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Association of TNF-α -308G/A Gene Polymorphism with the Risk of Autoimmune Diseases: A Meta-Analysis

by

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I dedicate this thesis to firstly Allah Almighty, Prophet Muhammad (SAW) and my parents, then my supervisor Dr. Shaukat Iqbal who support and motivate me throughout my thesis work.

CERTIFICATE OF APPROVAL

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Abstract

TNF-α play a key role in normal physiology, chronic inflammation, acute inflammation, cancer-related inflammation and autoimmune disease. TNF-α -308G/A showed association with many autoimmune diseases but the results are inconsistent. The aim of this study is to comprehensively evaluate the genetic risk of -308G/A gene polymorphism in TNF-α with few autoimmune diseases. We performed this meta-analysis to better evaluate the association between TNF-α -308G/A gene polymorphism with autoimmune diseases. Odd ratio (OR) and 95% confidence interval (CI) was calculated to assess correlation between TNF-α gene polymorphism and autoimmune disease. A total of 20 studies with 2840 cases and 3069 healthy controls was included in this meta-analysis. Our results showed that A allele of TNF-α -308 gene polymorphism was significantly associated with increased risk of multiple autoimmune diseases in overall analysis. Further subgroup analysis based on ethnicity, showed the significant association of TNF-α -308G/A gene polymorphism with increased risk of multiple autoimmune diseases, that was observed in allelic (A vs G) and heterozygous model (AG vs GG) in Asian populations and only in heterozygous model (AG vs GG) in European populations. But no association of TNF-α -308G/A gene polymorphism with risk of multiple autoimmune diseases in all other genetic models was observed in European populations and in African populations. Our findings indicated that TNF-α -308G/A gene polymorphism may serve as potential biological biomarkers for autoimmune disease in Asian population.

Keywords: Tumor necrosis factor-α, gene polymorphism, autoimmune diseases, meta-analysis

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Abbreviations

ACG	Angle-closing Glaucoma
AD	Alzheimer's Disease
ADMA	Asymetric Dimethylarginine
AF	Atrial Fibrillation
AIRE	Autoimmune Regulator
AMD	Age-related Macular Degeneration
APOE	Apolipoprotein E
BCG	Bacillus Calmaette-Guerin
CHD	Congenital Heart Disease
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRD	Cysteine Rich Domain
CVD	Cardiovascular Disease
DSP	Diastolic Blood Pressure
EM	Endometriosis
GLUT	Glucose transporter type
HLA	Human Leukocyte Antigen
HTN	Hypertension
ICD	Intracellular Domain
ICH	Intracerebral Hemorrhage
IGT	Impaired Glucose Tolerance
IL	Interleukin
IRF	Interferon Regulatory Factor
IRS	Insuilin Receptor Substrate

LPS	Lipopolysaccharides
LVH	Left Ventricular Hypertrophy
MHC	Major Histocompatibility
MI	Myocardial Infarction
MMP	Metalloproteinase
NF-κB	Nuclear Factor kappa B
OA	Osteoarthritis
OR	Odd ratio
PD	Periodontitis
PLAD	Pre-ligand Binding Assembly Domain
POAG	Primary Open Angle Glaucoma
PTPN22	Protein Tyrosine Non-receptor type 22
RA	Rheumatoid Arthritis
RIP	Receptor Interacting Protein
RPE	Retinal Pigment Epithelium
SBP	Systolic Blood Pressure
SNPs	Single Nucleotide Polymorphisms
SPPLs	Signal Peptide Peptidases
T2DM	Type 2 Diabetes Mellitus
TACE	TNF-α Converting Enzymes
TLab	T Lymphotoxin alpha
TNF	Tumor Necrosis Factor
TNFR	Tumor Necrosis Factor Receptor
TNF-α	Tumor Necrosis Factor-alpha
TNF-β	Tumor Necrosis Factor-beta
TRAF	TNF-associate factor
TRAIL	TNF-related Apoptosis Inducing Ligand
VP	Viral Protein
XFG	Exfoliation Glaucoma

Chapter 1

Introduction

1.1 Background

Major proinflammatory cytokine is the TNF-α that has been used to study due to its functions performed in normal physiology, chronic inflammation, acute inflammation, cancer-related inflammation and autoimmune disease [1]. Initially the word that is tumour necrosis factor, was divided into two forms, TNF-α that is also known as tumour necrosis factor derived from monocytes and TNF-β known as tumour necrosis factor derived from lymphocytes. In the 1970s, tumor necrosis factor (TNF-α) was indicated, in vivo and in vitro studies it was observed that a serum factor induced by endotoxin, provoke the death of most of the cells in different types of tumors [2]. It was initially obtained from the source i.e. serum of the mice that was infected with Bacillus-Calmette-Guerin after treatment occur with endotoxin and indicated to multiply the capability of endotoxin to develop haemorrhagic tumour necrosis [2]. TNF-α is the type II transmembrane proteins belongs to the constitute of a large superfamily of ligands and binds on the cell surface to two different homotrimeric receptors such as TNFRI and TNFRII [3].

