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Exploring the Impact of NF- KB1 Gene Polymorphism

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Abstract

This review article extensively explores the influence of NF-κB1 gene polymorphism on a diverse range of health issues. The NF-κB pathway, a crucial controller of immune response, is closely associated with numerous disease mechanisms. The NF-kB1 gene has undergone significant genetic changes, and these changes have shown strong connections with the onset and development of numerous disorders. This article investigates the intricate relationship between mutations in the NF-kB1 gene and a wide range of disorders through a thorough study of the literature. These conditions encompass inflammatory disorders, cancer, cardiovascular diseases (CVD), and various other medical ailments. The notable discoveries emphasized within this review underscore the essential role of NF-κB1 gene polymorphism in the development of a range of diseases. Furthermore, these discoveries have important ramifications that could help develop more specialized, successful treatment approaches. To sum up, this work sheds light on the different ways in which NF-kB1 gene variation influences the progression of disorders and highlights the urgent need for more research in this area.

Keywords: *NF-kB1 gene, Polymorphism, Genetic variation, Single nucleotide polymorphism (SNP), Inflammation, Immune response, Transcription factor, NF-κB pathway Cancer risk, Cytokine*

1. Introduction

The NF-κB1 gene is responsible for encoding the nuclear factor of kappa (κ) which is a light polypeptide gene enhancer in B cells 1 (NF-κB1).This gene is part of the Rel homology domain (RHD) family, comprising five proteins [1]. Within the human genome, NF-κB1 resides on chromosome 4q24 and gives rise to two distinct proteins. One of these is p50, which interacts with the N terminus of p105—a protein that lacks DNA-binding capacity [2][3]. Spanning 156 kb, the NF-κB1 gene encompasses 24 exons interspersed with introns of varying lengths, ranging from 40,000 to 323 bp [4]. A 105 kD protein is created at this genomic locus, and it is simultaneously translated by the 26S proteasome to produce a 50 kD protein. The 50 kD protein serves as a DNA binding element within the NF-B protein complex, whereas the 105 kD protein acts as a transcriptional inhibitor of the Rel protein. [5]. In its homodimer (p50/p50) form, the p50 component inhibits pro inflammatory cytokines while stimulating anti-inflammatory cytokines [6]. Numerous genes involved in immune response, proliferation, cell adhesion, differentiation, apoptosis and angiogenesis are regulated by NF-κB1 [7].

Rangen Sen and David Baltimore identified the NF-κB1 protein in 1986 [8] but, it is only lately started to be taken into consideration as a marker of therapy success in diverse malignant neoplasms [9] The primary physiological role of NF-κB1 is to rapidly alter the expression of a large number of genes (particularly proto-oncogenes) in response to infections, inflammation, and certain stress-related effects [10]. Inflammatory responses entail increased NF-κB1 activity [11]. In addition, NF-κB1 is implicated

in metastasis, enhanced cell survival, and proliferative activity [11]. By promoting angiogenesis, proliferation, anti-apoptosis, and suppressing immune response, NF-κB1 signalling is crucial for the growth and aggressiveness of tumours [12]. Numerous clinical disorders, including cancer, arthritis, chronic inflammation, asthma, neurological illnesses, and heart disease, are associated with the continuous activity of these transcription factors [13]. It has been demonstrated that NF-κB1 activation is linked to tumour resistance to a variety of treatment interventions, including radiation therapy [14].

2. Materials And Methods

After conducting an extensive search across databases, including PUBMED and others, we gathered a total of approximately 26,543 results. Subsequently, we meticulously curated around 80 articles for inclusion in this review paper. The primary aim of this review was to explore the relationship between polymorphisms in the NF-κB1 gene and a wide range of health conditions. This endeavor involved a comprehensive compilation of existing literature from diverse sources, encompassing research articles and reviews. To gain a comprehensive view, we carried out an exhaustive search across platforms such as PubMed, Google Scholar, and the National Library of Medicine (NLM), utilizing relevant keywords associated with NF-κB1 gene polymorphisms and specific diseases. The evaluation process entailed the integration of studies that investigated the impact of NF-κB1 gene polymorphisms on disease susceptibility, disease progression, and potential underlying mechanisms. Based on the findings of these studies, we developed a comprehensive perspective to provide a well-rounded understanding of the intricate role played by NF-κB1 gene polymorphisms in various disease contexts.

