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SNPs, transcriptional factor binding sites and disease

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Abstract

Single nucleotide polymorphisms (SNPs) located in non-coding regions of the human genome that have been found to be significantly associated with disease or sickness may affect gene regulation by altering binding sites for transcription factors (TF). There have been several reports to identify such punitive changes in transcriptional factor binding sites (TFBS) created by SNP alleles. A few of these reports have been reviewed for the Activating Transcription Factor 3 (*ATF*3), v-Akt Murine Thymoma Viral Oncogene Homolog 3 (*AKT*3), Adrenergic Beta Receptor Kinase 1 (G Protein-Coupled Receptor Kinase 2) (*ADRBK1*), Type 2 Deiodeinase (*DIO2*), Endothetal Per-Arnt-Sim(PAS)domain protein 1 *(EPAS1)*, Lysosomal Acid Lipase A (*LIPA*), Peroxisome Proliferator-activated Receptors (*PPARα/δ/γ*), Signal Transducer and Activator of Transcription 4 (*STAT4*), Thromboxane A2 Receptor (*TBXA2R*) and Vascular Endothelial Growth Factor (*VEGF)-A* genes. In each report the SNP alleles created punitive alterations in TFBS that could explain associated disease(s) or changes in a human condition.

Introduction

The human genome consists of approximately 2% coding DNA that makes up all of the genes and 98% non-coding DNA which comprises the structural, recombinatorial, origin of replication elements and transcriptional regulatory sequences [1]. Genome-wide association studies (GWAS) indicate that approximately 93% of disease or trait-predisposing single nucleotide polymorphisms (SNPs) believed to be associated with gene regulation fall in these non-coding regions [2-4]. SNPs that have been found to be significantly associated with disease are considered to be risk-associated and cause changes in gene expression [4]. A single nucleotide change in a transcriptional factor motif sequence or a transcriptional factor binding site (TFBS) may affect the process of gene regulation [5-7]. To date, a number of computational approaches and databases have been established to help identify transcriptional factor (TF) motif changes created by SNPs which have been associated with disease or a change in health conditions [8-18]. Of these approaches, there have been several investigations made using the JASPAR CORE [16,17] and ConSite [18] databases to identify alterations in TFBS created by SNPs from a single gene that have been shown to be significantly associated with human disease(s) or illness [19-30]. Using this computational approach has often identified a punitive TFBS created by a causative SNP allele significantly associated with the disease or illness. In an effort to verify which SNP allele is responsible for the significant association, the HaploReg [14] and RegulomeDB [15] databases were screened for the SNP allele substitution and altered TFBS that would most probably affect gene regulation [31]. Some of the research using the JASPAR CORE [16,17] and ConSite [18] databases are reviewed in this manuscript.

Activating Transcription Factor 3 (*ATF*3)

The activating transcription factor 3 (*ATF*3) gene is a member of the activating transcription factor/cAMP responsive element binding (CREB) protein family of transcription factors.This gene located on chromosome one has been shown to be up-regulated during sexual differentiation [32]. The gene has three SNPs (rs3125289 (C/T), rs1877474 (C/T) and rs11119982 (C/T) which span a 16 kb region of intron one have been independently found to be significantly associated with the risk of hypospadias [33]. Hypospadias is a congenital birth defect in which the opening of the urethra is on the underside of the penis instead of the normal position in the head. The rs3125289 *ATF*3-T allele creates the punitive fork head box A2 (FOXA2) and sex determining region Y (SRY) TFBS which are not found with the alternate C allele. Since the SRY TF located on the Y chromosome is a transcriptional regulator that controls a genetic switch in male development, this SNP might be expected to have an impact on male etiology as has been shown to be the case with its risk of hypospadias. The rs1877474 *ATF*3-T allele creates the punitive fork head box A1 (FOXA1) TFBS that does not occur with the alternate C allele. The TF which is involved with embryonic development and tissue differentiation might also have an impact on hypospadias. The rs11119982 *ATF*3-T allele creates the punitive AT rich interactive domain 3A (ARID3A), MYC associated factor X (MAX), v-mybmyeloblastosis viral oncogene homolog (MYB), upstream transcription factor 1 (USF1) and zinc finger E-box binding homeobox 1 (ZEB1) TFBS which do not occur with the alternate C allele. The TFs for these binding sites are involved the transcriptional machinery including transcriptional regulation and suppression [20] which may in part be involved with sexual differentiation and the hypospadias trait.