Various signalling networks are due to the interplay in-between the tumor necrosis factor (TNF) and its receptor molecule that are central to the maintenance of homeostasis in human immune system [4]. Major source of TNF-α is the activated

macrophages, that can be composed of the variety of other cells such as astrocytes, keratinocytes, smooth muscle cells, fibroblasts, Kupffer cells and keratinocytes and tumour cells. TNF-α is prepared as a 26 kDa pro-peptide bounded by membrane. TNF-α converting enzyme (TACE) can secreted it upon cleavage [5]. Three similar subunits of 157 amino acids are used to form compact timer of TNF. The topology of main chain is for a single subunit, formed essentially a β-sandwich structure from two antiparallel β-pleated sheets. In viral coat proteins, it was observed that the main chain fold correlated to the jelly roll motif [6,7]. Including the hemagglutinin molecule of influenza or VP1, VP2 and VP3 of rhinovirus. The first non-viral protein that have this motif is TNF [7].

The gene of the TNF-α lies in the chromosome 6 short arm (6 p21.33) inside the major histocompatibility complex [8]. TNF-α gene of the human located on the class III region present in major histocompatibility complex (MHC), estimated 250 kb centromeric of the class I Human Leukocyte Antigens-B (HLA-B) locus and locus of 850kb telomeric in class II HLA-DR. It has been reported that the polymorphism of the TNF-α gene of the 5'-flanking region contributed to transcriptional regulation related to TNF-α production [9]. In TNF genes structural or regulatory defects may cause the development of MHC related illness particularly with the help of autoimmune and inflammatory elements [10]. Its gene location is inside the major histocompatibility complex and due to the biological actions, has more probability of that polymorphisms inside this particular position, may results in harmful spread of vast range of infectious and also some autoimmune diseases [11]. In the gene of TNF-α, the polymorphic allele may associated with a specific clinical subordinate of a disorder [12].

In the TNF promoter region, it was recognized that ten single-base polymorphisms can be formed [9]. Inside the promoter region, several polymorphisms was identified located near to transcription start site, especially at -308 (G$\rightarrow$A) [13]. Among the TNF-α variants, a polymorphism positioned at -308 affects the TNF-α expression. The polymorphism in single base within the gene of TNF-α in the promoter consists of 2 allelic forms, in which one is guanine that is also known as the TNFA$*$1 common allele and the second one in which guanine is changed

by adenosine i.e. TNFA∗2, the rarer allele located at position -308. In each in vitro and in vivo, it has been revealed that the rarer TNFA∗2 allele presence is contributed to improved sudden or restorative synthesis of TNF-α [14].

Though, no association was found between receptors numbers and susceptibility to cell. The cytolytic effect of TNF relies on the specific receptor's afinity [15]. Mediation of cytotoxicity required the internalisation of TNF and/or its receptors, with the ligand being destructed through a lysosomally dependent mechanism [15]. Because of the antitumour properties in vivo and cytotoxicity in vitro to few transformed cell lines, then the TNF was characterized [2].

The effective trigger for TNF is lipopolysaccharides (LPS) [16] and LPS effects include shock and fever that is mediated by the TNF. TNF also exhibit antiviral properties [17] and in the malarial infections it plays a protective role [18]. Usually it is involves in the pathogenesis of cachexia (wasting) [19], inflammatory tissue destruction and rheumatoid arthritis [20], replication of viruses is also inhibited by TNF [21] and it may induce major histocompatibility complex (MHC) antigens as immuno-regulator like interferons [22].

Major cells that produce TNF in brain were microglia and when these are activated by LPS, produced much more TNF [23]. TNF-α causes pulmonary oedema, cardiomyopathy, left ventricular dysfunction and many other diseases, when it is over-expressed [24]. Patients with rheumatoid arthritis (RA), autoimmune unstable angina diseases, circulating level of TNF-α was measured [25].

Level of TNF-α and the genetic relationship with polymorphisms in gene are responsible for different disorder and clinical finishing line including rejection after kidney, liver and heart transplantation and many other disorders [26,27]. Normal cell proliferation is stimulated by TNF-α stimulates, that exerts cytolytic activity in response to tumour cells and results in antiviral, immunoregulatory and inflammatory effects [28]. Many additional functions performed by TNF-α that were associated with lipid metabolism, endothelial function, coagulation and insulin resistance. It was reported that it is an important cytokine enhancing immune and inflammatory responses [29].

When tissues and organs were exposed to harmful stimuli including toxic cellular components, microbial pathogens or irritants, results in formation of inflammation. To ensure regulation of the inflammatory mechanism by the process of recruiting appropriate leukocytes. A host of extracellular molecular regulators that controlled these events such as members belongs to the families of cytokine and also to the families of chemokine that enhance both complex intracellular signalling control and immune cell recruitment mechanisms that characterize inflammation [30]. When the immune system recognizes and attacks host tissue, result in occurrence of autoimmunity [31].

Host genes and the environmental factor controlled the autoimmune disorder. Through affecting the overall quality and reactivity of the cells of the immune system, both can increase susceptibility to autoimmunity. Antigen and organ specificity is influenced by antigen expression, antigen presentation and recognition and the state and response of the target organs. In general population, up to 3-5% autoimmune disorder occur. Several of these disorder is categorized according to what organs and tissues are affected by the damaging immune response [32].

Central vision is affected by the Age-Related Macular Degeneration (AMD), which retard one's ability to recognize faces, drive and read. The term age-related macular degeneration is used to describe hypo and hyper pigmentation occurred in Retinal Pigment Epithelium (RPE) cells of retina, enlargement is contributed to drusen. Major risk factors associated with AMD are age and family history about development of AMD in family members [33].