Overview of NF-κB Signaling Pathway

Belonging to a cluster of eukaryotic transcription factors with analogous structures, NF-κB proteins oversee diverse fundamental physiological processes such as cell growth, development, apoptosis, as well as immune and inflammatory reactions [13]. In the cytoplasm of cells, inactive NF-κB1 is frequently associated with inhibitory proteins referred to as κB (IκB) inhibitors. Among these, IκBα, IκBβ, and IκBε are considered the most notable, as suggested by Li and Nabel in 1997 [15]. NF-κB1 can be activated by a variety of extracellular stimuli, such as bacterial lipopolysaccharide, viruses, oxidants, inflammatory cytokines, and immunological stimuli [16]. There are two distinct pathways each having a unique activation mechanism, canonical and non-canonical NF-κB pathways [17, 18]. Cellular exposure to cytokines, such as tumour necrosis factor and interleukin-1, CD40 ligand, and lymphotoxin, or in response to inflammatory signals, such as bacterial lipopolysaccharide, results in the classical (canonical) pathway. An essential stage in initiating NF-κB signaling involves the phosphorylation of IκB molecules by IκB kinases (IKKs), constituting the principal mechanism for canonical NF-κB activation, which holds significant significance. Consisting of the regulatory component NF-κB essential modifier (NEMO) and two similar catalytic subunits, namely IKKα and IKKβ (also referred to as IKK1 and IKK2), the IKK complex is composed. This arrangement was detailed by Hacker and Karin [19]. IKK is required for conventional NF-B activation caused by pro-inflammatory cytokines and microbial metabolites, whereas IKK predominantly contributes to non-canonical NF-B activation [20, 21, 22].

Following NF-κB activation, IκBα degradation occurs, facilitating the translocation of the p50-p65 heterodimer into the nucleus, where it binds to specific DNA regions, notably promoters, to initiate gene expression [23, 24]. Recent studies have highlighted that the activation of the nuclear factor NF-κB introduces a novel mechanism linked to chemoresistance in Non-Small Cell Lung Cancer (NSCLC) and diverse other types of cancers [25, 26]. Constitutive or diminished NF-κB activation often results from flaws in components governing the release of NF-κB from IκBα. These components could encompass a range of kinases, phosphatases, and other signal transducers typically engaged in the pathways leading to NF-κB activation [27].

According to Sonenshein's perspective, alterations in NF-κB1 expression play a crucial role in safeguarding cells against apoptosis [28]. The commencement of NF-κB activation, leading to increased expression of its targeted genes, has been suggested as a pivotal factor in the advancement of carcinogenesis across various cancer types [29, 30, 31, 32]. The regulation of NF-κB through the modulation of its target genes, either by inhibition or activation, seems to be amplified in multiple pathological contexts, with NF-κB signaling implicated in fundamental cellular processes [33].

Impact of NF-κB in innate immunity

NF-κB mediated T cell responses

Hayden et al., reviewed that NF-κB exerts a significant influence over gene programs that govern T-cell activation, differentiation, proliferation, and effector function [34]. The primary emphasis of

research investigating NF-κB's role in T cell activation has predominantly centered on the examination of CD4+ T cells. The comprehensive understanding of NF-κB's role in CD8+ T cells has been hindered by historical limitations in generating CD8+ T-cell conditional knockouts and the specific depletion of CD8 cells when NF-κB is non-functional. Nonetheless, progress is being made in this domain, and recent years have witnessed renewed interest in this pursuit. While the differentiation of CD4+ T cells into either TH1 or TH2 subsets based on cytokine cues has long been established, a growing recognition of CD4+ helper T cells' capacity to differentiate into diverse effector cell types, including induced regulatory T cells, pro-inflammatory TH17 cells, TH22 cells, and TH9 cells, has prompted a reevaluation of NF-κB's impact on T cell differentiation and effector function [35].

