m^{6}A-SNP: From genetics to epigenetics (Review)

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Abstract. N^6-methyladenosine (m^{6}A), the most abundant RNA modification, can participate in various physiological functions and pathological processes by regulating the expression or structure of genes due to its involvement in all aspects of RNA metabolism. Thus, the genetic variant that influences m^{6}A, such as m^{6}A-associated single nucleotide polymorphism (m^{6}A-SNP), which is in close proximity to or in the methylation site, may be related to various pathological processes by increasing or decreasing the m^{6}A methylation level due to the alteration of the nucleotide. The present review summarizes the recent advances made in m^{6}A-SNPs. Both the mining of genome-wide association studies and the combined analysis of the m6Avar database with expression quantitative trait loci datasets have identified functional variants and causal genes associated with various diseases and have provided new direction for future studies on disease pathogenesis. In particular, some studies have indicated that base change in m^{6}A-SNPs lead to alterations in m^{6}A modification levels, a conversion from genetics to epigenetics, and the expression variation of corresponding genes, which may affect the biological behavior of cells and explain the association of m^{6}A-SNPs with the risk or prognosis of diseases. In bladder cancer, colorectal cancer, coeliac disease, and pancreatic ductal adenocarcinoma, the overexpression of a specific allele alone can significantly modify the function of corresponding genes. On the whole, m^{6}A-SNPs play a pivotal role in all stages of diseases. In the future, the identification of m^{6}A-SNPs as disease biomarkers and ascertaining the functions of these m^{6}A-SNPs may prove beneficial. This would help to identify susceptible individuals in a timely manner and clarify the roles of corresponding genes in the occurrence and progression of diseases, and would also aid in the development of novel treatment strategies, ultimately improving patients' survival.

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Contents

1. Introduction

N^6-methyladenosine (m^{6}A), the most abundant RNA modification, refers to the methylation at the N^6 position of adenosine mainly located in the RRACH sequence (R=A or G, H=A, C, or U) and is a dynamic and reversible process, in which the addition, removal, and recognition of methyl is responsible by methyltransferases, demethylases, and m^{6}A RNA binding proteins, respectively (1,2). m^{6}A can participate in various physiological functions, such as tissue development, heat shock response, DNA damage response, and circadian clock control. It can also participate in pathological process by regulating the expression or structure of genes due to its involvement in all aspects of RNA metabolism, including RNA processing, nuclear export, stability, translation, and degradation (3-17).

A proper m^{6}A level is necessary for sustaining normal bioprocesses, which mainly relies on the appropriate expression and function of methyltransferases and demethylases. m^{6}A can be found not only in mRNAs, but also in non-coding RNAs, such as microRNAs (miRNAs/miRs) and long non-coding RNAs (lncRNAs). The fate of m^{6}A-modified RNA is dependent on the protein that binds to it. By recognizing and binding to target mRNAs in an m^{6}A-dependent manner, YTH m^{6}A-binding protein 1 (YTHDF1) facilitates translation initiation and protein synthesis (8), while YTH m^{6}A-binding protein 2 (YTHDF2) enhances the degradation of target mRNA (7,18). YTH m^{6}A-binding protein 3 (YTHDF3) interacts with YTHDF1 or YTHDF2 to promote mRNA translation or increase mRNA degradation (19,20). YTH domain-containing 1 (YTHDC1) and YTH domain-containing 2 (YTHDC2) promotes the translocation of m^{6}A-modified mRNA from the nucleus to the cytoplasm and elevates the translation efficiency of m^{6}A-modified mRNA, respectively (21-25). Insulin like growth factor 2 mRNA binding protein (IGF2BP)1, IGF2BP2 and IGF2BP3 enhance mRNA stability (26). Heterogeneous nuclear ribonucleoprotein (HNRNP)C and HNRNPG regulate the alternative

splicing of mRNAs in an m^{6}A-dependent manner (11,27). HNRNPA2B1 promotes the maturation of miRNAs by recognizing m^{6}A on pri-miRNAs and interacting with DROSHA and DDGCR8 (28). m^{6}A modification on lncRNAs can influence the interaction of lncRNAs with RNA binding proteins through an 'm^{6}A switch' mechanism or the interaction between lncRNAs and miRNAs, which may lead to alterations in the gene expression of target RNAs (11,29). Thus, the genetic variant that influences m^{6}A, such as m^{6}A-associated single nucleotide polymorphism (m^{6}A-SNP) may be related to various pathological processes.