The complex syndrome recognized as asthma due to the chronic inflammation presence in the lower airways, result in varied obstruction in airflow and results in recurrent episodes of coughing, breathlessness, wheezing and chest tightness [34,35]. A complex interconnection between genetic variants and factors in environment that confer susceptibility causes asthma. The first specific chromosomal region implicated in asthma is HLA [36]. The pathogenic degeneration of the nervous system especially in brain is called Alzheimer's disease (AD) which is caused due to

synthesis of intracellular neurofibrillary tangles and extracellular amyloid plaques. The key pathological components of AD are neuro-inflammatory changes, including chronic microgliosis. By evoking the activity of pro-inflammatory cytokines mainly IL-6, IL-1β and tumor necrosis factor-α (TNF-α), contribute to disturb tissues surrounded the brain, after this activated microglia play a deleterious role. Multiple roles have been played by increased regulation of pro-inflammatory cytokines in all processes such as neuroprotection and also neurodegeneration [37]. The susceptibility for Alzheimer's disease considering different types of populations, was found to increase by APOE allele that is E4 allele known as Apolipoprotein E [38].

Endometriosis is the common, persistent, inflammatory and gynecological disease depends on estrogen. Endometriosis is caused by grafting of endometrial tissue outside of the uterus [39]. About 10–15% of all women of reproductive age are affected by endometriosis and endometriosis also affect the 30% of all infertile women [40]. The mediate pathogenesis of endometriosis by impaired suppression of immune response, chronic inflammation, oxidative stress and deficient fibrinolytic mechanisms. Inflammation, steroid response and tumor suppression are responsible for gene variations, may furthermore contribute to the occurrence of the disease [41].

The chronic effects in the supporting tissues of the teeth is considered as Periodontist. Periodontal tissues become inflamed, due to bacterial infection, and are gradually demolished due to activity of inflammatory process. The ligamentous support between teeth and alveolar bone become loosen, then in consequence the resorption of alveolar bone takes place by itself and the teeth starts to move and are finally fell down if the disease left untreated [42]. The gradual loss of the ganglion cells of retina, is due to neuro degenerative disease called Glaucoma [43], irreversible visual field defects are caused by this disease [44]. Over 60 million people worldwide are affected by irreversible blindness. For Primary Open Angle Glaucoma (POAG), five genes have been considered as causative gene. The new susceptibility loci have been developed for Primary Open Angle Glaucoma (POAG) such as regulatory region of 8q22 [45]. An autoimmune inflammatory

rheumatic disorder called Rheumatoid Arthritis (RA). Approximately 0.5–1% of the people is affected due to this disorder [46] and eventually leading to joint destruction and disability by causing chronic synovial inflammation [47].

A group of heart anomalies is represented by congenital heart disease that comprises valve defects, septal defects and some outflow tract abnormalities [48]. It is considered as common group of birth defects of more clinically severe condition when the prevalence would be 2–3 live births per 1000 in number, when including moderately sever congenital heart disease increasing to 6 per 1000 [49]. Exact genetic, epigenetic and environmental mechanism is like to be multifactorial. However, the identification of genetic reasons of abnormalities of the heart is accelerated by the new technologies development that includes next generation sequencing, also the copy number variants and single-nucleotide polymorphism [48]. The diagnoses of angina pectoris, silent myocardial ischemia and myocardial infarction E2 are included in coronary heart disease [50]. The factors which contribute to vascular inflammation and which are synthesized mainly by the innate immune system's cell are IL-18 [51], matrix metalloprotienase-9 (MMP-9) [52] and soluble CD40 ligand (sCD40L) [53]. The susceptibility of Coronary Heart Disease associated with tumour necrosis factor-α (TNF-α) [54].

Involvement of entire joint in an age-related condition is Osteoarthritis(OA), comprises of underlying subchondral bone, adjacent muscles, ligaments, the joint capsule and synovium. The other causative factors of diseases are osteophyte formation, loss of hyaline articular cartilage and subchondral sclerosis [55]. The most significant problem worldwide is Osteoarthritis (OA). The major impact on an individual's quality of life is pain and loss of joint function and society has significant economic burden due to loss of time at work and increasing health care costs. As a result of both environmental and genetic factors, there is variable involvement of the synovial joints in population. Obesity is the most important risk factors for this condition [56]. A spontaneous extravasation of blood is Intracerebral hemorrhage (ICH) into brain parenchyma and is the least treatable and fatal form of stroke often [57]. On the basis of the position of ruptured blood vessels inside the

brain, ICH is grouped into lobar or nonlobar. Vascular pathologies respose differently in different locations [58]. Impaired Glucose Tolerance (IGT) is primarily cause of Type 2 Diabetes Mellitus (T2DM), which induces dysfunctiong in islet β-cell and their subsequent destruction. The β-cell dysfunction effected many parts such as liver, also skeletal muscle and especially adipose tissues, there is ensuing insulin deficiency [59]. A metabolic disorder, Type 2 diabetes mellitus (T2DM) can be more clearly defined as multi-stimuli crucial factors, also pro-inflammatory enhancers played crucial role for the origination of insulin resistance and T2DM development due to enhanced activity of transcriptional mediator pathways and involvement of oxidative stress.

TNF-α as main proinflammatory mediator that determinly involved by causing inflammation of low-grade and tissue-specific by means of provoking some other molecular pathways enhanced by transcription, results in insulin resistance, also enhance the development of T2DM. Expression of serine phosphorylation of insulin receptor substrate-1 (IRS-1) and also the glucose transporter type 4 (GLUT4) is reduced by TNF-α which are considered as the critical enzymes for insulin synthsis. In peripheral tissues and adipocytes, the insulin resistance is elevated by the increased level of TNF-α, that contributed to progression of T2DM by disrupting the insulin signalling through serine phosphorylation [60].