Adaptive response initiation

The start of the adaptive immune response is still a vital step to accomplish effective and permanent pathogen elimination, even though the innate immune system exhibits powerful antimicrobial activity and protects the host defenses in a variety of situations [36]. A pivotal connection during this transition occurs through the activation and maturation of antigen-presenting cells (APCs), enabling effective communication between the innate and adaptive immune systems. The characteristics of pathogen-related molecular patterns (PAMPs), the signaling pathways activated by the pattern recognition receptors (PRRs) they correspond to, and the specific conditions that lead to pathogen recognition all play a significant role in how this interaction develops. The maturation of dendritic cells (DCs) driven by pathogen recognition is a decisive event in instigating the adaptive immune response [36]. To engage and activate naive T cells, DCs necessitate a transformation in their chemokine receptor repertoire, enabling them to migrate to lymphoid tissues. In the course of activation, DCs fine-tune their machinery for processing antigens, favoring the presentation of pathogen-derived epitopes. Additionally, the upregulation of co-stimulatory molecules such as B7.1/B7.2 (also known as CD80/CD86) takes place [36]. These co-stimulatory molecules engage with CD28, a co-stimulatory receptor on T cells, thereby delivering the essential second signal for complete T-cell activation. The response to pathogens is exquisitely tailored based on the distribution of PRRs across different cell types, influencing their interactions with T cells in a manner that imparts a particular bias.

In summary, the interplay between the innate and adaptive immune systems is orchestrated through the maturation and activation of APCs. This bridge between the two arms of immunity is a critical determinant of the ultimate efficacy and specificity of immune responses to various pathogens [36].

NF-κB mediated B cell responses

Numerous parallels exist in the roles played by NF-κB within T and B cells. NF-κB functions to facilitate proliferation, regulate apoptosis, and oversee the intricate processes of differentiation and maturation in B cells [37]. B-cell responses can be categorized into two main groups: thymus-dependent (TD) and thymus-independent (TI). In the context of TD responses, follicular B cells necessitate co-stimulatory signals from T helper (TH) cells expressing CD40L and certain cytokines like IL-4. This initiates a sequence of events culminating in the formation of germinal centres. Within these centers, crucial processes such as somatic hypermutation, isotype switching, and the differentiation of plasma cells take place [37]. Consequently, in individuals harbouring a mutation in CD40L, B cells encounter obstacles in undergoing class switch recombination in response to antigens reliant on T-cell assistance. The CD40 signalling pathway initiates both the conventional and non-conventional NF-κB pathways. However, evidence suggests that the non-canonical pathway might not be indispensable for thymus-dependent antigen responses [37]. This inference is supported by the fact that B cells devoid of p52 exhibit competent responses to thymus-dependent antigens upon transfer. Similarly, B cells sourced from mice lacking the RelB protein, while experiencing limitations in their proliferative capacities, still execute normal secretion of IgM and class switching [37]. The role of NF-κB in B cells mirrors its multifaceted functions in T cells. It is instrumental in supporting B-cell proliferation, regulating apoptosis, and steering differentiation and maturation processes. The response of B cells to thymus-dependent antigens involves intricate interactions with T cells via the CD40 signalling pathway, leading to germinal center formation and subsequent immunoglobulin diversification [37].

The Impact of NF-κB1 Gene Polymorphism on Specific Health Conditions

NF-κB1 haplo insufficiency was originally identified in three families with common variable immunodeficiency (CVID) in 2015 by Fliegauf et al., with symptoms ranging from increased viral susceptibility to skin lesions, malignant lympho proliferation, and autoimmune [38]. All of the mutations presented resulted in fast degradation of the mutant protein, resulting in a p50 haplo insufficient condition. Subsequently, over 50 extra mutations have been detected across different

domains of NF-κB1, with most of them situated in the N-terminal RHD, as observed by Lorenzini et al., [39]. A functional insertion/deletion (ins/del) polymorphism (94ins/delATTG) in the NF-κB1 promoter region has been discovered, with three genotypes: wild homozygous WW (ins/ins), variant homozygous DD (del/del), and heterozygous WD (ins/del) [6]. Numerous autoimmune and inflammatory diseases have been associated to the NF-B1-94ins/delATTG polymorphism [40, 41].