v-Akt Murine Thymoma Viral Oncogene Homolog 3 (*AKT*3)

The phosphatidylinositol 3-kinase (PI3K)/AKT pathway plays a key role in numerous cellular functions including proliferation, adhesion, migration, invasion, metabolism and survival [34]. The v-akt murine thymoma viral oncogene homolog 3 (*AKT*3) is one of three isoforms of the AKTs which are major downstream targets of growth factor receptor tyrosine kinases that signal through PI3K [35]. There have

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been seven SNPs from *AKT*3 intron one that have been significantly associated with chronic mountain sickness (CMS) [36], aggressive prostate cancer (PCA)[37] and renal cell carcinoma risk (RCC) [38]. The *AKT*3 SNP (rs4590656) (C/T) has been found to be significantly associated with Hb and Hct in Tibetan Chinese with CMS [36]. The *AKT*3-C allele creates two punitive TFBS not found with the alternate T-allele for the aryl hydrocarbon receptor nuclear translocator: aryl hydrocarbon receptor (ARNT:AHR) and hypoxia-inducible factor 1: aryl hydrocarbon receptor nuclear translocator (HIF1*α*:ARNT) TFs which are involved xenobiotic metabolism, cellular and systemic responses to hypoxia.

The *AKT*3 SNPs (rs10157763 (C/T), rs10927067 (G/A) and rs2125230 (G/A) are significantly associated with the risk of PCA[37]. The rs10157763 *AKT*3-C allele creates a TFBS not present with the alternate T-allele for the v-mycmyelocytomatosis viral related oncogene (MYCN) TF which it is a member of the MYC family and is associated with a variety of tumors including neuroblastoma. The rs10157763 *AKT*3-T allele creates a TFBS not present with the alternate C-allele for the CCCTC-binding factor (CTCF) TF which is a transcriptional regulator protein with 11 highly conserved zinc finger (ZF) domains. This gene is a member of the BORIS + CTCF gene family and encodes a transcriptional regulator. This nuclear protein is able to use different combinations of the ZF domains to bind different DNA target sequences and proteins. The TF is implicated in diverse genomic regulatory functions, including transcriptional activation/repression, insulation, imprinting [39]. The rs10927067 *AKT*3-G allele creates a TFBS not found with the alternate A-allele for the v-maf musculoaponeurotic fibrosarcoma oncogene homolog B (MAFB) TF which is important in the regulation of lineage-specific hematopoiesis. The rs10927067 *AKT*3-A allele creates a TFBS not found with the alternate G-allele for the hepatocyte nuclear factor 1 homeobox B (HNF1B) TF which has been shown to function in nephron development. This TF is a member of the homeodomain-containing superfamily of transcription factors and regulates development of the embryonic pancreas. The rs2125230 *AKT*3-A allele creates a TFBS not found with the alternate G-allele for the homeobox A5 (HOXA5) TFs which upregulates the tumor suppressor p53 and plays an important role in tumorigenesis.

The *AKT*3 SNPs (rs4132509 (C/A), rs12031994 (G/A) and rs2345994 (G/A)) are significantly associated with the risk of RCC [38]. The rs4132509 *AKT*3-C allele creates a TFBS not available with the alternate A-allele for the nuclear factor erythroid 2-related factor 1: MAF BZIP Transcription Factor G (NFE2L1:MAFG) TF, where NFE2L1 coordinates the up-regulation of cytoprotective genes via the antioxidant response element while MAFG is involved in cell differentiation of erythrocytes. The rs12031994 *AKT*3-G allele creates a TFBS not available with the alternate A-allele for the TF Forkhead box D1 (FOXD1) which plays a role in tumor formation and should have an effect on RCC. The rs12031994 *AKT*3-A allele creates a TFBS not available with the alternate G-allele for the T-cell acute lymphocytic leukemia 1: GATA binding protein 1 (TAL1: GALA1) TF which is involved with the genesis of hemopoietic malignancies and plays a role in hemopoietic differentiation and a positive regulator of erythroid differentiation. The rs2345994 *AKT*3-G allele creates two TFBS not found with the alternate A-allele for the SRY and SRY (sex determining region Y)-box 10 (SOX10) TFs which are part of a family of TFs involved in the regulation of embryonic development and in the determination of the cell fate. The rs2345994 *AKT*3-A allele creates the punitive Myocyte enhancer factor 2(MEF2A) TFBS not found with the alternate G-allele who's TF it activates many muscle-specific, growth factor-induced and stress-induced genes.