m^{6}A-SNP, which is in close proximity to or in the methylation site, results in the gain or loss of the m^{6}A methylation site due to the alteration of the nucleotide (30). It is generally acknowledged that SNPs in various regions of genes, such as the regulatory and coding regions may affect the expression, structure, or function of genes through disparate patterns. For example, SNPs in the regulatory region, including the promoter region, 5'-untranslated region (UTR), and 3'-UTR can influence the binding of transcription factors or miRNAs, and in turn alter the expression of genes (31-33). The coding region consists of exons and introns. Non-synonymous coding SNPs alter the composition of amino acids of the protein that the gene encodes and affect the structure and/or function of the protein (34-36). Although synonymous coding SNPs do not modify the amino acid sequence of the protein, they exert an effect on mRNA conformation, protein folding, and subcellular localization (37-39). SNPs in introns play a crucial role in regulating the functions of genes by affecting the activity of the splice site (40). The function of m^{6}A-SNP is not confined to the aforementioned layers, as the base substitution of m^{6}A-SNP causes the gain or loss of the methylation site. Furthermore, previous studies have demonstrated that m^{6}A-SNPs have a stronger association with diseases or clinical manifestations than non-m^{6}A-SNPs (41-43). Therefore, it is valuable to explore the role of m^{6}A-SNPs in the occurrence, progression, treatment, and prognosis of diseases. This may prove to be helpful in identifying susceptible individuals, determining patients' survival, clarifying disease pathogenesis, discovering new treatment targets, and improving patients' prognosis. The present review summarizes recent findings on m^{6}A-SNPs.

2. Data mining of genome-wide association studies

The development of the majority of diseases is attributed to the interaction of genetic and environmental factors. Genome-wide association studies (GWAS) have identified numerous disease-associated genetic variants and revolutionized the understanding of the genetic architecture of diseases. However, a major challenge that needs to be combatted is the identification of functional or causative variants among those disease-associated genetic variants.

A number of studies have identified some genes related to various diseases or traits based on the combined analysis of GWAS and other public data (Table I) (41-57). Firstly, disease-associated m^{6}A-SNPs were selected from GWAS according to the m6Avar database. Secondly, on the basis of expression quantitative trait loci (eQTL) datasets, those m^{6}A-SNPs with eQTL signals were selected. Thirdly, the expression of the corresponding genes harboring m^{6}A-SNPs that exhibited eQTL signals was further evaluated by means of expression datasets and differently expressed genes were ascertained. The base change of m^{6}A-SNP caused by germline variants modulates the m^{6}A level, alters the binding of protein and regulatory motifs, and affects the expression of genes, and is consequently linked to the development of diseases (Table II). For instance, rs3818978 is located in the 5'-UTR of MRPS21 and is predicted to change the binding of 33 protein and four regulatory motifs. Furthermore, rs3818978 is associated with the expression of MRPS21 and ADAMTSL4 in the aorta and with the plasma levels of seven proteins, which are enriched in the extracellular region and cytoplasmic vesicle. ADAMTSL4 has been reported to be associated with arterial fragility. Thus, rs3818978 may play a critical role in the occurrence of spontaneous coronary artery dissection (44). rs4829 in the 3'-UTR of TOM1L1 is near the m^{6}A modification site, according to sequence-based RNA adenosine methylation site predictor (SRAMP) and can interact with polyadenylate-binding protein cytoplasmic 1, which is considered to participate in the occurrence of breast cancer induced by small nucleolar RNA host gene 14 (SNHG14). Therefore, rs4829 may regulate the expression of TOM1L1 to be involved in the development of breast cancer by altering the m^{6}A modification level and protein binding (45).

Mo *et al* (58) jointly analyzed GWAS data of multiple sclerosis (MS) with eQTL data from four studies using summary data-based mendelian randomization (SMR) and found that the expression of 29 genes was significantly associated with MS ($P_{SMR}<5x10^{-6}$). Among the SNPs in these genes, m^{6}A-SNP rs923829 in methyltransferase-like protein (METTL)21B was not only associated with the risk of MS ($P=1.35x10^{-10}$), but was associated with the expression of METTL21B in 37 tissues (58). Moreover, the association of rs923829 with the expression of METTL21B was confirmed in 40 unrelated Chinese Han individuals. These results suggested the critical role of m^{6}A-SNP rs923829 in the development of MS by regulating the expression of METTL21B (58).