Inflammatory diseases

Inflammation is characterized by the sensation of heat, which is induced by increased blood flow through dilated arteries into the environmentally cooled extremities, resulting in increased redness and swelling (oedema) [42]. Today, inflammation is significantly more complex than the basic explanation provided above, and that it is a key immune system reaction to tissue injury and infection, albeit not all infections cause inflammation. Inflammation is also diverse, ranging from the acute inflammation caused by *S. aureus* skin infection to chronic inflammatory processes that result in remodelling of the artery wall in atherosclerosis, the bronchial wall in asthma and chronic bronchitis, and the debilitating destruction of the joints in rheumatoid arthritis (RA) [42]. The association between NF-κB1 gene polymorphism and inflammation has been extensively studied and several studies have shown the link between these two factors. To illustrate, a study published in the Journal of Immunology revealed a distinct polymorphism within the NF-κB1 gene linked to an elevated susceptibility to Crohn's disease [43]. Furthermore, research in the journal Nature Communications outlined a separate NF-κB1 gene polymorphism associated with an increased risk of systemic lupus erythematosus [44]. Through a meta-analysis, Liang et al., [45] established that the NF-kB1-94ins/delATTG promoter polymorphism is a contributing factor to Ulcerative colitis, an inflammatory bowel disease (IBD) characterized by digestive tract inflammation and ulcers [6].

Numerous studies have demonstrated an association between gastric cancer and variations in the promoter regions of the NF-KB1 gene [46]. As reported by Marko et al., in instances of sepsis, the absence of the deletion allele within the NF-κB1 promoter polymorphism led to decreased expression and reduced nuclear activity of the p50 subunit [47]. This change was linked to a worsened mitochondrial dysfunction, a stepped-up inflammatory response, and increased production of reactive oxygen species (ROS) [47].

According to Elkhawaga et al., [48], the NF-κB1-94ins/delATTG polymorphism has an impact on the severity and development of rheumatoid arthritis (RA) in Egyptian patients by modulating Interleukin (IL)-6 levels. As shown in investigations by Adamzik et al., in 2013 and 2007, the specific genetic variation (94 ins/del ATTG), designated as rs28362491, has been acknowledged as a contributing factor to the susceptibility to sepsis and acute respiratory distress syndrome [49, 50]. The presence of the D allele of the NF-B1 insertion-deletion (94ins/delATTG) polymorphism is associated with increased nuclear translocation of NF-B1, heightened coagulation response, and an increased 30-day death risk in patients with severe sepsis. As a result, some of the variability in results may be explained by genetic changes within the NF-B1 promoter and their molecular consequences resulting from altered nuclear translocation of NF-B1 [49]. The genetic study by Yalcin et al., offers some proof that the polymorphism -94ins/delATTG may have functional effects in Behçet's Disease (BD) which is a systemic immune inflammatory disease [51]. Yenmis et al., examined rs28362491 promoter variation in 89 individuals with BD and 190 healthy controls [52]. According to their research, people with the ins/ins genotype and the ins allele of rs28362491 in the NF-B1 gene had a higher risk of getting BD. Such patients with the ins/ins genotype and the ins allele of rs28362491 exhibited a 2.5- and 1.8-fold higher risk of contracting the ailment, respectively [52].

It is important to note that while these studies provide evidence for the link between NF-κB1 gene polymorphism and inflammation, further research is needed to fully understand the complex relationship between these two factors and how they contribute to the development different inflammatory diseases. Nonetheless, the intricate connections between the modified nuclear behavior of NF-κB subunits within the framework of the NF-κB1 polymorphism and its impact on inflammation and organ dysfunction remain to be elucidated [52].