Adrenergic Beta Receptor Kinase 1 (G Protein-Coupled Receptor Kinase 2) (*ADRBK1*)

The *ADRBK1* gene, which transcribes the G protein-coupled receptor kinase 2 (GRK2), is an important regulator of adrenergic signaling and plays a central role in heart failure pathology [40-42]. The GRK2 gene is an important regulator of beta-adrenergic signaling and plays a central role in heart failure (HF) pathology [43-45]. Consequently, the inhibition of GRK2 has become an emerging treatment option of HF since the inhibition appears to be a powerful the rapeutic approach and appears to provide complementation to β-blockade [44]. *ADRBK1* SNPs resulting in TFBS changes have been examined with respect to cardiovascular disease in the black population [21]. The rs1894111 *ADRBK1* SNP from intron one has been found to be significantly associated with blood pressure (BP) levels in a white population [43]. The rs1894111 *ADRBK1*-C allele in blacks creates a TFBS not found with the alternate T-allele for the aryl hydrocarbon receptor nuclear translocator: aryl hydrocarbon receptor (ARNT:AHR)TF which participates in xenobiotic metabolism. The rs1894111 *ADRBK1*-T allele creates three TFBS not found with the alternate C-allele for the E74-like factor 5 (ELF5), v-ets avian erythroblastosis virus E26 oncogene homolog (ERG) and zinc finger protein 354C (ZNF354C) TFs where ELF5 and ERG are members of the erythroblast transformation-specific (ETS) family of transcription factors while Zinc finger protein 354C (ZNF354C) functions as a transcription repressor. The rs7128315 SNP *ADRBK1*-G allele creates TFBS not found with the alternate A-allele for the sterol regulatory element binding transcription factors 1 & 2 (SREBF 1 & 2) TFs which are involved with the cholesterol synthesis pathway and are required for lipid homeostasis and regulate transcription of the LDL receptor gene. The rs948988 SNP *ADRBK1*-A allele creates a TFBS not found with the alternate G-allele for the estrogen receptor 2 (ESR2) TF which is required for normal function of the cardiovascular system.

Type 2 Deiodeinase gene (*DIO2*)

The type 2 deiodeinase gene (*DIO2*) encodes a deiodinase that coverts the thyroid prohormone, thyroxine (T4), to the biologically active triiodothyronine (T3) hormone where T3 is involved in the vital role of regulating energy balance and glucose metabolism [46-49]. DIO2 is found in the thyroid gland, cardiac and skeletal muscle, brown adipose tissue, placenta, pituitary, central nervous system (CNS) and at low levels in kidney and pancreases [50-52]. Several SNPs have been found in the gene which have been studied is association with mental retardation (MR) [53], osteoarthritis [54], early-onset type 2 diabetes mellitus (T2DM) [55] and insulin resistance (IR) [56,57]. *DIO2* SNPs resulted in TFBS changes have been examined with respect to these diseases and human conditions [22]. One of the SNPs, rs225017 (T/A) *DIO2*-T allele creates a punitive TFBS not found with the alternate A-allele for the pancreatic and duodenal homeobox 1 (PDX1) TF which is involved with insulin activation. This SNP has been found to be significantly associated with insulin resistance [56,57] suggesting that the elimination of the PDX1 binding site by the A-allele may result in this human condition. Another *DIO2* SNP rs6574549 (T/G) is associated with fasting insulin, insulin action and energy expenditure in Pima Indians [55]. The rs6574549 SNP *DIO2*-T allele creates a punitive TFBS not found with the alternate G-allele for the hepatocyte nuclear factor 1 homeobox B (HNF1B) TF which is involved with embryonic pancreas development suggesting that the elimination of the HNF1B binding site by the G-allele may be in part responsible for early-onset T2DM [55].