A skin disorder of common acquired depigmentation is known as Vitiligo, spread by the presence of white macules in skin. The disease develops at a rate of approximately 1–4% of the world population. Currently, a multifactorial hypothesis is the most famous theory of development of vitiligo according to which, specific environmental and genetic factors induces the vitiligo macules to occur [61]. The harmful effects of end-organ injury increases by hypertension, total mortality and maternal/fetal vulnerability. It causes the death of almost 7.5 million of population in every year, throughout world. For hypertension, potential molecular therapeutic targets comprises the asymmetric dimethylarginine (ADMA), toll-like receptors, molecular patterns associated with some danger, interferon-γ, interleukin-17α, aminopeptidase A, interleukin-6 and endothelin-1 receptors [62].Chronic Obstructive Pulmonary Disease (COPD) is defined as obstruction of airflow associated

with emphysema, this obstruction of airflow may be assisted by hyper-reactivity of airways and may be partially alters and/or as a disorder state characterized by the chronic bronchitis presence [63]. Levels of Tumour necrosis factor(TNF)-α enhanced inside the airways of affected people suffering from chronic obstructive pulmonary disease and have some contribution to progression of disease. By remodelling of the airways and disturbed function of smooth muscle (i.e. airway hyperresponsiveness), TNF-α may contribute to pathogenesis of COPD. At location -308 of the TNF-α gene promoter (TNF1/2) a guanine to adenine substitution has been associated with COPD [64]. Many studies were conducted to find the association of TNF-α with several disorder including Age-Related Macular Degeneration [65], Asthma [66], Alzheimer's Disease [67], Endometriosis [68], Periodontitis [69,70], Congenital Heart Disease [71], Coronary Heart Disease [72], Hypertension [73], Glaucoma [74], Osteoarthritis [75], Rheumatoid Arthritis [76], Type 2 Diabetes Mellitus [77], Vitiligo [78], Chronic Obstructive Pulmonary Disease [79]. A single study might show less significant results for the overall effects because of a minor size of sample and a comprehend analysis may show significant verification about the linkage of the gene polymorphism with risk of disease in the different studies. Yet, meta-analysis has not been done to assess the interrelation of TNF-α gene polymorphism with different disease.

1.2 Problem Statement

To evaluate the more significant association TNF-α gene polymorphism with different types of disease, meta-analysis was performed.

1.3 Aim

Genetic factors, activation of cytokines and immune-inflammatory process contributed to pathogenesis of various autoimmune diseases. Data about tumor necrosis factor-alpha (TNF-α) polymorphism with many disorders in previous years are

conflicting. So present work aimed to assess the association of TNF-α 308G/A polymorphism to the progression of various autoimmune diseases by using meta-analysis.

1.4 Objectives

The objectives of our study are:

- To analyze the association between TNF-α -308 G/A with various autoimmune diseases by using meta-analysis on overall basis.
- To assess the association of TNF-α -308 G/A with autoimmune diseases on the basis of subgroups based on ethnicity.

Chapter 2

Literature Review

2.1 Background

Microbial invasion, injury or inflammatory agents threaten the immune system to produce humoral factors and cytokines to protect host. The complex defence system restores normal homeostatis successfully in some cases. However, on the high level of immune regulators may become the cause of deletion of the host. Various immune regulatory injuries are investigated by researchers likewise autoimmune diseases, anaphylactic shock and other immune-related diseases [80].

Immune pathways are stimulated by interaction of genetic predisposition with environmental variables that results in tissue destruction. The primary function of immune system is to provide defence as well as safety against microbes. The pathology is induced by two major categories of pleiotropic immune system. One in which immune system and their components fail to respond defensively in response to pathogens in case of immune-deficient syndrome. This disruption in tolerance is the result of initiation of autoimmune disease [81]. Hence, classifying autoimmunity, its two types named; pathological as well as pathological [82]. The transient or short-lived without appearance of clinical sign of diseases is considered in physiological autoimmunity [83]. It helps to eliminate maintain homeostasis by

degrading self-antigens and foreign antigens. Classical or pathological autoimmunity develops due to disturbance in immune tolerance. Autoantibodies as well as self-reactive lymphocytes also take part in inflammation, which can cause tissue damage [81].

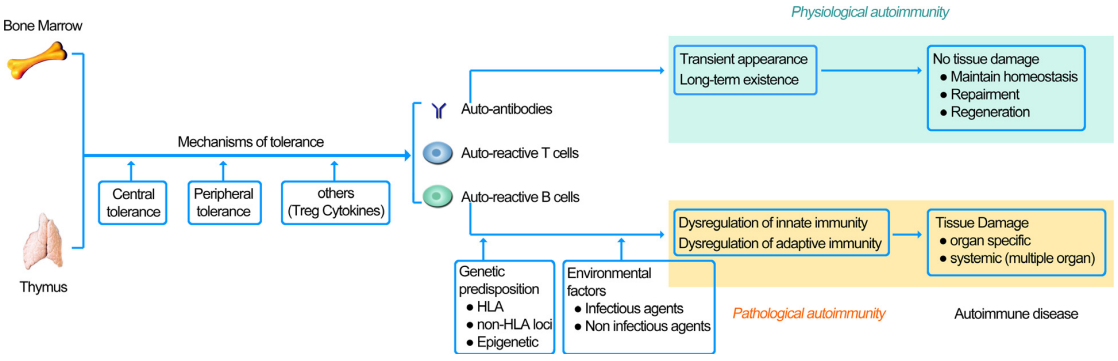

FIGURE 2.1: The Progression of Autoimmune Disease [81].