Cancer

Cancer is a multifaceted and multifactorial ailment that emerges from the interplay of genetic and environmental elements. Studies have shown the activation of the NF-κB pathway in various cancer categories, including breast, prostate, lung and colorectal cancer. Several genes, including NF-κB1, regulate this pathway. An operational insertion/deletion polymorphism (-94ins/delATTG) within the NF-κB1 promoter, responsible for encoding the p50 subunit of NF-κB, is associated with various

diseases, among them bladder cancer and oral squamous cell carcinoma (OSCC) [50, 6, 53, 32]. Zou et al., [54] identified a noteworthy genetic correlation between the NF-κB1-94ins/delATTG promoter polymorphism and cancer across both Asian and Caucasian populations. In a similar vein, Lin et al., revealed that alleles such as NF-κB1 94 ATTG2, NF-κBIA 826 T, and NF-κBIA 881 G are associated with the onset of oral carcinogenesis [55]. The amalgamation of NF-κB1 or NFKBIA gene polymorphisms with environmental carcinogens seems to be linked with an elevated susceptibility to oral cavity cancer. Particularly noteworthy is the potential role of the NF-κBIA 519 genetic polymorphism as a risk determinant for distal metastases in oral squamous cell carcinoma (OSCC) cases within the Taiwanese population. A risk for Hodgkin's lymphoma, breast cancer, multiple myeloma, gastric cancer, colorectal cancer, prostate cancer and melanoma has been linked to polymorphic variations in the promoter regions of the NF-κB1 gene NF-κB1 and the IκBα gene NF-κBIA as well as in the 3′-untranslated region (3′-UTR) of NF-κBIA [56, 57, 58]. Simonian et al., found a strong association between rs696 polymorphism and colorectal cancer risk [59]. A meta-analysis conducted by Li and Zhang discovered that the risk of head and neck cancers (HNCs) was substantially connected with rs28362491 polymorphism but not with rs2233406 polymorphism [60]. Furthermore, for the first time, a substantial association between the rs28362491 polymorphism and susceptibility to neck cancers (NC) was discovered. Within the Chinese population, genetic alterations in NF-κB1 play a role in elevating susceptibility to liver cancer. An adjusted odds ratio (OR) of 1.54 (with a 95% confidence range (CI) from 1.04 to 2.28) is particularly present for the NF-B1 rs28362491 ins/del or del/del genotypes, indicating an elevated risk. Similar to rs230496, the AG and GG genotypes are associated with a higher risk of developing liver cancer, with an adjusted odds ratio (OR) of 1.53 (with a 95% confidence interval (CI) from 1.03 to 2.26).By adopting an additive model, it was discerned that individuals harboring the NF-κB1 GA and AA (rs230525-rs230530) haplotypes manifested a heightened susceptibility to liver cancer [61]. Tang et al., revealed that the prevalence of the ATTG2 allele was markedly elevated in patients afflicted with bladder cancer [62]. This finding suggests that the functional NF-κB1 promoter polymorphism is associated with an augmented vulnerability to superficial transitional cell carcinoma of the bladder [62].

Lin et al., conducted an assessment on the interplay between NF-κB1 gene polymorphisms, environmental carcinogens, and the susceptibility to oral cancer [63]. They unveiled a heightened risk of oral carcinogenesis when betel nut consumption and smoking were combined with the NF-κB1 94 insertion/deletion ATTG polymorphism. This combined risk might arise from alterations in binding affinities between constituents of tobacco and betel nut and the promoter of the polymorphic NF-κB1 gene. Prior investigations have indicated that tobacco and betel nut components could activate NF-κB in oral keratinocytes [63, 64]. Directing interventions towards the NF-κB pathway, which encompasses the NF-κB1 gene, has surfaced as a promising route for potential cancer treatments. Several drugs designed to inhibit the NF-κB pathway, particularly with a focus on NF-κB1, are currently under evaluation in clinical trials.

Rheumatoid arthritis

Immune cells infiltrate synovial tissue in rheumatoid arthritis (RA), which is recognized as an autoimmune and inflammatory condition [65]. This process is closely related to ongoing inflammation and the subsequent degeneration of bone and cartilage tissues. A significant player within RA's inflammatory context is NF-κB, an inflammatory mediator that has attracted research focus through investigations involving both animal models and human participants. Notably, several initial studies have reported the activation of NF-κB within the synovial tissue of individuals afflicted with RA [65].