A third DIO2 SNP rs225014 (T/C) has been shown to have a significant association with symptomatic osteoarthritis in Dutch women [54]. The rs225014 SNP *DIO2*-C allele creates a TFBS not found with the alternate T-allele for the NK3 homeobox 2 (NKX3-2) TF which are involved with the negative regulation of the chondrocyte maturation suggesting that the elimination of the NKX3-2 binding site by the T-allele may in part be responsible for the symptomatic osteoarthritis in Dutch women [54].

Endothetal Per-Arnt-Sim (PAS) domain protein 1 *(EPAS1)*

The endothetal Per-Arnt-Sim (PAS) domain protein 1 *(EPAS1)* gene which encodes hypoxia-inducible-factor-2alpha (*HIF2α)* is a transcription factor that is involved in the response to hypoxia. Hypoxia is a major geographical condition associated with high-altitude environments [58]. *EPAS1* is expressed in organs that are involved in oxygen transport and metabolism, such the lung, placenta and vascular endothelium [59], and is associated with many biological processes and diseases related to metabolism [60], angiogenesis [61,62], inflammation [63,64] and cancer [65-67]. *EPAS1* SNPs (rs56721780, rs6756667, rs7589621 and rs1868092) resulted in TFBS changes have been examined with respect to these diseases and human conditions [23]. The rs56721780 (G/C) SNP *HIF2γ*-G allele creates punitive unique TFBS, which not found with the alternate C-allele, for the V-Rel Avian Reticuloendotheliosis Viral Oncogene Homolog (REL), V-Rel Avian Reticuloendotheliosis Viral Oncogene Homolog A (RELA), Runt-Related Transcription Factor 1 (RUNX1), Activating Enhancer Binding Protein 2α (TFAP2A), Activating Enhancer Binding Protein 2β (TFAP2B), Activating Enhancer Binding Protein 2γ (TFAP2C) TFs. These TFs are involved with inflammation, immunity, differentiation, cell growth, tumorigenesis, apoptosis, hematopoiesis, transcriptional activation and repression, respectively [23] and the elimination of these TFBS by the alternate C-allele should have a tremendous impact on gene regulation. As an example, RUNX1 is a heterodimeric transcription factor that binds to the core element of many enhancers and promoters and can either activate or suppress transcription. The rs6756667 (A/G) SNP *HIF2α*-A allele creates two unique punitive TFBS for the Nuclear Factor I/A (NFIA) and Nuclear Factor I/C (NFIC) TFs which are capable of activating transcription and replication [23]. The alternate *HIF2γ* -G allele creates a unique punitive TFBS not found with the A-allele for the MGA, MAX Dimerization Protein (MGA) TF which can act as a repressor or an activator. The rs7589621 (G/A) SNP *HIF2γ*-G allele creates two unique punitive TFBS not found with the alternate A-allele for the Nuclear Receptor Subfamily 3, Group C, Member 1 & 2 (Glucocorticoid Receptor) (NR3C 1 & 2) TFs. These TFs modulate immune responses through suppression of chemokine and cytokine production and protecting cells from oxidative stress and damage as well as mediates aldosterone actions on salt and water balance within target cells [23]. The rs1868092 (A/G) SNP *HIF2α*-A allele creates three unique punitive TFBS not found with the alternate G-allele for the Nuclear Receptor Subfamily 2, Group C, Member 2 (NR2C2), YY1 & 2 TFs which are involved with the repression or activation of transcription, and positive and negative control of transcription at the transcription start site, respectively [23].

Lysosomal Acid Lipase A (*LIPA*)

