SNPs in Sites for DNA Methylation, Transcription Factor Binding, and miRNA Targets Leading to Allele-Specific Gene Expression and Contributing to Complex Disease Risk: A Systematic Review

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Keywords

Complex disease · Single nucleotide polymorphisms · microRNAs · Transcription factors · DNA methylation · Allele-specific gene expression

Abstract

Introduction: The complex genetic diversity among human populations results from an assortment of factors acting at various sequential levels, including mutations, population migrations, genetic drift, and selection. Although there are a plethora of DNA sequence variations identified through genome-wide association studies (GWAS), the challenge remains to explain the mechanisms underlying interindividual phenotypic disparity accounting for disease susceptibility. Single nucleotide polymorphisms (SNPs) present in the sites for DNA methylation, transcription factor (TF) binding, or miRNA targets can alter the gene expression. The systematic review aimed to evaluate the complex crosstalk among SNPs, miRNAs, DNA methylation, and TFs for complex multifactorial disease risk. **Methods:** PubMed and Scopus databases were used from inception until May 15, 2019. Initially, screening of articles involved studies assessing the interaction of SNPs with TFs, DNA methylation, or miRNAs resulting in allele-specific gene expression in complex multifactorial diseases. We also included the studies which provided ex-

perimental validation of the interaction of SNPs with each of these factors. The results from various studies on multifactorial diseases were assessed. **Results:** A total of 11 articles for SNPs interacting with DNA methylation, 30 articles for SNPs interacting with TFs, and 11 articles for SNPs in miRNA binding sites were selected. The interactions of SNPs with epigenetic factors were found to be implicated in different types of cancers, autoimmune diseases, cardiovascular diseases, diabetes, and asthma. **Conclusion:** The systematic review provides evidence for the interplay between genetic and epigenetic risk factors through allele-specific gene expression in various complex multifactorial diseases.

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Introduction

The phenotypic variability at the population and individual levels is largely dictated by genetic variations. The study of genetic variations using genome-wide association studies (GWAS) has generated a large amount of data to enable a better understanding of the existing interindividual phenotypic variability. However, the majority of these variations failed to obtain clinical translation with few exceptions, such as exfoliation glaucoma, age-related macular degeneration, and T1DM [1]. Most

Fig. 1. Interaction of SNPs with TFs, DNA methylation, and miRNA resulting in ASGE. ASGE, allele-specific gene expression; SNPs, single nucleotide polymorphisms; TFs, transcription factors.

frequently, the failure has been attributed to missing heritability and the modest contribution of identified variations in the susceptibility to complex traits [2]. Another possible explanation is that many of the genetic variations, that is, single nucleotide polymorphisms (SNPs), exhibit their effects by interaction with other factors or epigenetic mechanisms, which include DNA methylation, transcription factors (TFs), and miRNAs (Fig. 1). The interaction of SNPs with these epigenetic factors results in the preferential expression of 1 allele, thereby leading to an allele-specific gene expression (ASGE) (Fig. 1). ASGE is a phenomenon by which the product of a gene is exclusively or dominantly transcribed from either of the 2 alleles [3]. The ASGE is a characteristic feature of eukaryotes with diploid genomes, where each gene has 2 copies, one inherited from each parent [3]. There has been an earlier assumption that each allele is expressed alike, thus called bi-allelic expression; however, with studies, many exceptions have come to light [4]. Among them, X chromosome inactivation (XCI) is the best studied example where transcriptional silencing of 1 X chromosome in female cells leads to dosage compensation [5]. The unique feature of XCI is that the allele-spe-

cific expression (ASE) is chromosome-wide instead of gene specific [5]. The other well-studied example for ASGE is genomic imprinting, which is a phenomenon by which the genes that are expressed in a cell, tissue, or organism follow a parent-of-origin pattern [6]. Genomic imprinting has been observed in human diseases, namely, Prader-Willi syndrome, Angelman syndrome, and male infertility [7–9]. With the advent of sequencing technologies, the understanding of XCI and genomic imprinting has improved [10]. Presently, the ability to quantify the expression of the 2 alleles using RNA sequencing or probe-based methods has led to the observation that the 2 alleles of the same gene exhibit variation in expression output [11].

The phenomenon of ASGE has been attributed to both genetic and epigenetic variations [12, 13]. The idea that ASGE is heritable and may be implicated in multifactorial human diseases comes from the underlying genetic and epigenetic factors [12, 13]. The most widely studied genetic variation, which is implicated in interindividual differences, human diseases, and drug response, is SNP [14]. The majority of research was focused on deciphering the functions of SNPs in functional and protein-coding re-

regions of the genome [12]. GWAS were performed to reveal the interindividual differences in the risk of complex diseases [15]. However, with the advances in the field of epigenetics, the interaction of these SNPs in noncoding regions of the genome with different epigenetic factors such as DNA methylation, miRNAs, and TFs was shown to have a profound impact on phenotypic variations, human diseases, and drug response [16]. According to the present hypothesis, the individual is susceptible to a complex multifactorial disease because of the interaction of genetic variants with environmental factors acting through epigenetic mechanisms. Thus, a proper understanding of the interaction of genetic and epigenetic variations is necessary for unraveling the etiology of common diseases. In the present study, we conducted a systematic review to evaluate the interaction among SNPs, DNA methylation, TFs, and miRNAs for multifactorial disease risk.

Methods

Literature Search

A systematic review using PubMed and Scopus databases was performed to select articles highlighting the complex interaction of SNPs with DNA methylation, miRNA, or TFs to result in ASGE in complex multifactorial diseases. The keywords, namely, SNPs, DNA methylation, miRNA, TFs, and ASGE, were used for searching the articles in different combinations. The articles published up to May 2019 were included in the study. The articles were assessed for relevance, and duplicates were removed. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (<http://prismastatement.org/>) were followed for conducting the systematic review (see online suppl. Table 1; see www.karger.com/doi/10.1159/000510253 for all online suppl. material).