Inflammatory bowel disease

Inflammatory bowel diseases (IBD), including ulcerative colitis and Crohn's disease, are persistent inflammatory conditions that impact the gastrointestinal tract. These conditions are believed to originate from irregular inflammatory responses triggered by intestinal microbes [66]. The complex development of these disorders involves a variety of cell types within the mucosal immune system, including innate immune cells (macrophages and neutrophils), T cells, innate lymphoid cells, and intestinal epithelial cells [67].

A wealth of compelling evidence firmly associates NF-κB with the development of inflammatory bowel disease (IBD). Prolonged activation of NF-κB has been unequivocally detected in inflamed colon tissues of individuals grappling with IBD. Moreover, genetic mutations that impact immune receptors responsible for activating NF-κB, such as NOD2, as well as NF-κB target genes like IL-12 and IL-23, have been associated with human IBD [68]. Genetic variations and mutations within the NFKB1 gene, which encodes the p105 IκB-like molecule and its processed form p50, have also demonstrated links

with IBD [6]. These genetic alterations seem to impede the expression of the NFKB1 gene or disrupt the stability and functionality of the protein products. Consistent with this, mice that have been genetically modified with a knockin mutation in the NFKB1 gene, causing a disruption in p105 production, display spontaneous intestinal inflammation that closely resembles characteristics observed in IBD [56].

The role of NF-κB in the development of inflammatory bowel diseases is emphasized by its activation within inflamed tissues, genetic correlations, and findings from mouse models. These aspects collectively underscore the importance of comprehending NF-κB's involvement in these intricate disorders and the potential for its targeted intervention [56].

Multiple sclerosis

The central nervous system (CNS) is impacted by the inflammatory disease known as multiple sclerosis (MS). The involvement of CNS-specific CD4+ T cells, which belong to the Th1 and Th17 cell subsets, distinguishes it from other autoimmune conditions [70]. Through large genome-wide association analyses, a probable connection between the NF-B signaling system and multiple sclerosis has been identified. These inquiries have revealed several constituents related to NF-κB as potential susceptibility factors, encompassing Bcl10, NIK, RelA, IκBα, IκBz, and MALT1 [71]. The importance of this connection is highlighted by the realization that experimental autoimmune encephalomyelitis (EAE), a widely used animal model that closely resembles multiple sclerosis, progresses as a result of both the conventional and non-conventional NF-B pathways playing significant roles. Mice are vaccinated against EAE using peptides derived from CNS proteins, like myelin oligodendrocyte glycoprotein [72]. The intricate interplay between NF-κB signaling and the pathogenesis of multiple sclerosis is increasingly evident, supported by genetic associations and animal models. Understanding these connections holds promise for advancing our comprehension of MS and potentially unveiling novel avenues for therapeutic intervention [72].

Atherosclerosis

Atherosclerosis, a progressive inflammatory condition, impacts the arterial wall and is marked by the buildup of low-density lipoprotein (LDL) particles and immune cells within the subendothelial space. This intricate progression of the ailment involves an array of cell types, including endothelial cells, monocytes, and T cells The complex advancement of the condition entails a variety of cell types, including monocytes, endothelial cells, and T cells [73]. The majority opinion suggests that the activation of endothelial cells, which causes them to create cell adhesion molecules and chemotactic factors that regulate the inflow of blood monocytes into the artery intima, is the first step in the disease. This causes these monocytes to change into macrophages, which then become lipid-rich foam cells after ingesting LDL particles, aiding in the development of atherosclerotic plaques. It's significant to note that NF-B plays a crucial function in controlling the expression of a variety of genes implicated in different aspects of atherosclerotic pathogenesis [74].

Inside vascular endothelial cells, NF-κB functions as a mediator that initiates the generation of chemotactic factors, pro-inflammatory cytokines, and adhesion molecules. In this capacity, NF-κB significantly contributes to the recruitment of monocytes, thereby exacerbating the progression of the disease. The complex cascade of events in atherosclerosis, marked by the accumulation of lipids and immune cells in arterial walls, is substantially influenced by NF-κB-mediated gene expression. Understanding these molecular mechanisms offers insights into potential therapeutic targets for managing the progression of atherosclerosis [74].