The lysosomal acid lipase A (*LIPA*) gene encodes lysosomal acid lipase (LAL) which hydrolyzes cholesteryl esters and triglycerides in the cell lysosome to generate free cholesterol and fatty acids [68]. Alterations in the LAL enzyme activity could produce an accumulation of triglycerides and cholesterol esters in the cell which would result in foam cell formation, complement activation, an inflammation process and atherosclerotic plaque formation [69]. Un-esterified cholesterol is a distinguishing characteristic of atherosclerotic lesions [70]. Cholesteryl ester hydrolysis has been shown to be a critical step in the enzymatic modification of low density lipoprotein (LDL) particles in the intima [71,72] where the particles create a risk for cardiovascular disease (CD). The *LIPA* SNPs (rs1412444 and rs2246833) which are in linkage disequilibrium (LD) have been found to be significantly associated with coronary artery disease (CAD) [73,74]. These SNPs were found to create alterations in punitive TFBS and these potential changes were examined with respect to disease [75]. The rs1412444 (C/T) SNP *LIPA*-C allele is located in a unique punitive TFBS not found with the alternate T-allele for the GA binding protein transcription factor (GABPA) TF. This TF is involved in the activation of cytochrome oxidase expression and nuclear control of mitochondrial function. Consequently individuals carrying T allele maybe at risk for mitochondrial related diseases such skeletal muscles, kidney and the endocrine and respiratory systems. In fact, the T allele has been significantly associated with CAD [73,74,76,77] where the T allele frequency was found to change from 0.491 in a control group compared to 0.561 in the CAD group [74].The rs2246833 SNP *LIPA* T allele has also been found to be significantly associated with CAD [73,74] which is not surprising since the two SNPs are strongly linked as indicated by the high LD value ($r^2 = 0.937$).

Peroxisome Proliferator-activated Receptors (*PPARα/δ/γ*)

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 [78-80]. There are three PPAR isotypes, PPARα, PPARβ/δ and PPARγ. *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 [81]. There has been much published concerning the PPARs significant involvement in the progression of human disease [78,80,82-84]. There have been several PPARα/δ/γ SNPs significantly associated with various human diseases or conditions [85-93]. Some of the *PPARα/δ/γ* SNPs were found to create alterations in punitive TFBS and these potential changes were examined with respect to disease [94]. The rs1800206 *PPARα* SNP (C/G) has been associated with variation in lipid serum levels in Caucasian and Indian populations [95,96], hypertriglyceridemia risk, dyslipidemia risk and low-density lipoprotein-cholesterol risk in Han Chinese [86,87,92]. The minor G allele generates a unique punitive T-Box 4 (TBX4) TFBS not found with the common G-allele [94]. The TBX4 transcription factor is associated with the disease heritable pulmonary arterial hypertension [97], 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 occurrence of the G allele in the Han Chinese population is 0.02 [94] which is 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 [95,96,98,99].

The *PPARδ* gene is expressed in high levels in liver, kidneys, cardiac and skeletal muscle, adipose tissue, brain, colon and vasculature [100]. One of its SNPs (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 [85,90,93]. The rs2016520 SNP (A/G) common A-allele creates unique punitive TFBS for the neuronal differentiation 2 (NEUROD2) and oligodendrocyte transcription factor 3 (OLIG3) TFs which do not occur with the minor G-allele [94]. The NEUROD2 TF is a transcriptional regulator implicated in neuronal determination while the OLIG3 TF promotes formation and maturation of oligodendrocytes, especially within the brain. These TFs could in part be associated with obesity risk and intracerebral hemorrhages. The rs9794 SNP (C/G) common C allele creates unique punitive TFBS for glial cells missing homolog 1and 2 (GCM 1 & 2) TFs which bind to the trophoblast specific element 2 (TSE2) of the aromatase gene enhancer and act as a master regulator of parathyroid development. 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 [86,93].

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 [101]. One of its SNPs (rs10865710) has been associated with obesity risk, systemic sclerosis and low-density lipoprotein-cholesterol in Han Chinese [85,89,92]. The rs10865710 SNP (C/G) common C-allele creates a unique punitive TFBS for the POU class 2 homeobox 2 (POU2F2) which does not occur with the minor G-allele [94]. This TF is found in immunoglobulin gene promoters and the absence of this BS with the minor G-allele in part may be responsible for the association of this SNP with systemic sclerosis. In addition, the creation of the motor neuron and pancreas homeobox 1 (MNX1) and regulatory factor X3 (RXF3) TFBS by the common C-allele and not the minor G-allele as well as the creation of the NK6 homeobox 1 (NKX6-1) TFBS with the minor G-allele and not the major C-allele may in part be responsible for association of this SNP with obesity risk and low-density lipoprotein-cholesterol since these TFs are involved with the pancreas development and function as well as insulin gene regulation, respectively [94].

The rs12629751 *PPARγ* SNP (C/T) has been associated with osteoarthritis in southeast Chinese [88]. The common C-allele creates a unique punitive TFBS not found with the minor T-allele for the NK6 Homeobox 1 (NKX3-2) TF which 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 [94].