Inclusion and Exclusion Criteria

The eligibility criteria for including the studies were (a) the study should address the role of the interaction of SNPs with any of the 3 factors, viz., DNA methylation, miRNA, or TFs, to produce ASE; (b) the study must be conducted on human samples, or cells established or derived from humans; (c) it should address the role of SNPs in a multifactorial complex human disease; and (d) the interaction of SNPs with epigenetic factors must be functionally validated. The article search was constrained to the English language. We excluded studies that are focused on rare genetic disorders. The studies which used nonhuman samples for functional characterization or performed only in silico analysis were also excluded from the review. The selected studies were referred for deriving information on identified SNPs, which result in ASGE through DNA methylation, miRNA, or TFs in complex multifactorial human diseases.

Data Extraction and Presentation

Data extraction was performed in a structured manner by 2 investigators using data collection forms independently, and the

duplicates were removed in the end. The studies presented here followed the candidate gene approach. The PRISMA flow diagram is prepared and presented in the results. The extracted data are also presented in the form of concise tables comprising details regarding the studies selected for the present systematic review. The data were classified into 3 parts: (a) SNPs which affect the binding of TFs and lead to ASGE, (b) SNPs which affect DNA methylation to cause ASGE, and (c) SNPs which affect miRNA binding to cause ASGE.

Results and Discussion

We identified 5,569 and 6,941 entries from PubMed and Scopus sources, respectively, for SNPs interacting with TFs to confer ASGE. For SNPs interacting with DNA methylation, we identified 533 and 9,862 entries from PubMed and Scopus sources, respectively. Similarly, 785 and 705 entries from PubMed and Scopus sources were identified for SNPs, which affect miRNA binding to cause ASGE. After removing duplicates, title, and abstract screening and evaluating the full text in a sequential order, we selected 30 articles for SNPs interacting with TFs, 11 articles for SNPs interacting with DNA methylation, and 11 articles for SNPs in miRNA binding sites (Fig. 2).

SNPs in TF Binding Sites Can Cause ASGE

The binding of TFs is pivotal for the initiation of the transcription process. SNPs in TF binding sites or motifs can affect the gene regulation process. There are reports of SNPs in TF binding sites in various diseases, such as autoimmune diseases, cancers, cardiovascular diseases (CVDs), and diabetes [17–20].

Disease-Associated with the Immune System

Asthma is a complex multifactorial disease triggered either by an allergen or sometimes by an autoimmune response [17]. The *PHF11* gene was identified as a determinant of serum IgE levels through the positional cloning of human chromosome 13q14 [21]. Holt et al. [22] showed that the A-allele of rs1046295 has a higher affinity for TF Oct-1 than the G-allele. The TF Oct-1 is expressed ubiquitously and is involved in both negative and positive regulation of transcription based on the binding site on DNA [23, 24]. Reports on rs1046295 highlight the association of the G-allele with asthma and IgE levels [21, 25]. The interaction of rs1046295 with Oct-1 assigns a regulatory role to the variant in transcription modulation and asthma susceptibility [22]. Furthermore, 2 polymorphisms, namely, rs4065275 and rs8076131, in the *ORMDL3* gene were also found to be associated with asthma susceptibil-

Fig. 2. PRISMA plot for selection of articles. SNPs, single nucleotide polymorphisms; TF, transcription factor; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

ity [26]. *ORMDL3* regulates calcium homeostasis and, in turn, mediates T-cell responses such as Th2 cytokine production [27–30]. The *ORMDL3* gene has an important role in the immune response. The presence of risk alleles for rs4065275 and rs8076131 in the gene's regulatory region alters the binding ability of TFs of the SP family and USF1/USF2 complex, respectively [26]. Alternately, the presence of non-risk alleles promotes the binding of SPs and converts USF1/USF2 into a repressor, leading to the lowering of the *ORMDL3* gene and, subsequently, the immune response [26].

The variant rs2240032 in the *RAD50* gene is linked to atopic disease [31]. The introns of the *RAD50* gene are known to harbor *cis*-regulatory elements for cytokine genes [32]. The variant rs2240032 is present in the *RHS7* gene, which is essential for the T-cell differentiation [33]. Kretschmer et al. [31] showed that rs2240032 modifies the binding of SMAD3 TF. SMAD TFs are well characterized in transforming growth factor- β pathways and play an essential role in T-cell growth, function, and differentiation [34]. The causative variant rs2240032 that modifies the SMAD3 binding can regulate the expression of Th2 cytokine genes and skew the immune response. Another variant rs612529 in the *VSTM1* gene has been

shown to alter the binding of PU.1/YY1 in an allele-specific manner [35]. In monocytes, the expression of the *VSTM1* gene is controlled by rs612529, and the presence of C-allele decreases the expression of the gene [35]. The *VSTM1* gene inhibits monocyte-derived pro-inflammatory reactions and ROS production. Kumar et al. [35] showed that ROS production through the *VSTM1* gene depends on the rs612529 genotype and is also involved in skin homeostasis.

In autoimmune diseases, the differential binding of TFs to candidate SNPs has been indicated as an essential mechanism for gene-to-protein expression [36]. Butter et al. [36] used proteome-wide analysis of the SNPs approach and identified the SNPs in the *IL2RA* gene, namely, rs12722508, rs12722522, rs41295061, and rs2104286, to alter the binding of RUNX1, LEF1, CREB, and TFAP4 TFs. However, only rs12722508 was validated for allele-specific binding of RUNX1 TF using a reporter assay [36]. Butter et al. [36] suggested that many SNPs in a haplotype may have a cumulative effect on the expression of the gene by the binding of different TFs. In another study, the functional role of rs4794067 in the *TBX21* gene is mediated by the binding of YY1 TF, leading to the suppression of the promoter activity [37]. The wild-type T-allele for

rs4794067 was linked to the risk of systemic lupus erythematosus and protection against HBV infection [37]. The T- and C-alleles of rs4794067 were also evaluated for the effects on human CD4+ T-cell differentiation. In individuals with the T-allele, the T-bet levels were significantly elevated in comparison with the C-allele [37]. T-bet is known to control the IFN- γ production and influence the IL-4 levels [38]. Thus, different alleles in the TBX21 gene are speculated in variable Th1/Th2 outcomes [37].