Cardiovascular diseases

Cardiovascular diseases (CVDs), which include ischemic heart disease, stroke, heart failure, peripheral arterial disease, and several other cardiac and vascular illnesses, are the world's leading cause of mortality and significantly lower life expectancy [75]. The -94 ATTG ins/del mutation in the NF-B1 gene promoter (rs28362491), according to Luo et al., [76], is a risk factor for coronary artery disease (CAD). An independent predictor of a poor long-term outcome in CAD patients was the NF-B1 mutant DD genotype. A study by Wang et al., [77] found that the mutant D allele at the rs28362491 locus may increase the susceptibility to CAD, suggesting that people who have this mutant D allele may be more susceptible to the condition. Vogel et al., [78] discovered that bearers of the del-allele of NF-κB1 ATTG ins/del have a greater risk of coronary heart disease (CHD) and lower plasma C-reactive protein (CRP) levels. The rs28362491 DD genotype of the NF-B1 gene has shown a substantial link with an increased prevalence of myocardial infarction (MI) and a larger severity of coronary artery lesions in the Chinese Han population [79]. In a similar vein, research by Jin et al., [80] points to a significant association

between the NF-B1 mutant DD genotype and vulnerability to acute coronary syndrome (ACS), as well as an increased degree of coronary artery involvement.Consequently, identifying this mutation could potentially offer an alternative approach to enhance diagnostic capabilities and evaluate ACS risk in susceptible patients.

The functional 94 ATTG insertion/deletion polymorphism within the NF-κB1 promoter is connected to an increased prevalence of endometriosis. Furthermore, the rs28362491 mutation in the NF-κB1 gene has been recognized as an independent predictor of adverse long-term outcomes in major adverse cardiovascular events (MACCEs). Consequently, identifying individuals with the NF-κB1 gene rs28362491 mutation could be valuable in guiding systematic care for those at a heightened risk of cardiovascular disease (CVD) [81].

Other diseases

NF-κB1 gene polymorphism contributes to a spectrum of other diseases as well. Within a family afflicted by antibody deficiency, a detrimental missense variation in NF-κB1 (691 C>T, p.R230C) was identified, confirmed through Sanger sequencing, and predicted to have deleterious effects through computational analyses [82]. The single nucleotide polymorphism (SNP) rs4648068, a functionally significant site that significantly affects cell motility and proliferation, has been linked to the transcriptional activity of NF-B1. Chen et al., [83]. Individuals may be predisposed to preferentially eradicate genotype B of the hepatitis B virus (HBV) due to the varied genotypes of SNPs in the NF-BIA promoter region. The variant genotypes of rs2233406 lead to reduced IκBα expression and heightened immune selection of HBV-related mutations, subsequently elevating the risk of hepatocellular carcinoma (HCC) in chronic HBV-infected patients [84]. A link between the NF-B1 gene polymorphism rs4648068 and an elevated risk of osteoporosis was discovered by Bogacz et al., [85]. Dilated cardiomyopathy (DCM) and the NF-B1-94 insertion/deletion ATTG polymorphism are related. Notably, the control group's genotype distribution for this polymorphism differed noticeably from that of DCM patients. A higher sensitivity to DCM was demonstrated in carriers of the ATTG2 variation (ATTG1/ATTG2 + ATTG2/ATTG2) [86].

The NF-B1 gene polymorphism in the Czech population showed a diverse range of 15 alleles (CA-repeats), with lengths ranging from 114 to 142 base pairs and comprising a range of 10 to 25 CA repeats. It's crucial to draw attention to the fact that persons with type 1 diabetes mellitus (T1DM) have an elevated prevalence of the NF-B1 gene's A7 allele (P 0.01). The proportion of the NF-BIA gene's A and G alleles, on the other hand, did not significantly differ between the control group and the sick group. However, Katarina et al., [87] found that the NF-BIA gene's AA genotype was associated with latent autoimmune diabetes in adults (LADA) (P 0.05). Interestingly, a diminished occurrence of the C allele was noted when comparing individuals with ischemic stroke to control subjects. According to these results, the NF-B1 gene promoter SNP (rs11940017, 1727, C/T) may have an effect on the Korean population's vulnerability to ischemic stroke [88]. In the study of Li et al., Chinese patients with the NF-B1-94 ins/delATTG WW genotype were shown to be more susceptible to developing psoriasis vulgaris [89]. This association was more pronounced within specific subgroups defined by characteristics such as an onset age below 40, a psoriasis area and severity index (PASI) greater than 20, being male, and occurrences appearing sporadically. Moreover, the NF-κB1 mutations rs7667496 and rs28362491 were identified as independent risk factors for type 2 diabetes (T2DM) [90].

