional regulator which is important for the differentiation and maintenance of me-so-diencephalic dopaminergic (mdDA) neurons during development.
POU2F1	POU Class 2 Homeobox 1	Transcription factor that binds to the octamer motif (5-ATTTGCAT-3) and activates the promoters of the genes for some small nuclear RNAs (snRNA) and of genes such as those for histone H2B and immunoglobulins.
POU2F2	POU class 2 homeobox 2	The protein encoded by this gene is a homeobox-containing transcription factor of the POU domain family. The encoded protein binds the octamer sequence 5'-ATTTGCAT-3', a common transcription factor binding site in immunoglobulin gene promoters.
POU3F1	POU Class 3 Homeobox 1	Transcription factor that binds to the octamer motif (5-ATTTGCAT-3). Thought to be involved in early embryogenesis and neurogenesis.
POU3F2	POU Class 3 Homeobox 2	This gene encodes a member of the POU-III class of neural transcription factors. The encoded protein is involved in neuronal differentiation and enhances the activation of corticotropin-releasing hormone regulated genes. Overexpression of this protein is associated with an increase in the proliferation of melanoma cells.
POU5F1B	POU Class 5 Homeobox 1B	has been shown to be a weak transcriptional activator and may play a role in carcinogenesis and eye development.
POU6F1	POU Class 6 Homeobox 1	Transcription factor that binds preferentially to a variant of the octamer motif (5-ATGATAAT-3).
RAX	Retina And Anterior Neural Fold Homeobox	This gene encodes a homeobox-containing transcription factor that functions in eye development. The gene is expressed early in the eye primordia, and is required for retinal cell fate determination and also regulates stem cell proliferation.
REL	v-*rel* avian reticuloendotheliosis viral oncogene homolog	Proto-oncogene that may play a role in differentiation and lymphopoiesis. NF-kappa-B is a pleiotropic transcription factor which is present in almost all cell types and is involved in many biological processed such as inflammation, immunity, differentiation, cell growth, tumorigenesis and apoptosis.
RFX3	Regulatory factor X3	Transcription factor required for ciliogenesis and islet cell differentiation during endocrine pancreas development. Essential for the differentiation of nodal monocilia and left-right asymmetry specification during embryogenesis. Required for the biogenesis of motile cilia by governing growth and beating efficiency of motile cells. Also required for ciliated ependymal cell differentiation.
RFX4	Regulatory factor X4	This gene is a member of the regulatory factor X gene family, which encodes transcription factors that contain a highly-conserved winged helix DNA binding domain. The protein encoded by this gene is structurally related to regulatory factors X1, X2, X3, and X5. It has been shown to interact with itself as well as with regulatory factors X2 and X3, but it does not interact with regulatory factor X1.
RHOXF1	RhoxHomeobox Family Member 1	This gene is a member of the PEPP subfamily of paired-like homoebox genes. The gene may be regulated by androgens and epigenetic mechanisms. The encoded nuclear protein is likely a transcription factor that may play a role in human reproduction.
RUNX1	Runt-related transcription factor 1	Core binding factor (CBF) is a heterodimeric transcription factor that binds to the core element of many enhancers and promoters. The protein encoded by this gene represents the alpha subunit of CBF and is thought to be involved in the development of normal hematopoiesis.

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SNAI2	Snail Family Transcriptional Repressor 2	This gene encodes a member of the Snail family of C2H2-type zinc finger transcription factors. The encoded protein acts as a transcriptional repressor that binds to E-box motifs and is also likely to repress E-cadherin transcription in breast carcinoma.
SOX10	SRY (sex determining region Y)-box 10	This gene encodes a member of the SOX (SRY-related HMG-box) family of transcription factors involved in the regulation of embryonic development and in the determination of the cell fate.
SP1	Sp1 Transcription Factor	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.