In multiple sclerosis, the *CD58* gene variant has been shown to induce higher CD58 mRNA levels and protection from the disease [39]. *CD58* stimulates the regulatory T cells by binding to the CD2 receptor, which is essential for suppressing autoimmune responses in specific tissues [40]. The C-allele of rs1335532 creates an enhancer-binding site for Ascl2, which increases the promoter activity of the gene [40]. The increased activity of *CD58* is biologically relevant in monocytes as they are attracted to multiple sclerosis lesions [41]. In osteoarthritis, the 5'-UTR methylation and rs143383 on the *GDF5* gene were shown to have a combined effect on DEAF1, SP1, and SP3 binding in an allele-specific manner [42]. *GDF5* is a signaling molecule for skeletal development. The presence of methylation in the 5'-UTR region of the *GDF5* gene and T-allele of rs143383 represses the gene expression due to the binding of SP1, SP3, and DEAF1 [42]. The expression's shift is toward the C-allele of rs143383, which was observed in the joint tissue [42]. The *SOST* gene is a regulator of osteoblastic bone formation. Ye et al. [43] showed that SNPs in the *SOST* gene interact with TFs and miRNA and have possible implications on osteoporosis. Among TFs, FOXA1, MAFF and MAFK, and CTCF binding were observed on rs1230399, rs7220711, and rs1107748 alleles, respectively [43]. The polymorphism rs1230399 influences the binding of FOXA1. The differential FOXA1 binding is implicated in estrogen-induced carcinomas and is important for estrogen receptor-chromatin interactions [44]. FOXA1 is critical for the androgen receptor and estrogen receptor- α [45]. Many studies have shown that testosterone increases and estrogen suppresses the *SOST* production. The differential binding of estrogen-linked FOXA1 on rs1230399 may be the reason for the altered *SOST* levels [43]. The polymorphism rs7220711 lies in the enhancer histone marks and is present in the binding site for Maf TFs MAFF and MAFK, whereas rs1107748 affects the binding of the CTCF-binding element to bring about allele-specific transcription activity in osteoblast cells [43]. The impact of SNP in the *SOST* gene on miRNA is discussed in the later section. Another SNP, rs6426749 present at 1p36.12, has been

linked to osteoporosis [46]. Chen et al. [46] showed that the lncRNA, namely, LINC00339 expression, is regulated by long-range chromatin loop formation mediated by the binding of TFAP2A TF at the rs6426749 G-allele. The LINC00339, in turn, regulates CDC42 expression, which is essential in bone metabolism in osteoblast cells [46].

Cancer

The impact of SNPs leading to allele-specific binding of TFs has been studied in different types of cancers. In breast cancer, polymorphism in the promoter region of the *ER β* gene has been shown to modulate the binding of YY1 TF [18]. *ER β* plays a vital role in suppressing breast cancer as it is known to regulate *ER α* activity [47, 48] negatively. The expression of the *ER β* gene declines during the progression of breast cancer [49]. Chen et al. [18] showed that the rs1271572 polymorphism present in the *ER β* gene is associated with decreased gene expression. It was also shown that the T-allele for rs1271572 disrupts the binding site for YY1 TF and leads to a reduction in the *ER β* promoter activity [18]. Another gene *ODC* is known to be involved in polyamine synthesis, which is essential for the development and tissue repair process in mammals [50]. Abnormalities in polyamine metabolism have the potential to promote tumorigenesis [51]. Zell et al. [52] showed that +316 *ODC1* SNP is linked to survival in colorectal cancer individuals. They further showed that E-box TFs bind at the SNP site and are associated with allele-specific transcription activity [52]. The A-allele in the reporter elements is associated with higher effects of the activator c-MYC and the repressor MAD1 than the G-allele [52]. A polymorphism rs6983267 at the 8q24.21 locus is a significant cancer-associated SNP and related to colorectal cancer [53, 54]. Studies have highlighted that the risk allele-G of rs6983267 possess a binding site for TF, namely, TCF4/LEF1, which further leads to the increased transcription of *MYC* [55, 56]. In colorectal cancer, *MYC* overexpression contributes to the development and progression of colorectal cancer [57]. Moreover, the risk allele-G of rs6983267 is frequently observed in the cancer cells [58]. Sugimachi et al. [59] showed that the development of colorectal cancer requires activation of *MYC* through the retention of the G-allele of rs6983267.

Allele-specific binding of TFs was observed in Ewing sarcoma, a pediatric malignancy arising from neural crest- or mesoderm-derived stem cells [60, 61]. The sarcoma is caused by the fusion of *EWSR1* and genes in the *ETS* family [62, 63]. The fusion results in the formation of an oncogenic TF, which binds to GGAA motifs [62, 64, 65]. The *EGR2* gene expression is increased in Ewing sar-

coma and associated with variations in the gene [66]. Grünewald et al. [67] showed that the risk allele-A of rs79965208 in the *EGR2* gene is linked to adjacent GGAA repeats as it converts a GGAT motif into a GGAA motif. This leads to an increase in EWSR1-FLI1-dependent enhancer activity and increases *EGR2* expression in Ewing sarcomagenesis [67].

Gastric cancer is another multifactorial type of cancer influenced by factors such as tobacco addiction, *Helicobacter pylori* infection, genetic polymorphisms, and exposure to carcinogens [68–70]. The progression of cancer occurs through the remodeling of the extracellular matrix, which is modulated mainly by matrix metalloproteinases (MMPs) [71, 72]. *MMP7* is a matrilysin that degrades gelatin, elastin, type IV collagen, vitronectin, fibronectin, laminin, aggrecan, entactin, and proteoglycans [73, 74]. The *MMP7* gene is mainly expressed in tumor tissues [75, 76] and is involved in tumor progression by inhibiting apoptosis, inducing angiogenesis, and reducing cell adhesion [77]. Kesh et al. [78] showed that rs11568818 (–181A→G) in the *MMP7* gene is associated with gastric cancer in the Indian population and the enhanced promoter activity of the G-allele is due to the creation of a binding site for cyclic AMP-response element domain (CREB). They showed that nicotine intake increased the phosphorylation of CRE, and the increased expression of *MMP7* is due to the allele-specific binding of pCREB on the *MMP7* promoter [78].