In Finnish APSI families have mutations in gene of autoimmune regulator (AIRE) that was detected with the help of positional cloning [84]. In thymus, self-antigen can be presented by influencing negative selection [85]. MHC is found on genes position on the short of chromosome 6 that is responsible for antigen presentation and is mandatory in distinction of self from non-self. Human-leucocyte antigens (HLAs) are gene products of MHC in humans. Role of genetic variables in association with autoimmune diseases have been reported by many linkage studies [86].

The gene of protein tyrosine phosphatase non-receptor type 22 (PTPN22), is found on hematopoietic cells. Immune signalling is regulated by dual role of PTPN22. In specific immune system, T cell stimulation is prevented by the PTPN22. While in case of non-specific immune responses, myeloid type 1 interferon production is enhanced by PTPN22. Pre-disposition of genes within families provide information about role of other loci such as IRF5-TNPO3 encoding interferon regulatory factor 5 and transportin 3. Gene has important role in Toll-like receptor (TLR) signalling cascade and regulate the apoptosis stimulated by ligand that is TNF-related apoptosis-induced. However, dendritic cell development is induced by this gene as well as its crucial role in polarization of inflammatory macrophage. IRF5-TNPO3 is susceptibility gene for RA, UC, PBC as well as SLE [87]. BTB and

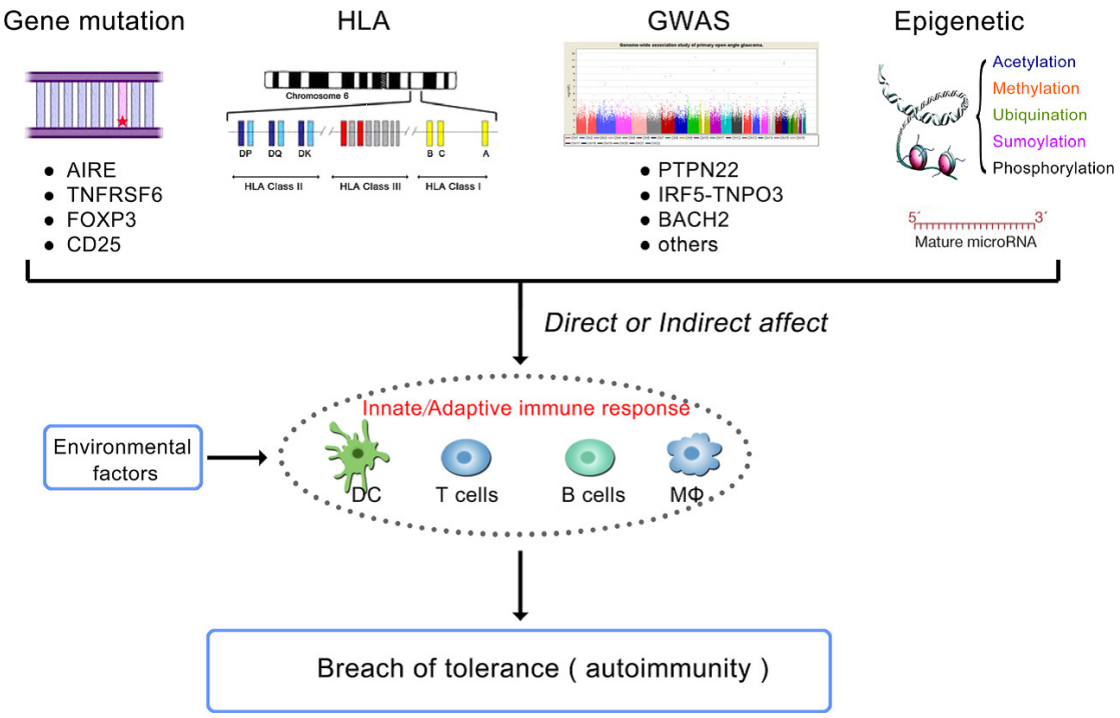

FIGURE 2.2: Genetics of Autoimmunity. Several Variations in Multiple Genes, HLA Susceptible, Non-HLA Loci as well as Epigenetic Mechanisms Showed in Determined Autoimmune Disorders [81].

CNC homolog 2 (BACH2) is a transcription inhibitor mandatory regulator for specific as well as non-specific immunity [88], formation of B and T cells [89,90]. BACH2 has been recognized as mediator that maintains the equilibrium between immunity and the tolerance and can also causes the loss of tolerance [91].

The concordance rate in monozygotic twins may vary in the range of 12-67% [92], demonstrated that factors excluding genetic susceptibility may be present. DNA methylation is the example of epigenetic mechanisms, that contributed to the loss of tolerance [93]. Several events in epigenetic mechanisms may serve as a support that link the environmental and genetic interaction that results in autoimmunity [94]. Nutrition, hormones, the microbiota, silica solvents, infectious responses, tobacco smoke, pharmaceutical agents, heavy metal, ultraviolet light, silica solvents, vaccines are considered as environmental factors [95]. Infectious agents was vast studied factor of environment [96]. The example of the molecular mimicry is acute rheumatic fever which results in tolerance loss and the synthesis of the T-cells [97]. In 1964, the term molecular mimicry was first develop [98]. Cytokines are considered as important modulators of inflammation, that participates in acute

and chronic inflammation. Important pro-inflammatory cytokines are interleukin-1 (IL-1), IL-6 and tumour necrosis factor (TNF-α), all of them activate by type I cytokine receptors.