Following an integrated analysis of GWAS data, m^{6}A peaks of HeLa and HepG2 epithelial cell lines, and expression data, five genes harboring m^{6}A-SNPs including C6orf47 and SNAPC4 were identified to be involved in inflammatory bowel disease (IBD) (59). Subsequent research indicated that the total m^{6}A modification levels and the expression of METTL3 and YTHDF1 were enhanced in HCT116 cells treated with IFNγ, and cytokine levels were upregulated in the intestinal mucosa of patients with IBD (59). Moreover, the overexpression of METTL3 and the interference of YTHDH1 led to the altered expression of C6orf47 and SNAPC4, respectively. Therefore, m^{6}A modification played key roles in the occurrence of IBD (59).

Ruan *et al* (60) identified acyl-CoA synthetase medium chain family member 5 (ACSM5) as a candidate gene for thyroid cancer by jointly analyzing GWAS data, thyroid eQTL data and m^{6}A-SNPs. ACSM5 was found to be downregulated in thyroid cancer tissues, which was associated with the poor prognosis of patients with thyroid cancer. According to prediction by SRAMP, m^{6}A modification sites with very high confidence all contained an SNP site, the base change of which resulted in the loss of m^{6}A modification

Table I. Disease-associated genes identified by mining the data of GWAS.

Disease/condition	No. of m^{6}A-SNPs	P<0.05	P<0.001	P<0.0001	P<1.25x10^{-5}	P<5x10^{-5}	No. of eQTLs	No. of DEGs	(Refs.)
SCAD	11,464	519	7				7		(44)
Breast cancer (2021)						113	86	6	(45)
Colorectal cancer			402				98	3	(46)
Type 2 diabetes	15,124					71	56	11	(47)
Periodontitis	1,938	104					65	48	(48)
Adiposity	20,993					230	215	88	(49)
IS (2021)	4,216	305					158	84	(50)
Blood lipids	1,655	HDL-C, 139; LDL-C, 162; TC, 150; TG, 147					93	HDL-C, 22; LDL-C, 33; TC, 31; TG, 27	(41)
CAD	4,390	304					50	45	(51)
IS (2019)	4,000	AIS, 310; LAS, 305; CES, 279; SVS, 205;			AIS, 9; LAS, 4; CES, 1; SVS, 1;		6	4	(52)
BMD	BMD, 1,919; eBMD, 9,854	FN-BMD, 138; LS-BMD, 125; eBMD, 993		FN-BMD, 8; LS-BMD, 6; eBMD, 88			47	26	(42)
RA	3,883	Asians, 227; Europeans, 308		Asians, 26; Europeans, 42			Asians, 13; Europeans, 20	20	(53)
BP	1,236	SBP, 761; DBP, 799;					SBP, 217; DBP, 246		(43)
Oral ulcer		7,490				30	25	19	(54)
Breast cancer (2022)		981					4	3	(55)
Parkinson's disease	657	12					9	3	(56)
Bladder cancer		673					221	11	(57)

GWAS, Genome-wide association studies; m^{6}A-SNPs, m^{6}A-associated single nucleotide polymorphisms; eQTLs, expression quantitative loci; DEGs, differentially expressed genes; SCAD, spontaneous coronary artery dissection; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, cholesterol; TG, total triglycerides; CAD, coronary artery disease; IS, ischemic stroke; AIS, arterial ischemic stroke; LAS, large artery stroke; CES, cardioembolic stroke; SVS, small vessel stroke; BMD, bone mineral density; FN, femoral neck; LS, lumbar spine; eBMD, quantitative heel ultrasounds; RA, rheumatoid arthritis; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.

sites (60). Furthermore, the knockdown of METTL3 decreased the m^{6}A modification level and the expression of ACSM5. Hence, it was suggested that m^{6}A-SNPs participated in disease development and progression by affecting expression of ACSM5 (60).

3. Combined analysis of m6Avar database and eQTLs

The combined analysis of the m6Avar database and eQTLs associated with sepsis has revealed 15,720 m^{6}A-cis-eQTLs in 1,321 genes. Among these genes, 17 genes were enriched in

Table II. Disease-associated m^{6}A-SNPs affecting the m^{6}A modification level and the binding of proteins, and altering regulatory motifs.