Meyer et al. [79] identified a transcriptional regulator element associated with *PVT1* gene expression at the 8q24 locus. They found an SNP, namely, rs378854, present in the DNase I hypersensitive sites, to be a functional variant for prostate cancer [79]. It was observed that YY1 TF binds to the G-allele of rs378854 and prevents the formation of the DNase I hypersensitive site [79]. The repressor YY1 protein was proposed as a mediator for protection against cancer susceptibility [79]. In another study, Huang et al. [80] showed that the T-allele of rs339331 is involved in the enhanced binding of HOXB13 TF and can upregulate the *RFX6* gene. This was in concordance with the observed expression of the *RFX6* gene associated with the T-allele in prostate tumors [80]. *RFX6* is involved in the cellular transformation in prostate cancer [80]. *RFX6* expression correlates with the severity and progression of prostate cancer [80]. Gao et al. [81] also worked on prostate cancer to identify a regulatory role of rs11672691 in disease progression. It was known that rs11672691 results in fatal prostate cancer. Gao et al. [81] showed the presence of rs11672691 in the enhancer element for *HOXA2*, which further drives *PCAT19* and

CEACAM21 gene expression. The *CEACAM21* encodes for a transmembrane protein that belongs to the carcino-embryonic antigen family and is involved in cell invasion, adhesion, and metastasis [82, 83]. The expression of lncRNA *PCAT19* was found to be high in malignant prostate tumors [81]. The G-allele of rs11672691 was shown to enhance the chromatin binding of *HOXA2* [81]. This led to elevated expression of *PCAT19* and *CEACAM21* [81]. These results provide plausible targets for tailoring therapy and may help in differentiating high-risk group individuals as well.

Cardiovascular Disease

The concept of allele-specific binding of TFs has been tested for genes involved in CVD risk. The *PEAR1* gene codes for the platelet-endothelial aggregation receptor 1 protein which is highly expressed in endothelial cells and platelets [84]. The expression of the *PEAR1* gene was associated with rs12041331, a noncoding SNP in platelets [85]. The minor allele-A of rs12041331 attributed to the risk of CVD events [86]. Izzi et al. [19] showed that the rs12041331 G-allele marks the methylation at a CpG island upstream of *PEAR1*, which leads to the lower affinity of CTCF protein. This further increases the region's enhancer activity harboring rs12041331 and leads to higher gene expression [19]. In the presence of the risk A-allele, the methylation is less, and the CTCF protein binds at the CpG island, and enhancer activity of the site is diminished [19]. *GRK2* gene expression has been linked to heart failure, decreased adrenergic signaling, and myocardial contractility [87]. Klenke et al. [88] studied the impact of early growth response 1 (EGR-1) TF, which is involved in cardiovascular pathobiology [89] on *GRK2* gene expression. They showed that the promoter region of the *GRK2* gene harbors a binding site for EGR-1 TF [88]. They also showed that the polymorphism rs182084609 is present in the binding site and EGR-1 preferentially binds to the G-allele of rs182084609 [88]. Klenke et al. [88] proposed the inhibition of EGR-1 binding to *GRK2* may be useful for adrenergic desensitization.

In the case of hypertension, one of the most widely studied genes is *AGT*, which codes for angiotensinogen involved in the renin-angiotensin system [90]. SNPs in the *AGT* promoter region are implicated in high blood pressure [91]. Park et al. [90] studied the role of rs5050 in the *AGT* promoter region and showed that the SNP is present in the E-box sequence which harbors the binding site for USF1 and USF2. However, it was observed that only the C-allele and not A-allele of rs5050 has a higher affinity for USF1 and USF2 TFs [90]. This provided the

link between the ASE of the *AGT* gene and USF1 and USF2 TFs [90]. Another variant in the *ARHGAP42* gene was linked to blood pressure [92]. The *ARHGAP42* gene encodes for Rho-specific GTPase-activating protein which controls muscle contractility in smooth muscle cells [93]. Bai et al. [94] showed that the T-allele of rs604723 present in the intron regulatory element promotes serum response factor binding, which results in the increased expression of *ARHGAP42*. This provides evidence for the effect of the noncoding variant in the risk of CVDs which might be used for individualizing therapy.

Ischemia is known to induce the accumulation of triacylglycerol in the myocardium [95]. The *MTTP* gene expression is linked to the concentration of triacylglycerol in the myocardium [95]. *MTTP* codes for the microsomal triglyceride transfer protein, which is important for the formation of apolipoprotein B [96]. Aminoff et al. [97] showed that the rs1800804 T-allele in the promoter region has a strong affinity for C/EBP TF binding. The C-allele lowers the transcriptional activity and increases susceptibility to ischemic heart disease [97]. They proposed that a decrease in *MTTP* expression results in higher accumulation of lipids, and thus, use of inhibitors for *MTTP* can increase long-term side effects [97].

Vascular remodeling is the structural rearrangement of blood vessels' walls in response to repair and inflammation [98]. Vascular remodeling is the hallmark for pulmonary arterial hypertension, atherosclerosis, and scleroderma [98]. The *NKX2-5* gene involved in the development of blood vessels during embryogenesis [99, 100] was also observed in the vessels undergoing remodeling [101, 102]. Dritsoula et al. [98] showed that the rs3095870 C-allele in the *NKX2-5* gene results in allele-specific binding of TEAD1 and YAP1. This leads to transcriptional activation and increases in *NKX2* gene expression, which is further associated with features of vascular remodeling [101, 102].