The rs1805192 *PPARγ* SNP (C/G) has been associated with hypertriglyceridemia, dyslipidemia and low-density lipoprotein-cholesterol in Han Chinese [86,87,92]. The common C allele creates a unique punitive TFBS not found with the minor G-allele for the estrogen receptor α (ERS2) TF which is expressed in many tissues including pulmonary epithelial cells. The minor G-allele creates a unique punitive TFBS not found with the common C-allele for the myocyte enhancer factor 2C (MEF2C) TF which is a transcriptional activator that controls cardiac morphogenesis and myogenesis, and is also involved in vascular development [94]. The occurrence of these punitive unique TFBS for the opposite SNP alleles may in part be responsible for hypertriglyceridemia, dyslipidemia, low-density lipoprotein-cholesterol found in Han Chinese.

Signal Transducer and Activator of Transcription 4 (*STAT4*)

The Janus Kinase-Signal Transducers and Activators of Transcription (JAK-STAT) pathways play a critical role in immune, neuronal, hematopoietic and hepatic systems [102]. JAK-STAT is a principal signal transduction pathway in cytokine and growth factor signaling as well as regulating various cellular processes such as cell proliferation, differentiation migration and survival [103]. JAK-STAT provides the principle intracellular signaling mechanism required for a wide array of cytokines [104,105]. The STAT portion of the signaling cascade has seven mammalian family members which are STAT1, 2, 3, 4, 5a, 5b and 6 [104,105]. These STATs bind thousands of transcriptional factor binding sites (TFBS) in the genome and regulate the transcription of many protein-coding genes, miRNAs and long noncoding RNAs [105]. The *STAT4* gene which is important for signaling by interleukins (IL-12 and IL-23) and type 1 interferons [105] has been found to have several SNPs associated with human disease [106-113]. *STAT4* transduces IL-12, IL-23 and type 1 interferon-mediated signals into helper T (Th) cells (Th1 and Th17) differentiation, monocyte activation, and interferon-gamma production[113,114]. The *STAT4*-dependent cytokine regulation is found in the pathogenesis of autoimmune disease [115,116] such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and inflammatory bowel disease (IBD)[117,118].

Several SNPs in the gene have been significantly association with Behcet's Disease [119], diabetes risk [107], hepatitis B virus-related hepatocellular carcinoma [107,111,120,121], inflammatory bowel disease [122], juvenile idiopathic arthritis [123], primary biliary cirrhosis and Crohn's disease [124], severe renal insufficiency in lupus nephritis [109], systemic lupus erythematosus [106] and ulcerative colitis [125]. Some *STAT4* SNPs were found to create alterations in punitive TFBS and these punitive changes were examined with respect to these disease or conditions [25].

The rs7574865 *STAT4* SNP (G/T) has been found to be significantly associated with diabetes [112], hepatitis B virus-related hepatocellular carcinoma [107,111,120,121], inflammatory bowel disease [122], juvenile idiopathic arthritis [123], primary biliary cirrhosis and Crohn's disease [124], severe renal insufficiency in lupus nephritis [109], systemic lupus erythematosus [106] and ulcerative colitis [125]. The minor T-allele for the SNP creates a unique punitive TFBS not found with the common G-allele for the nuclear receptor subfamily 1, group H, member 3: retinoid X receptor, alpha (NR1HE:RXRα TF which is a key regulator of macrophage function, controlling transcriptional programs involved in lipid homeostasis and inflammation [25]. Since the NR1HE: RXRα protein duplex is part of the NR1 subfamily of the retinoid nuclear receptor superfamily, the presence of its TFBS created by the T allele could in part be responsible for many of the diseases or conditions mentioned above that are significantly associated with this SNP.

The rs11889341 STAT4 SNP has been found to be significantly associated with diabetes [112], hepatitis B virus (HBV) infection, HBV-related cirrgisus and hepatocellular carcinoma [124], severe renal insufficiency in lupus nephritis [109], and systemic lupus erythematosus [106]. The common C-allele of the rs11889341 STAT4 SNP (C/T) creates a unique punitive TFBS not found with the minor T-allele for the androgen receptor (AR) which is a steroid-hormone activated transcription factor that stimulates transcription of androgen responsive genes expressed in bone marrow, mammary gland, prostate,

testicular and muscle tissues [25]. The absence of this TFBS with the minor T-allele should have a major effect relating to the diseases or conditions mentioned above.The T-allele of the SNP creates two unique punitive TFBS not found with the C-allele for the myocyte enhancer factor 2C (MEF2C) TFs which controls cardiac morphogenesis and myogenesis, and is also involved in vascular development and consequently the presence or absence of this TFBS should have an impact on the disease.