Disease/condition	m^{6}A-SNP	Ref base	Alt base	Gene	SNP function annotation	m^{6}A function	Proteins bound	Motifs changed	(Refs.)
SCAD	rs3818978	T	A	MRPS21	5'-UTR	Functional loss	33	4	(44)
	rs12758270	A	G	RPRD2	3'-UTR	Functional loss		2	
Breast cancer (2021)	rs4829	C	T	TOM1L1	3'-UTR	Functional loss		11	(45)
	rs9610915	C	G	MAFF	3'-UTR	Functional loss	2	4	
Colorectal cancer	rs178184	T	G	NOVA1	Intronic	Functional loss		2	(46)
	rs35782901	C	T	HTR4	Intronic	Functional gain			
	rs60571683	G	A	SLCO1B3	Synonymous	Functional loss			
Type 2 diabetes	rs4993986	C	G	HLA-DQB1	3'-UTR	Functional loss	3	6	(47)
Periodontitis	rs2723183	A	G	IL-37	Missense	Functional loss		1	(48)
Adiposity	rs8024	C	A	IPO9	3'-UTR	Functional loss	3		(49)
IS (2021)	rs1803439	A	G	DYRK1A	3'-UTR	Functional loss			(50)
	rs8124907	A	G	LAMA5	Synonymous	Functional loss		1	
Blood lipids	rs6859	A	G	PVRL2	3'-UTR	Functional loss	3	4	(41)
CAD	rs12286	G	A	ADAMTS7	3'-UTR	Functional gain		5	(51)
IS (2019)	rs2013162	C	A	IRF6	Synonymous	Functional loss	1	2	(52)
	rs2273235	T	G	NDST1	Synonymous	Functional loss		3	
BMD	rs1110720	G	A	ESPL1	Synonymous	Functional gain		5	(42)
	rs11614913	C	T	MIR196A2		Functional gain		1	
BP	rs9847953	A	G	ZNF589	Missense	Functional loss	32	1	(43)
	rs197922	G	A	GOSR2	Missense	Functional loss		4	
	rs1801253	G	C	ADRB1	Missense	Functional loss	2	1	
	rs7398833	T	C	CUX2	3'-UTR	Functional gain		1	
Oral ulcer	rs11266744	A	C	CCRL2	Synonymous	Functional loss		3	(54)
Breast cancer (2022)	rs76563149	G	T	ZNF354A	5'-UTR	Functional loss	11	2	(55)
	rs11614913	C	T	MIR196A2		Functional gain		1	
	rs1801270	C	A	CDKN1A	Missense	Functional loss	2	4	
Parkinson's disease	rs75072999	G	A	GAK	Synonymous	Functional gain		2	(56)
	rs1033500	G	A	C6orf10	Missense	Functional gain		5	
Bladder cancer	rs3088107	G	A	RNFT2	3'-UTR	Functional loss		2	(57)
	rs9418589	T	C	PDSS1	Intronic	Functional loss		4	
	rs1550116	A	G	CENPO	Missense	Functional loss		2	
	rs7611841	T	C	CRTAP	Intronic	Functional loss	4	2	
	rs4385847	T	C	BDNF	Intronic	Functional loss		6	
	rs4147971	C	T	ABCA8	Intronic	Functional loss		8	
	rs1053433	T	G	KCTD12	3'-UTR	Functional loss		2	
	rs2466791	T	C	FBN1	Intronic	Functional loss		2	
	rs12275254	T	C	DLG2	Intronic	Functional loss		1	
	rs7070678	G	T	SVIL	Synonymous	Functional gain			
	rs3748338	A	T	RNASE4	Missense	Functional loss		3	

m^{6}A-SNP, m^{6}A-associated single nucleotide polymorphism; Ref base, reference base; Alt base, alternative base; SCAD, spontaneous coronary artery dissection; CAD, coronary artery disease; IS, ischemic stroke; BMD, bone mineral density; BP, blood pressure; BMI, body mass index.

platelet degranulation process, a typical biomarker of sepsis, and 12 genes gathered in the pathway of *Staphylococcus aureus* infection, the most common pathogenic bacterium in sepsis, which suggested that m^{6}A-SNPs played key roles in sepsis (61).

Both the mining of GWAS and the combined analysis of the m6Avar database with eQTLs have facilitated the identification of functional variants and causal genes associated with various diseases, and have helped to provide new direction for future studies on disease pathogenesis. Moreover, a relatively broad significance threshold was adopted to analyze the association between m^{6}A-SNP and diseases, which avoided missing valuable information. However, there are some limitations in the aforementioned studies. Firstly, the associations between m^{6}A-SNPs and diseases were not validated in additional independent studies. Secondly, the inconsistency of samples used in eQTL analysis and in the analysis of differentially expressed genes might have some degree of influence on the results due to the tissue specificity of gene expression. Thirdly, whether m^{6}A-SNPs affected m^{6}A modification levels and the expression of corresponding genes were not examined experimentally. Recently, some studies on the effects of m^{6}A SNP and the underlying mechanisms were conducted, as described below.