Diabetes Mellitus

Diabetes is a multifactorial condition in humans, which has been linked to several SNPs [103]. The functional impact of many of these SNPs is still unknown. Hiramoto et al. [20] studied the role of rs2074196 in the *KCNQ1* gene associated with diabetes and showed that the risk allele for the polymorphism has an allele-specific preference for nuclear transcription factor-Y. SNPs in the *TNF- α* gene have also been associated with diabetes [104]. Susa et al. [105] showed the IVS1G + 123A polymorphism present in the promoter region aids the recruitment of YY1 and acts to enhance the transcription. This suggested the role of IVS1G + 123A polymorphism

as a *cis*-element in increasing the risk of diabetes [105]. In the islet donors of heterozygous rs3783355 (G/A), an intronic enhancer in the *MEG3* gene showed allelic specificity for TFs PDX1, FOXA2, and NKX2.2 [106]. The *DLK1-MEG3* locus is dysregulated in the islets of diabetes individuals [107]. The suppression of *MEG3* increases the susceptibility of β -cells toward cytokines [106]. The region harboring the variant in the *DLK1-MEG3* locus was shown to act as a novel regulatory region in human cells [106].

Other Diseases

There are examples of allele-specific binding of TFs in Parkinson's disease and chronic fatigue syndrome. Parkinson's disease is a common neurodegenerative disorder that results from the complex multifactorial interaction of environmental and genetic risk factors. The *SNCA* gene was identified as a strong risk locus in association with Parkinson's disease [108]. Soldner et al. [109] showed rs356168 in the *SNCA* gene results in allele-specific changes in TF binding sites of *EMX2* and *NKX6-1* in Parkinson's disease. Functional polymorphisms have been identified in the serotonin receptor 2A (*HTR2A*) gene in association with chronic fatigue syndrome [110]. Falkenberg et al. [111] showed that rs6311 in the *HTR2A* gene could disturb both DNA methylation and TF binding (Table 1).

SNPs Affect DNA Methylation Levels, Resulting in ASGE

DNA methylation in humans occurs predominantly at CpG sites in the genome and is associated with transcriptional silencing of genes across the genomes. The role of DNA methylation in the etiology of various diseases, namely, cancer, CVDs, type 2 diabetes, and asthma, has been acknowledged [19, 111–119]. However, the SNPs nearby or in CpG sites can either create or abolish CpG site methylation, leading to an alteration in the expression of the genes. Moreover, it has also been shown that changes in methylation of one CpG site can influence the methylation levels of flanking CpG sites. In the literature, there are some examples where SNPs in the methylation sites affect the methylation levels and result in differential allelic expression.

A polymorphism rs2240032 in the *RAD50* gene on chromosome 5q31 previously associated with asthma affects methylation of the downstream located *IL13* promoter region [119]. Schieck et al. [119] showed that locus can influence DNA methylation and has an impact on IgE levels in children.

Table 1. Interactions between SNPs and epigenetic variations in multifactorial diseases or traits

S. No	Complex traits or diseases	Loci	SNPs	TFs	DNA methylation	miRNA	Inference	Ref.
<i>Diseases associated with the immune system</i>								
1	Asthma	<i>PHF11</i>	rs1046295	Oct-1	-	-	rs1046295 acts as a regulatory variant, alters asthma susceptibility	Holt et al. [22]
		<i>ORMDL3</i>	rs8076131 and rs4065275	SP-1, SP-3, SP-4, USF-1, and USF-2	-	-	Polymorphisms rs8076131 and rs4065275 were identified to drive difference in TF binding	Schedel et al. [26]
		<i>IL-13</i>	rs2240032	-	Promoter	-	Polymorphism rs2240032 in the RHS7 region results in allele-specific TF binding, affects methylation of the IL-13 promoter region	Schieck et al. [119]
2	Atopy	<i>RAD50</i>	rs2240032	SMAD3 and SP1	-	-	rs2240032 impacts transcriptional activity and allele-specific binding of SMAD3, SP1, and additional putative protein complex partners	Kretschmer et al. [31]
3	Atopic dermatitis	<i>VSTM1</i>	rs612529	YY1 and PU.1	-	-	In monocytes, the T-allele of this SNP facilitates binding of the TFs YY1 and PU.1	Kumar et al. [35]
4	Autoimmune disease	<i>IL2RA</i>	rs12722508, rs12722522, rs41295061, and rs2104286	RUNX1, LEF1, CREB, and TFAP4	-	-	Differential, allele-specific binding of the TFs RUNX1, LEF1, CREB, and TFAP4 is due to rs12722508, rs12722522, rs41295061, and rs2104286 in IL2RA.	Butter et al. [36]
5	Autoimmune, infectious, and allergic diseases	<i>TBX21</i>	rs4794067	YY1	-	-	TBX21 T-1993C polymorphism represses TBX21 expression and Th1 cytokine production through control of YY1	Li et al. [37]
6	Multiple sclerosis	<i>CD58</i>	rs1335532	ASCL-2	-	-	The presence of the minor (c) allelic variant of SNP rs1335532 enhances CD58 production in B cells	Mitkin et al. [40]
7	Multidrug resistance and immunological diseases	<i>TAP2</i>	rs241456	-	-	hsa-miR-1270	hsa-miR-1270 binds to the T-allele of rs241456 in an allele-specific manner	Knox et al. [131]
8	Osteoarthritis	<i>GDF5</i>	rs144383	SP1, SP3, and DEAF1	-	-	rs143383 exerts a joint-wide effect on GDF5 expression, with expression of the OA-associated T-allele being significantly reduced relative to the C-allele	Reynard et al. [42]
9	Osteoporosis	<i>SOST</i>	rs1230399, rs7220711, rs1107748, and rs75901553	FOXA-1 MAFF, MAFK, and CTCF	-	miR-98-5p	The study established the roles for FOXA1, CTCF, small MAFs, and miR-98-5p in SOST expression regulation through an allele-specific interaction with SNPs rs1230399, rs7220711, rs1107748, and rs75901553, respectively	Ye et al. [43]
		<i>Ip36.12</i>	rs6426749	TFAP2A	-	-	rs6426749-G allele binds to TF TFAP2A and increases LINC00339 expression	Chen et al. [46]
<i>Cancer</i>								
10	Breast cancer	<i>Erβ</i>	rs1271572	YY1	-	-	TT genotype of rs1271572 results in loss of the YY1 binding site and reduces the transcription activity of the promoter in the ERβ gene	Chen et al. [18]
		<i>BMPRIIB</i>	rs1434536	-	-	miR-125b	Allele-specific regulation of <i>BMPRIIB</i> by miR-125b through rs1434536	Saetrom et al. [122]
11	Colon cancer	<i>ODCI</i>	rs2302615	c-MYC and MAD1	-	-	In colon cancer cells, the <i>ODCI</i> SNP, flanked by 2 E-boxes, directs the <i>ODCI</i> promoter activity	Zell et al. [52]
12	Colorectal cancer	<i>MYC</i>	rs6983267	TCF4/LEF1	-	-	The development of CRC requires MYC activation through retention of the risk allele of rs6983267	Sugimachi et al. [59]
		<i>MGMT</i>	rs16906252	-	Promoter methylation	-	The presence of the T-allele of the linked C/T germline SNP within the transcriptional enhancer element of <i>MGMT</i> plays a key predictor of <i>MGMT</i> promoter methylation in colorectal cancer	Hawkins et al. [112]