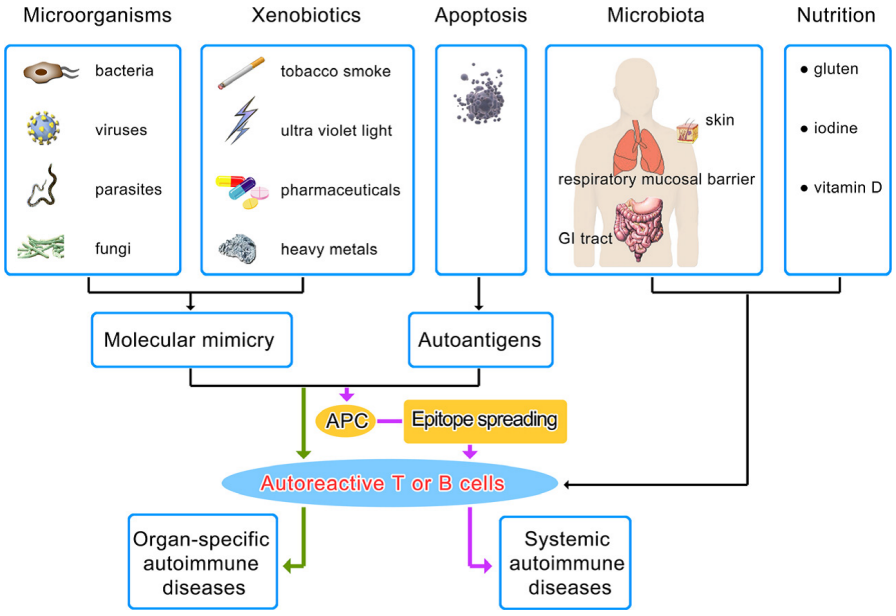

FIGURE 2.3: Environmental Factors Involved in Autoimmunity [81].

2.2 Cytokines Classification on the Basis of Immune Response

Cytokines can be grouped on the basis of inhibition and promotion of inflammation, receptors used for signalling or adaptive immune system. The cytokine that is Cachectin or Tumor necrosis factor is significantly involved in the pathophysiology of diverse diseases. The TNF exerts toxic effects on host cells by interacting with other harmful enhancers such as interferon-γ and interleukin-1 [80].

2.3 Tumor Necrosis Factor-alpha (TNF-α)

Firstly, tumour necrosis factor was divided into two factors such as tumour necrosis factor derived by monocytes that is TNF-α and tumour necrosis factor derived by

lymphocytes that is TNF-β . TNF-α is the typical constituent of the superfamily of TNF of type II transmembrane proteins that contains 19 interacting ligands and 30 receptors with crucial activities in differentiation of cell, immunity, inflammation or apoptosis [30].

2.3.1 Discovery

Crude bacterial extracts was used by Dr. Williams B. Coley to treat tumor patients more than 100 years ago. He observed that bacterial extract is responsible for causing tumor necrosis.

As tumors were regressive, patients after getting bacterial extracts induced systematic infammatory. Later on in 1975, the major inflammatory enhancers was described as a major factor to induce lysis in tumor cells. The protein factor that present in endotoxin-treated animal serum cause lysis in tumor cell. So it was termed as tumor necrosis factor.

The gene of TNF was identified and defined in 1984. A gene that was extracted from T lymphocytes, encoding the protein in 1968 and known as T lymphotoxin alpha (TLα) and also characterization and isolation of the gene has been done. Both these genes belong to the identical family. So, TNF was termed as TNF-α, while TLa was termed as TNF-β.

In 1985, a protein was purified by Nobel Prize Winner Dr. Bruce Beutler and his colleagues, known as cachectin, source was unabsorbed endotoxin treated macrophages. In affected murine, this protein produced the septic shock and wasting (cachexia) [1].

2.3.2 Synonyms

Endotoxin induced factor in serum is also known as tumor necrosis factor alpha (TNF-α), differentiation inducing factor or cachectin.

2.3.3 Definition

Family of tumor necrosis factor consists of TNF-α, TNF-β, Fas ligand (FasL), CD40 ligand (CD40L), LIGHT (receptor activated due to T lymphocytes), TNF-related apoptosis inducing ligand (TRAIL) or many crucial cytokines contribute in induction of acute phase reaction, apoptosis, processes of physiology, lysis of tumor or systematic inflammation.

2.3.4 Sources

Macrophages produces TNF-α. But TNF-β is mainly synthesized due to T lymphocytes. Even in low concentration, TNF-α and TNF-β can also be expressed by other types of cells.

2.3.5 Production

A report was generated that gram negative bacteria, *Serratia marcescens* used in vivo for the synthesis of soluble factor in response to endotoxin and result in tumor necrosis. Tumor necrosis factor was also synthesized in response to endotoxin present in serum of animal infected with Bacillus Calmette-Guerin (BCG). These animal's serum has cytotoxic effect on tumor cells especially in vitro instead of in vivo and it was reported that for cellular source of TNF is the macrophages. Matthews was one who demonstrates that in vitro, macrophages synthesized TNF [99]. Activated macrophages secretes it primarily, it may be synthesized by other types of type of cells like T-cells, mast cells, monocytes, NK, fibroblasts, neurons and keratinocytes [30].