SP2	Sp2 Transcription Factor	This gene encodes a member of the Sp subfamily of Sp/XKLF transcription factors. Sp family proteins are sequence-specific DNA-binding proteins characterized by an amino-terminal trans-activation domain and three carboxy-terminal zinc finger motifs. This protein contains the least conserved DNA-binding domain within the Sp subfamily of proteins, and its DNA sequence specificity differs from the other Sp proteins. It localizes primarily within subnuclear foci associated with the nuclear matrix, and can activate or in some cases repress expression from different promoters.
SP3	Sp3 Transcription Factor	Transcriptional factor that can act as an activator or repressor depending on isoform and/or post-translational modifications. Binds to GT and GC boxes promoter elements. Competes with SP1 for the GC-box promoters. Weak activator of transcription but can activate a number of genes involved in different processes such as cell-cycle regulation, hormone-induction and house-keeping.
SP8	Sp8 Transcription Factor	Transcription factor which plays a key role in limb development. Positively regulates FGF8 expression in the apical ectodermal ridge (AER) and contributes to limb outgrowth in embryos.
SPIB	Transcription factor Spi-B	SPI1 and SPIB are members of a subfamily of ETS transcription factors. ETS proteins share a conserved ETS domain that mediates specific DNA binding. SPIB and SPI1 bind to a purine-rich sequence, the PU box (5-prime-GAGGAA-3-).
SRY	Sex determining region Y	Transcriptional regulator that controls a genetic switch in male development.
STAT1	Signal transducer and activator of transcription 1	In response to cytokines and growth factors, STAT family members are phosphorylated by the receptor associated kinases, and then form homo-or heterodimers that translocate to the cell nucleus where they act as transcription activators. This protein can be activated by various ligands including interferon-alpha, interferon-gamma, EGF, PDGF and IL6. The protein mediates the expression of a variety of genes, which is thought to be important for cell viability in response to different cell stimuli and pathogens.
STAT3	Signal transducer and activator of transcription 3 (acute-phase response factor)	Signal transducer and transcription activator that mediates cellular responses to interleukins, KITLG/SCF and other growth factors
TBX4	T-Box 4	This gene is a member of a phylogenetically conserved family of genes that share a common DNA-binding domain, the T-box. T-box genes encode transcription factors involved in the regulation of developmental processes. Associated with the human disease of Heritable Pulmonary Arterial Hypertension.
TBX5	T-Box 5	DNA-binding protein that regulates the transcription of several genes and is involved in heart development and limb pattern formation.
TCF3	Transcription Factor 3	Transcriptional regulator. Involved in the initiation of neuronal differentiation. Heterodimers between TCF3 and tissue-specific basic helix-loop-helix (bHLH) proteins play major roles in determining tissue-specific cell during embryogenesis, like muscle or early B-cell differentiation.
TCF4	Transcription Factor 4	Transcription factor that binds to the immunoglobulin enchancer Mu-E5/KE5-motif. Involved in the initiation of neuronal differentiation. Activates transcription by binding to the E box (5-CANNTG-3).
TEAD1	TEA Domain Family Member 1	This gene encodes a ubiquitous transcriptional enhancer factor that is a member of the TEA/ATTS domain family. This protein directs the transactivation of a wide variety of genes and, in placental cells, also acts as a transcriptional repressor.
TEAD3	TEA Domain Family Member 3	This gene product is a member of the transcriptional enhancer factor (TEF) family of transcription factors, which contain the TEA/ATTS DNA-binding domain. It is predominantly expressed in the placenta and is involved in the transactivation of the chorionic somatomammotropin-B gene enhancer.
TEAD4	TEA Domain Family Member 4	Transcription factor which plays a key role in the Hippo signaling pathway, a pathway involved in organ size control and tumor suppression by restricting proliferation and promoting apoptosis.

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TEF	TEF, PAR BZIP Transcription Factor	This gene encodes a member of the PAR (proline and acidic amino acid-rich) subfamily of basic region/leucine zipper (bZIP) transcription factors. It is expressed in a broad range of cells and tissues in adult animals, however, during embryonic development, TEF expression appears to be restricted to the developing anterior pituitary gland, coincident with the appearance of thyroid-stimulating hormone, beta (TSHB)
TFE3	Transcription Factor Binding To IGHM Enhancer 3	This gene encodes a basic helix-loop-helix domain-containing transcription factor that binds MUE3-type E-box sequences in the promoter of genes. The encoded protein promotes the expression of genes downstream of transforming growth factor beta (TGF-beta) signaling.