Table 1 (continued)

S. No	Complex traits or diseases	Loci	SNPs	TFs	DNA methylation	miRNA	Inference	Ref.
13	Ewing sarcoma	<i>EGR2</i>	rs79965208	EWSR1-FLI1	-	-	EWSR1-FLI1 preferentially binds to the A risk allele and increases global and allele-specific EGR2 expression	Grünewald et al. [67]
14	Gastric cancer	<i>MMP7</i>	rs11568818	CREB	-	-	Specific binding of phosphorylated CREB to the G-allele-carrying promoter enhances MMP7 expression	Kesh et al. [78]
15	Glioblastoma	<i>MGMT</i>	rs16906252	-	Promoter	-	Temozolomide-treated patients with the rs16906252 T genotype have better survival, irrespective of tumor methylation status	Rapkins et al. [113]
16	Lung adenocarcinomas	<i>MGMT</i>	rs16906252	-	Promoter	-	TMZ treatment may benefit a subset of lung cancer patients methylated for <i>MGMT</i>	Leng et al. [114]
17	Pancreatic cancer	<i>LINC00673</i>	rs11655237	-	-	miR-1231	miR-1231 binding diminishes the effect of LINC00673 in an allele-specific manner and, thus, confers susceptibility to tumorigenesis	Zheng et al. [123]
18	Prostate cancer	<i>8q24</i>	rs378854	YY1	-	-	The risk allele (G) of rs378854 reduces binding of the TF YY1	Meyer et al. [79]
		<i>6q22/REF6</i>	rs339331	HOXB13	-	-	The risk-associated T-allele at rs339331 increases binding of HOXB13 to a transcriptional enhancer, conferring allele-specific upregulation of the rs339331-associated gene <i>REF6</i>	Huang et al. [80]
		<i>HNF1B</i>	rs11649743 and rs3760511	-	Promoter	-	Prostate cancer risk SNPs, rs11649743 and rs3760511, are linked with elevated <i>HNF1B</i> gene expression and allele-specific epigenetic silencing	Ross-Adams et al. [115]
		19q13	rs11672691	<i>HOXA2</i>	-	-	CRISPR/Cas9-mediated single-nucleotide editing highlighted the direct effect of rs11672691 on PCAT19 and CEACAM21 expression and PCa cellular aggressive phenotype	Gao et al. [81]
19	Sessile and traditional serrated adenomas	<i>MLH1-93</i>	rs1800734	-	Promoter	-	BRAF mutant microsatellite stable colorectal cancers with the AA genotype most likely arise in traditional serrated adenomas	Finnell et al. [121]
CVDs								
20	CVDs (include lipid phenotypes, cardio-metabolic phenotypes, hypertension, blood pressure, coronary heart disease, ischemic heart disease, and ischemic stroke)	<i>PEAR1</i>	rs12041331	CTCF	First untranslated exon	-	A genetic predisposition reinforces <i>PEAR1</i> enhancer activity through allele-specific DNA methylation	Izzi et al. [19]
		<i>GRK2</i>	rs182084609	EGR-1	-	-	EGR-1 overexpression resulted in a >2-fold increase in <i>GRK2</i> promoter activity but only in the presence of the G-allele ($p = 0.04$)	Klenke et al. [88]
		LPL	rs13702	-	-	miR-410	rs13702 induces the allele-specific regulation of LPL by miR-410	Richardson et al. [124]
		FADS1	rs174545	-	-	miR-181a-2	Polymorphisms in miRNA binding sites can both positively and negatively affect miRNA-mediated regulation of cardio-metabolic genes	Ghanbari et al. [126]
		LPL	rs1059611	-	-	miR-136		
		LPL	rs13702	-	-	miR-410		
		FN3KRP	rs1046875	-	-	miR-34a		
		MKRN2	rs7956	-	-	miR-154		

Table 1 (continued)