TNF-α has a molecular mass of 26kDa and is formed like transmembrane precursor protein (mTNF-α), after which rough endoplasmic reticulum is responsible for its transfer to Golgi complex and then recycling endosome to surface of cell. Before the breakdown of TNF-α monomers due to metallopretease, these monomers combine on the plasma membrane in the form of non-covalent trimers. TNF-α converting

enzyme is TACE or ADAM17. Soluble TNF-α (sTNF-α) of 17kDa breakdown due to TACE results in the manufacture of ecto-domain and it is the trimer of sTNF-α which consists of the strong ligand which initiates receptors of TNF. After the cleavage by TACE, signal peptide peptidases (SPPLs) SPPL2a and SPPL2b purified the membrane stub. This cleavage develops intracellular domain (ICD) which translocate towards nucleus and initiates signalling of pro-inflammatory cytokine, specifically IL-12 expression. So, the forerunner of TNF-α factor is participated to lot of events of cleavage to produce vigorous modulators of infection [30].

2.3.6 TNF-α Receptors

The attachment of any of these receptors such as TNFR1 and TNFR2 [99], through which molecular actions of extracellular sTNF-α and mTNF-α occurred. Two different TNFR elements differ on the basis of molecular mass, glycosylation, proteolytic fingerprints, ligand-binding affinity or immune-reactivity. Molecular mass of TNFRα is 75 kD, While TNFRβ have 55kDs. Monoclonal antibodies used for half refined TNFR fragments by which confirmed the existence of two distinct receptors, two antibodies classes were identified which reacted particularly with either TNFRα or TNFRβ. In several cell types, the receptors are expressed in a relatively different amount starting from 100-1000 molecules for every cell [100]. In different cell types the receptors were expressed such as endothelial cells and leukocytes, TNFR1 more frequently expressed, while TNFR2 is predominantly expressed. It was studied that different types of biological effects have been affected by these two TNFRs. Pro-inflammatory effects of TNF-α seems to be enhanced mainly due to TNFR1.

Single transmembrane glycoproteins were in both TNFR1 and TNFR2 with 28% similarities in extracellular regions. In this area, four cysteine-rich domains (CRDs) are the most common one, one and all consist of a pre-ligand binding assembly domain (PLAD) and three cysteine-cysteine disulphide bonds that are found to be

contributed to receptor's trimerisation. Carboxyl-end of TNFR1 have an intrracellular death domain (DD) due to variation in receptors by interacting with some adaptor factors, contributed to cause the inflammation or apoptosis. For both signalling pathways, it required the replacement of TRADD into TNFR1. Later on, one of two complexes is generated, either following internalization (complex II) or at the surface of cell (complex I). Formation of complex I required TNF-associated factor 2 (TRAF2) and receptor-interacting protein (RIP), results in the kinase pathways which provoke gene expression of pro-inflammatory factors. On other hand, the first complex unable to function properly, formation of Complex II causes apoptosis. Inside the Complex II, the recruitment of pro-caspase-8 and FADD occurred to synthesize death-inducing signalling complex due to proteolysis and internalization in the receptor.

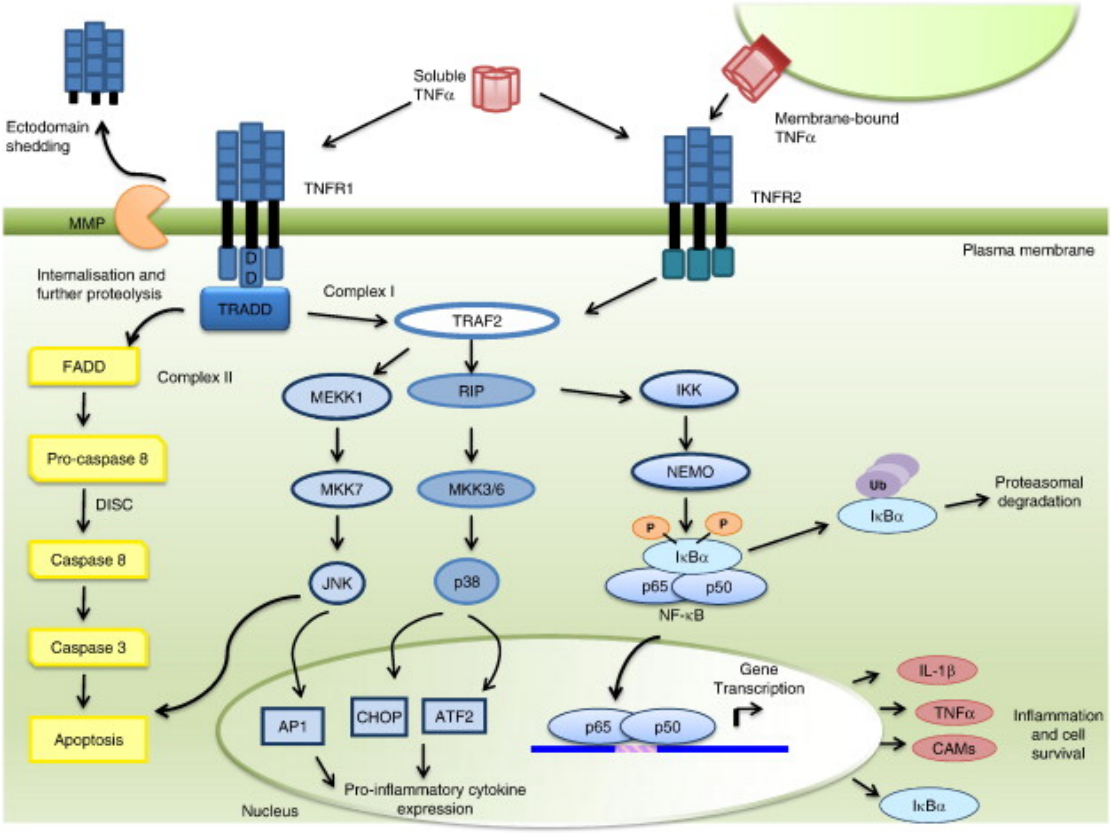

FIGURE 2.4: Signalling Via The TNFRI and TNFRII [99].