The rs8179673 STAT4 SNP has been found to be significantly associated with diabetes [112], hepatitis B virus (HBV) infection, HBV-related cirrgisus and hepatocellular carcinoma [124] and systemic lupus erythematosus [106]. The minor C-allele of the rs8179673 STAT4 SNP (T/C) creates two unique punitive TFBS not found with the common T-allele for the hepatocyte nuclear factor 1 homeobox A (HNF1a) and the hepatocyte nuclear factor 4, gamma (HNF4g) TFs which regulate the tissue specific expression of multiple genes, especially in pancreatic islet cells and in liver [25]. The occurrence of these TFBS with the minor allele and not the major allele could very well explain why the SNP is significantly associated with the above diseases.

The rs7574070 and rs7572482 STAT4 SNPs have been found to be significantly associated with Behcet's disease [119]. The common A-allele of the rs7574070 STAT4 SNP (A/C) creates three unique punitive TFBS not found with the minor C-allele for the CCAAT/enhancer binding protein (C/EBP), beta (CEBPβ), Regulatory Factors 1 & 5 (RFX1 & 5) TFs [25]. The CEBPα-TF is an important transcriptional activator regulating the expression of genes involved in immune and inflammatory responses while the RFX1 & 5 TFs are important regulatory factors essential for MHC class II gene expression and the loss of these BS with the presence of the minor C allele could have an impact on Behcet's disease. The minor C-allele of the SNP STAT4-C allele creates a unique punitive TFBS not found with the A-allele for the STAT4 TF which is an important in regulating genes associated with systemic lupus erythematosus and rheumatoid arthritis and could also have an impact on Behcet's disease.

The common A-allele of the rs7572482 STAT4 SNP (A/G) creates two unique punitive TFBS not found with the minor G-allele for the FBJ Murine Osteosarcoma Viral Oncogene Homolog (FOS) and POU5F1:SOX2 TFs. The FOS TF is a regulator of cell proliferation, differentiation and transformation while the POU Class 5 Homeobox 1: SRY (Sex Determining Region Y)-Box 2 (POU5F1:SOX2) TF play a key role in embryonic development and stem cell pluripotency which both could have an impact on the disease.

Thromboxane A2 Receptor (*TBXA2R*)

The thromboxane A2 receptor (TBXA2R) gene 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 [126]. 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 [127]. 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 [128]. There are TBXA2R SNPs that have been associated with asthma in Asians. The rs4523 TBXA2R SNP has been found to be associated with adult asthma in a Japanese population [129] and childhood atopic asthma in a Chinese population [130], while the rs11318632 SNP was found to be associated with atopic asthma in a Korean population [131]. 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 [132]. This suggests that these SNPs may be part of a regulatory network for the TBXA2R gene in Asian populations. TBXA2R SNPs were found to create alterations in punitive TFBS and these punitive changes were examined with respect to asthma in Asians [133].

The minor G-allele of the rs2238631 TBXA2R SNP (A/G) creates two unique punitive TFBS not found with the common A-allele for the Fork Head box C1 (FOXC1) and APα (TFAP2α) 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 [133]. The minor T-allele of the rs2238632 TBXA2R SNP (C/T) creates five unique punitive TFBS not found with the common C-allele for the aryl hydrocarbon receptor nuclear translocator (ARNT), cAMP responsive element binding protein 1 (CREB1), hypoxia-inducible factor 1:Aryl hydrocarbon receptor nuclear translocator(HIF1α: ARNT), MYC associated factor X (MAX) and upstream transcription factor 1 (USF1) TFs which are involved with xenobiotic metabolism, circadian rhythmicity, cellular and systemic responses to hypoxia, transcriptional regulator and a cellular TF, respectively [133]. The minor C-allele of the rs1131882 TBXA2R SNP (T/C) creates a unique punitive TFBS not found with the common T-allele for the insulinoma-associated 1 (INSM1) TF which is a sensitive marker for neuroendocrine differentiation of human lung tumors [133]. The major T-allele of the rs4523 TBXA2R SNP (T/C) creates a unique punitive TFBS not found with the C-allele for the Krueppel-like factor 4 (KLF4) TF which acts as an activator, a repressor and regulates the expression of key TFs during embryonic development. The minor C-allele of the SNP creates a unique punitive TFBS not found with the major T-allele for the nuclear receptor subfamily 3, group C, member 1 (NR3C1) TF which is involved in inflammatory responses, cellular proliferation, and differentiation in target tissues [133].