S. No	Complex traits or diseases	Loci	SNPs	TFs	DNA methylation	miRNA	Inference	Ref.
21	Systemic sclerosis-associated pulmonary hypertension	CDKN2B	rs3217992			miR-138-2-3p		
		HSD17B13	rs11735092			miR-375		
		PVRL2	rs6857			miR-320e		
		IKZF3	rs907091			miR-326		
		GDF15	rs1054564			hsa-miR-1233-3p	rs1054564 confers allele-specific translational repression of <i>GDF15</i> via hsa-miR-1233-3p	Teng et al. [127]
		AGT	rs5050	USF1			C-allele of rs5050 has a higher affinity for USF1 and USF2 TFs	Park et al. [90]
		ARHGAP42	rs604723	USF2				
				Serum binding factor			DNA binding and transcription assays demonstrated that the minor T-allele variation at rs604723 increased the activity of this fragment by promoting serum response TF binding to a cryptic <i>cis</i> -element	Bai et al. [94]
		NPPA	rs61764044			miR-155	miR-155 and miR-105 repressed NPPA mRNA in an allele-specific manner	Wu et al. [128]
		TCF21	rs5067			miR-105		
22	Diabetes mellitus	MTTP	rs12190287			miR-224	miR-224 interaction with the TCF21 transcript contributes to an allelic imbalance of this gene	Miller et al. [125]
		ALOX5AP	rs1800804	C/EBP			The major -164T allele is homologous to the C/EBP response element	Aminoff et al. [97]
			rs4073259		Promoter		IS-associated CpG-SNP rs4073259 may affect the expression level of <i>ALOX5AP</i> through allele-specific methylation	Shi et al. [116]
		NKX2-5	rs3095870	TEAD1 and YAP1			rs3095870 C-allele results in allele-specific binding of TEAD1 and YAP1	Dritsoula et al. [98]
		KCNQ1	rs2074196	NF-Y			NF-Y specifically bound to the non-risk allele of the SNP rs2074196 region and stimulated the transcriptional activity of an artificial promoter containing SNP rs2074196 in an allele-specific manner	Hiramoto et al. [20]
		TNF- α	rs1800630	OCT-1,			YY1 TF bound allele-specifically to the SNP region and had an increase in luciferase expression compared with the G-allele	Susa et al. [105]
			rs1799724	OCT-1				
			rs1800610	YY1				
		MEG3	rs3783355	NKX2.2, FOXA2, and PDX1			Intronic MEG3 enhancer plays an important role in the regulation of ASE at the imprinted DLK1-MEG3 locus in human B cells	Kameswaran et al. [106]
		THADA	rs7578597		CpG sites		Five CpG sites, including those flanking rs7578597, showed differential methylation between diabetic and nondiabetic donor islets	Prasad et al. [117]
23	Parkinson disease	SNCA	rs356168	EMX2 and NKX6-1			rs356168 in the SNCA gene causes allele-specific changes in TF binding sites	Soldner et al. [109]
		5HT2AR	rs6313		First exon		Methylation of allele-C-specific CpG sites in the first exon correlated significantly with the expression of DNMT1	Poleskaya et al. [118]

Table 1 (continued)

S. No	Complex traits or diseases	Loci	SNPs	TFs	DNA methylation	miRNA	Inference	Ref.
25	Schizophrenia	<i>FURIN</i>	rs4702	-	-	miR-338-3p	Schizophrenia was shown to be associated rs4702 G-allele-specific downregulation of <i>FURIN</i> by miR-338-3p	Hou et al. [129]
<i>Other diseases</i>								
26	HBV-associated liver diseases	<i>PDI</i>	rs10204525	-	-	hsa-miR-302c, has-miR-541, and hsa-miR-4717	miR-4717 may allele-specifically regulate PD-1 expression through interaction with the 3'-UTR of <i>PDI</i> mRNA, leading to the alteration of immune regulation and affecting the susceptibility and disease course of chronic HBV infection	Zhang et al. [130]
27	Chronic fatigue syndrome	<i>HTR2A</i>	rs6311	E41, GR, Sp1	Promoter	-	rs6311 can affect both TF binding and promoter methylation, and this along with an individual's stress response can impact the rate of <i>HTR2A</i> transcription in a genotype- and methylation-dependent manner	Falkenberg et al. [111]

SNP, single nucleotide polymorphism; TF, transcription factor; ASE, allele-specific expression; CVDs, cardiovascular diseases; LPL, lipoprotein lipase; NF- κ B, nuclear transcription factor- κ B; DNMT1, DNA methylase 1.

MGMT codes for a DNA repair protein and is frequently methylated in sporadic colorectal cancer [112]. However, *MGMT* promoter methylation is influenced by a *cis*-acting rs16906252 present within the transcriptional enhancer element in colorectal cancer, glioblastoma, and lung adenocarcinoma [112–114]. The *HNF1B* gene plays a major role in the development of ovarian and prostate cancers [115]. rs11649743 and rs3760511 in the *HNF1B* gene were shown to be associated with allele-specific epigenetic silencing in prostate cancer [115]. A mismatch repair protein is coded by the *MLH1* gene, and loss of its expression is implicated in microsatellite instability [120]. In sessile and traditional serrated adenomas, a minor A-allele of rs1800734 was associated with increased methylation levels in *MLH1* promoter [121].

In the case of CVDs, the *PEAR1* gene and *ALOX5AP* gene have been associated with the disease [19, 116]. *PEAR1*, as discussed earlier, plays a role in cardiovascular events. The *ALOX5AP* gene codes for 5-lipoxygenase-activating protein and is a risk factor for ischemic stroke. Two CpG SNPs, namely, rs12041331 in the *PEAR1* gene and rs4073259 in the *ALOX5AP* gene, affect the expression of genes through allele-specific methylation and contribute to platelet reactivity and ischemic stroke, respectively [19, 116].

In type 2 diabetes, among the known SNPs for disease susceptibility, rs7578597 in the *THADA* gene showed parent-of-origin expression and was linked to differential methylation of 2 flanking CpG sites near to the SNP [117]. Allele-specific methylation has also been observed in genes associated with psychiatric disorders and chronic fatigue syndrome. SNPs, namely, rs6311 and rs6313, present in the promoter and first exon, respectively, are shown to have allele-C-specific methylation in psychiatric disorders and chronic fatigue syndrome [111, 118] (Table 1). These reports provide evidence for the role of methylation in driving ASE complex phenotypes.