4. Effects and mechanisms of m^{6}A SNPs

The A allele of rs5746136 in superoxide dismutase 2 (SOD2) was previously found to be associated with a reduced risk of bladder cancer. A mechanistic analysis demonstrated that the transition of base from G to A led to an increased m^{6}A modification level of SOD2 and increased the binding of HNRNPC with SOD2 followed by the upregulation of SOD2. The overexpression of SOD2 inhibited the proliferation, migration, and invasion of bladder cancer cells, which suggested that SOD2 functioned as tumor suppressor gene for bladder cancer (62).

Another study demonstrated that the transversion of the C to the G allele of rs3088107 resulted in a decreased m^{6}A modification level of ring finger protein, transmembrane 2 (RNFT2) in 293T cells and reduced the expression of RNFT2 in bladder cancer cells (57). Moreover, the G allele of rs3088107 inhibited the proliferation and migration of bladder cancer cells compared to the C allele of rs3088107 (57).

The A allele of rs1800241 in ankyrin repeat and LEM domain containing 1 (ANKLE1) has been linked to a decreased risk of colorectal cancer, which may be attributed to the enhanced expression of ANKLE1 by elevating the m^{6}A modification level of ANKLE1 mediated by METTL3, METTL14, or WTAP and increasing binding of YTHDF1 with ANKLE1. Furthermore, the overexpression of ANKLE1[A] repressed the proliferation of colorectal cancer cells and promoted genomic stability more effectively than the overexpression of ANKLE1[G] (63).

Individuals carrying the exportin 1 (XPO1) gene rs3087898 T allele were previously shown to be more susceptible to coeliac disease (CD) than those carrying the rs3087898 C allele (64). The XPO1 mRNA transcript with the T allele was shown to have a higher m^{6}A modification level and higher translation efficiency by increasing the binding of YTHDF1 with the XPO1 mRNA than transcription with the C allele. Subsequent experiments indicated that the allele-specific increase of XPO1 activated the NF-κB signaling pathway to facilitate the development of CD (64).

The GT genotype of rs142933486 in phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta (PIK3CB) was previously found to predicted the poor survival of patients with pancreatic ductal adenocarcinoma (PDAC) (65). Cell biology experiments revealed that the overexpression of the T allele reduced the m^{6}A modification level of PIK3CB, decreased the binding of YTHDF2 with PIK3CB, and in turn, increased the mRNA stability and expression of PIK3CB. Consistently, a higher PIK3CB expression was associated with the poor prognosis of patients with PDAC, particularly in patients with PTEN deficiency. Further analyses demonstrated that the overexpression of PIK3CB[T] activated the AKT signaling pathway to promote the proliferation and migration of PTEN-deficient PDAC cells, with a more prominent effect than the overexpression of PIK3CB[G] (65).

The aforementioned studies have indicated that the base change of m^{6}A-SNPs leads to alterations in m^{6}A modification levels, a conversion from genetics to epigenetics, and the expression variation of corresponding genes, which is dependent on the RNA binding proteins that recognize m^{6}A methylation. Furthermore, the expression variation of genes affects the biological behavior of cells, which explains the association of m^{6}A-SNPs with the risk or prognosis of diseases. In particular, in bladder cancer, colorectal cancer, CD, and PDAC, the overexpression of a specific allele alone can significantly modify the function of corresponding genes. All these findings may provide an experimental foundation for the development of novel therapeutic strategies. For example, XPO1 and PIK3CB have the potential to function as therapeutic targets for CD and PDAC, respectively.

5. Conclusion

In conclusion, m^{6}A-SNPs play a pivotal role in all stages of diseases. In the future, the identification of m^{6}A-SNPs as disease biomarkers and ascertaining the functions of these m^{6}A-SNPs may prove beneficial, as it may help to identify susceptible individuals in a timely manner. It may also clarify the role of corresponding genes in the occurrence and progression of diseases, and may thus aid the development of novel treatment strategies, ultimately improving the survival of patients.

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Availability of data and materials

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

Authors' contributions

CN participated in the literature collection, reading and analysis, and drafted the manuscript. RZ participated in the design of the study and in the revision of the manuscript. Data

authentication is not applicable. Both authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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