Table 1: NF-κB1 gene polymorphism and associated diseases

Sl. No.	Polymorphism	Disease	Reference
1	94ins/delATTG	Ulcerative colitis	[46]
2	94ins/delATTG	Rheumatoid arthritis	[49]
3	94 ins/del ATTG (rs28362491)	Sepsis and acute respiratory distress syndrome	[48][49]
4	94ins/delATTG	Behçet's disease	[50]
5	94ins/delATTG	Cancer	[53]
6	rs28362491	Head and neck cancers	[59]
7	mutant D allele at rs28362491	Coronary artery disease	[76]
8	ATTG ins/del	Coronary heart disease	[77]
9	rs28362491	Major adverse cardiovascular events	[80]
10	rs4648068	Osteoporosis	[84]
11	rs11940017, 1727, C/T	Ischemic stroke	[87]
12	rs7667496 and rs28362491	Type 2 diabetes	[90]

Future Directions for NF-κB1 Gene Polymorphism Studies

The investigation into NF-κB1 gene polymorphisms has attracted significant research attention due to their potential links to a wide array of diseases and conditions, spanning from cancer to inflammatory and autoimmune disorders. Despite notable strides in unraveling the role of NF-κB1 gene polymorphisms in diseases, there exists a considerable realm of unexplored territory within this intricate genetic field.

Several promising avenues for delving into NF-κB1 gene polymorphisms include: Delving Deeper into Functional Implications: While many studies have established associations between distinct NF-κB1 gene polymorphisms and various diseases, the underlying mechanisms establishing these connections to disease susceptibility are still relatively enigmatic. Future investigations could focus on comprehending the functional ramifications of specific NF-κB1 gene variations, particularly how they impact NF-κB1 expression or activity. Such efforts could provide more profound insights into how these genetic changes contribute to diseases.

Complex disorders frequently result from the confluence of genetic and environmental factors. Subsequent research endeavors might explore the intricate interplays among NF-κB1 gene polymorphisms, additional genetic elements, and environmental influences to acquire a holistic comprehension of their collective impact on susceptibility to diseases. Innovative Approaches to Personalized Medicine: The realm of personalized medicine, which incorporates an individual's distinct genetic composition, is rapidly advancing to tackle a range of health conditions. Subsequent inquiries might delve into how understanding a patient's NF-κB1 gene polymorphisms could shape the creation of customized treatment strategies for conditions impacted by NF-κB1 activity.

Exploring NF-κB1 Polymorphisms and the Aging Process: Indications point to the possible engagement of NF-κB1 activity in the processes of aging and longevity. To deepen our understanding, upcoming research could explore the potential connections between NF-κB1 gene polymorphisms and age-related ailments, alongside the possible effects of these genetic variations on overall lifespan.

4. Conclusion

This review article has elucidated the far-reaching implications of genetic variations in the NF-κB1 gene across a broad spectrum of health conditions. The current body of research underscores the substantial influence of these genetic variations on the emergence and advancement of various diseases, encompassing cancer, inflammatory disorders, and cardiovascular problems. These findings underscore the essential role of NF-κB1 gene polymorphism in shaping the advancement of diseases, suggesting its potential as a promising avenue for personalized therapeutic strategies. The insights derived from this examination underscore the need for further research to fully comprehend the influence of NF-κB1 gene polymorphism on overall health outcomes. Nonetheless, the knowledge gained from this review provides a strong foundation for ongoing exploration and underscores the vital importance of genetic investigations in the realm of personalized medicine.

Conflict Of Interest

The authors declare that there is no conflict of interest.

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