SNPs in miRNA Target Sites Cause Differential Allelic Expression

miRNAs are known to regulate gene expression by binding to the 3'-UTR region of the gene. For years, it has been thought that changes in the target sequence can result in improper binding of miRNA and lead to dysregulated gene expression. This has been, at times, supported by evaluations in normal physiological conditions and in different types of cancer. A polymorphism in the *BM-PR1B* gene, that is, rs1434536 (C>T) associated with breast cancer, was found to be present in the binding site of miR-125b [122]. It was shown that miR-125b binds to

the C-allele and results in allele-specific regulation of the *BMPRI1B* gene [122]. In the case of pancreatic cancer, a polymorphism rs11655237 in the *LINC00673* gene was shown to affect the miR-1231 binding in an allele-specific manner and thus lead to susceptibility to cancer [123].

SNPs associated with other complex diseases such as CVDs have also affected miRNA binding. For example, rs13702 (T>C) leads to allele-specific regulation of the lipoprotein lipase (*LPL*) gene by miR-410, with miRNA having a more binding affinity for the T-allele [124]. *TCF21* rs12190287 associated with coronary heart disease interacts with miR-224 and induces an allelic imbalance of the *TCF21* gene [125]. A comprehensive study on cardiometabolic phenotypes showed 7 SNP and miRNA pairs, namely, rs1059611 (*LPL*:miR-136), rs174545 (*FADS1*:miR-181a-2), rs13702 (*LPL*:miR-410), rs7956 (*MKRN2*:miR-154), rs1046875 (*FN3KRP*:miR-34a), rs11735092 (*HSD17B13*:miR-375), and rs3217992 (*CDKN2B*:miR-138-2-3p), which abolish miRNA-dependent gene regulation [126]. This study also showed 2 SNP and miRNA pairs, namely, rs907091 (*IKZF3*:miR-326) and rs6857 (*PVRL2*:miR-320e), which create the binding site for miRNAs and thus induce miRNA-dependent gene regulation [126]. Another study showed allele-specific translational suppression by miR-1233-3p binding to the G-allele of the rs1054564 *GDF15* gene, which is a strong predictor of CVD events [127]. The *NPPA* gene that encodes for atrial natriuretic peptide involved in regulating blood pressure was shown to be regulated by miR-155 and miR-105 in an allele-specific manner, affecting wild alleles of rs61764044 and rs5067, respectively [128].

Apart from CVDs, rs4702 *FURIN* gene polymorphism identified as *cis*-expression quantitative trait loci in association with schizophrenia is shown to be regulated by miR-338-3p [129]. Furthermore, the downregulation of the *FURIN* gene has been shown to reduce the maturation of brain-derived neurotrophic factor in schizophrenia [129]. Other gene polymorphisms, rs10204525 *PD1* and rs241456 *TAP2*, are present in the binding site for miR-4717 and miR-1270, respectively [130, 131]. These polymorphisms have been implicated in immune regulation and immunological diseases (Table 1).

Future Directions

Studies can consider the characterization of known GWAS-associated variations, which can potentially affect epigenetic patterns and regulate gene expression, as a starting point to conclusively determine the role of vari-

ants as a determinant of multifactorial human disease. Precisely, the identification of SNPs in potential TF binding sites, DNA methylation, and miRNA binding sites must be pursued in a high-throughput and cost-effective manner to illustrate the effects of imbalance in RNA transcripts for disease risk. However, SNPs' proper characterization in potential T binding sites, DNA methylation, and miRNA binding sites remains a significant challenge [132]. This is major because all epigenetic changes show tissue specificity [133]. Therefore, the evaluation of these interactions in different tissues becomes essential. The effect of environmental exposures may also influence the levels of TFs, DNA methylation, and miRNAs [134] and, thus, is critical for deriving proper conclusions. Last, upcoming high-throughput sequencing technologies may be considered for simultaneous evaluations of a large number of samples [135]. Finally, the patterns of SNP segregation and prevalence in different ethnic groups are thought to inflict a complex phenotype through different environmental exposures and epigenetic modulations. These interactions between SNPs and disease susceptibility may be evaluated in different ethnic groups [136]. Nonetheless, the present study's analysis highlights the information in hand regarding complex human diseases and compiles the different results obtained from different evaluations. This forms the present study's strength and provides compelling evidence for future evaluations of complex phenotypes and traits.

Conclusion

The genetic variants identified through GWAS or a candidate gene approach concerning multifactorial complex human phenotypes or diseases show accumulating evidence of interaction with TFs, DNA methylation, and miRNA to confer ASGE and, hence, result in increased susceptibility to diverse diseases [132]. The investigations which have studied the crosstalk of SNPs with TFs, DNA methylation, and miRNA have shown both positive and negative effects in various pathologies [132, 137]. The SNPs in promoter or 5'-UTR regions have been shown to inflict or abolish TF binding sites, leading to an aberrant increase or decrease in transcripts from an allele [138]. Similarly, SNPs in CpG sites can create or destroy the methylation sites and act as a *cis*-acting factor for methylation of flanking CpG sites and can potentially alter proper binding of TFs as well [139]. miRNA interacts with SNPs in various locations of the gene and regulates gene expression in an allele-specific manner. These inter-

actions result in a subsequent change in the allelic dose, which seems to play an essential role in disease risk. Wang et al. [132] have postulated this phenomenon as a working model and termed it as an “SNP intensifier.” With the existing evidence in hand, the future targets should be to test the mechanisms by which SNPs contribute to susceptibility for complex human phenotypes or traits.

Statement of Ethics

The authors have no ethical conflicts to disclose. The present study is a systematic review; hence, no ethical clearance was obtained.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Formulation of the research and research questions: Manik Vohra and Padmalatha S. Rai. Study design: Manik Vohra, Anu Radha Sharma, and Padmalatha S. Rai. Carrying out the study: Manik Vohra, Anu Radha Sharma, and Navya Prabhu B. Writing the manuscript: Manik Vohra and Anu Radha Sharma. Proofreading and editing: Manik Vohra, Anu Radha Sharma, Navya Prabhu B, and Padmalatha S. Rai.

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