Vascular Endothelial Growth Factor (*VEGF*)-A

The vascular endothelial growth factor (VEGF) is a family of key regulators in critical physiological and pathological angiogenesis [134] including tissue growth, wound healing, rheumatoid arthritis, proliferative retinopathies, cardiovascular disease, and cancer [135], and is a growth factor activator for angiogenesis, vasculogenesis, and endothelial cell growth. In most [136-141] but not all [142] studies, It has been shown that the VEGF is an important component of the pathogenesis of high altitude adaptation and sickness. Presently, seven VEGF family members and 14 alternative splicing variants have been identified in humans [143-145]. Of the 14 splicing variants, 12 are VEGFA isoforms [145] with three (VEGFA-121, -165 and -189) being differentially expressed in humans visiting or living in high altitude environments and also in chronic mountain sickness (CMS) patients [137,138]. Among all family members, VEGFA is the most potent and best-known angiogenic protein and exerts its' biologic effect through interaction with cell-surface receptors, which triggers a cascade of downstream dimerizations and phosphorylations [146]. VEGFA is a signaling protein involved in the regulation of angiogenesis, vasculogenesis and endothelial cell growth. It induces endothelial cell proliferation, promotes cell migration, inhibits apoptosis and induces

permeabilization of blood vessels.VEGFA is also a key regulator of hypoxia.There are several VEGFA SNPs associated with high altitude sickness that create alterations in punitive TFBS for the gene [26-28,147-149].

The major C-allele of the rs699947 VEGFA SNP (C/A) creates a unique punitive TFBS not found with the minor A-allele for the hypoxia-inducible factor 1α:aryl hydrocarbon receptor nuclear translocator (HIF1β:ARNT) which plays an essential role in cellular and systemic responses to hypoxia and is detrimental to the individual's ability to respond to hypoxia. The minor T-allele of the rs79469752 VEGFA SNP (C/T) creates two unique punitive TFBS not found with the common C-allele for the Nuclear Receptor subfamily 2, group C, member 2 (NR2C2) and Runt-related transcription factor 1 (RUNX1) TFs which plays a role in protecting cells from oxidative stress and damage induced by ionizing radiation as well as the involvement in the development of normal hematopoiesis, respectively. The major C-allele of the rs2010963 VEGFA SNP (C/G) creates a unique punitive TFBS not found with the minor G-allele for the GA-binding protein γ chain (GABPα TF which is likely involved in the activation of cytochrome oxidase expression and nuclear control of mitochondrial function. The major C-allele of the rs3025039 VEGFA SNP (C/T) creates two unique punitive TFBS not found with the minor T-allele for the estrogen receptor α (ESR2) and the HIF1β:ARNT TFs where ESR2 is expressed by many tissues including blood monocytes and tissue macrophages, colonic and pulmonary epithelia cells while the function of the HIF1a:ARNT TF is mentioned above.

The rs3025039 VEGFA SNP also affects the has-miR-591 predicted binding target CA[C/T]GGTC in the 3'UTR, where a VEGFA-C allele would eliminate the binding site for the miRNA. These VEGFA SNPs cause alterations in punitive TFBS for the gene and should have an effect on high altitude sickness among humans.

Conclusion

Non-coding SNPs identified by GWAS that have shown to be been significantly associated with human disease or sickness are considered risk-associated SNPs [4]. Those near a gene causing changes in gene expression levels are considered regulatory (r) SNPs [150]. Such SNPs located in TFBS can alter the binding ability of the respective TF. 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 [19-30]. In this review a number of examples from previously reports were discussed with an emphasis on the more important dynamics from the reports.

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