TFEB	Transcription Factor EB	Transcription factor that specifically recognizes and binds E-box sequences (5-CANNTG-3). Efficient DNA-binding requires dimerization with itself or with another MiT/TFE family member such as TFE3 or MITF. In association with TFE3, activates the expression of CD40L in T-cells, thereby playing a role in T-cell-dependent antibody responses in activated CD4(+) T-cells and thymus-dependent humoral immunity.
TFEC	Transcription Factor EC	Transcriptional regulator that acts as a repressor or an activator. play roles in multiple cellular processes including survival, growth and differentiation.
TFCP2	Transcription Factor CP2	This gene encodes a transcription factor that binds the alpha-globin promoter and activates transcription of the alpha-globin gene. The encoded protein regulates erythroid gene expression, plays a role in the transcriptional switch of globin gene promoters, and it activates many other cellular and viral gene promoters.
TFAP2a	Transcription Factor AP-2 Alpha	The AP2a protein acts as a sequence specific DNA-binding transcription factor recognizing and binding to the specific DNA sequence and recruiting transcription machinery.
TFAP2b	Transcription Factor AP-2 Beta	This gene encodes a member of the AP-2 family of transcription factors. AP-2 proteins form homo-or hetero-dimers with other AP-2 family members and bind specific DNA sequences.
THAP1	THAP domain containing, apoptosis associated protein 1	DNA-binding transcription regulator that regulates endothelial cell proliferation and G1/S cell-cycle progression.
USF1	Upstream transcription factor 1	This gene encodes a member of the basic helix-loop-helix leucine zipper family, and can function as a cellular transcription factor. The encoded protein can activate transcription through pyrimidine-rich initiator (Inr) elements and E-box motifs.
USF2	Upstream transcription factor 2, C-Fos Interacting	This gene encodes a member of the basic helix-loop-helix leucine zipper family of transcription factors. The encoded protein can activate transcription through pyrimidine-rich initiator (Inr) elements and E-box motifs and is involved in regulating multiple cellular processes.
VAX2	Ventral Anterior Homeobox 2	Transcription factor that may function in dorsoventral specification of the forebrain. Plays a crucial role in eye development and, in particular, in the specification of the ventral optic vesicle.
YY1	YY1 transcription factor	YY1 is a ubiquitously distributed transcription factor belonging to the GLI-Kruppel class of zinc finger proteins. The protein is involved in repressing and activating a diverse number of promoters. YY1 may direct histone deacetylases and histone acetyltransferases to a promoter in order to activate or repress the promoter, thus mplicating histone modification in the function of YY1.
ZBTB7A	Zinc Finger And BTB Domain Containing 7A	Plays a key role in the instruction of early lymphoid progenitors to develop into B lineage by repressing T-cell instructive Notch signals.
ZBTB7B	Zinc Finger And BTB Domain Containing 7B	This gene encodes a zinc finger-containing transcription factor that acts as a key regulator of lineage commitment of immature T-cell precursors.
ZBTB7C	Zinc Finger And BTB Domain Containing 7C	May be a tumor suppressor gene.
ZBTB18	Zinc Finger And BTB Domain Containing 18	Transcriptional repressor that plays a role in various developmental processes such as myogenesis and brain development. Plays a key role in myogenesis by directly repressing the expression of ID2 and ID3, 2 inhibitors of skeletal myogenesis.
ZEB1	Zinc Finger E-Box Binding Homeobox 1	This gene encodes a zinc finger transcription factor. The encoded protein likely plays a role in transcriptional repression of interleukin 2.
ZNF354C	Zinc Finger Protein 354C	May function as a transcription repressor. Suppresses osteogenic effects of RUNX2. Binds to 5-CCACA-3 core sequence. May be involved in osteoblastic differentiation.
ZNF740	Zinc Finger Protein 740	May be involved in transcriptional regulation