TNFR1 activation stimulates the expression of NF-κB to a potential in large proportion as compared to the TNFR2. Scatchard analysis that included binding of ligand to both receptors reported that TNFR1 show greater closeness to TNF-α.

So, for the enhancement in the pathways of proinflammatory signalling, TNFR1 was crucial one [30].

2.3.7 Genes of TNF-α

Murine or human genes of TNF-α lie on the region in chromosome 17 and also the chromosome 6, and following by gene of TGF-β. A single copy contains both genes, contains 4 exons and are approximately 3 kilobases in size. In nuclear factor kappa B, the DNA attachment sites was reported inside the TNF-α gene promoter region. TNF-α exist in two appearance such as soluble form (sTNFα) and membrane-bound form (mTNFα). mTNFα of human consist of 157 amino acids and leader sequence of 76 amino acids. While only the soluble form of TNF-β (sTNFβ) subsists. 80% similarity were found among human TNF and mouse TNF [1].

2.3.8 Primary Structure of TNF

Long protein having 157 amino acid and at position 69 and 101, two cysteine residues are present and function of these residues is the synthesis of disulphide bridge. In human, mouse or rabbit TNF have no methionine residues. Tryptophan residues in TNF are species-specific. Adjoining arginine residues are present at 31 and 32 position and the residue at 32 position favours instability to TNF. About 79% similarities exists among the amino acid sequences in human TNF amino acid and murine TNF.

2.3.9 Secondary Structure of TNF

Chou-Fassman method predict the TNF secondary structure and it was reported that about 60% of β-sheet is present in the protein. This analysis also describe in TNF structure consists of alpha-helix and also β-sheet breakers. The presence of TNF disulphide bond in the surface of protein was reported.

2.3.10 Tertiary Structure of TNF

X-ray crystallography analysis have showed TNF crystal structure. It was observed that anti-parallel β-sheet are present in every subunit of trimeric molecule and it indicated the unique edge-to-face packing. A jelly-roll motif showed by crystal structure, which is the feature of viral coat proteins. It was reported that the trimer is the biologically active form of TNF.

2.3.11 Structure Function Relationship of TNF

It was studied that the structure of TNF showed some effects in biological properties. It was observed that that cleavage of 10 amino acid residues result in significant biological activity loss. The other cause of loss of biological actions was due to substitution of residues at different locus [100].

The gene group of TNF lies within MHC in adjacent locality with some responsible genes of immune regulation. Self-reactive and highly expressed T cells have been removed by apoptosis was due to TNF. TNF and related cytokines in the TNF regions contributed to the progression of several infections and some processes to protect from disorders was considered as significant way for discovering good therapeutic drug targets [10].

2.3.12 TNF-α Molecular Mechanisms

The TNF's effects have been studied extensively due to the mechanism of molecule. Importantly, researcher studies showed the action of TNF where it initiates action of the protein such as of mitogen-activated protein kinase (MAPK)/AP-1 pathways and Ikappa B (IκB) kinase (IKK)/NF-κB, that became necessary for the action of pro-inflammatory cytokines, also acknowledge the induction of apoptosis and necrosis. TNF can sticks to its receptors TNFR1 and TNFR2, that are may soluble or membrane bound. TNFR1 and TNFR2 each link with both mTNFα and sTNFα. Therefore, signalling of TNFR1 is immensely initiated due to each

forms such as sTNFα and mTNFα, but signalling of TNFR2 may be initiated because of mTNFα. TNFR1 express all over, on the other hand TNFR2 usually manifest on cells of endoepithelium and lymphocytes.

On binding, homodimer is formed due to both receptors, moreover they cannot have formed a TNFR1/TNFR2 heterodimer. Domain of death is present in TNFR1, that enables to link with other proteins having domain of death but no domain of death is present on TNFR2 [1].

2.3.13 TNF Inhibitory Proteins

In human serum and urine, two protein was identified which can stopped TNF process in culture of cell. These proteins are known as TNF-BP I and TNF-BP II can stick with TNF-α to a lesser for TNF-β. When TNF-BP partial amino acid sequences were known, then TNF-BP considered as shorten pieces of outer area of particular TNFR [100].

2.3.14 Biological and Pathological Functions of TNF-α

TNF play significant roles in pathological and physiological activities. It was studied that both TNF-α- or TNFR-deficient mice take part in the maintenance of embryonic growth and awakening cycle necessary for follicle of lymph node or formation of germinal centre and also host defence opposing viral or bacterial infection. An endogenous pyrogen was shown by TNF that causes fever. Cachexia, depression and wasting syndrome were caused due to less quantity of TNF.

In critical inflammatory reactions, TNF is key mediator. It produces itself and also induces synthesis of some chemokines and inflammatory cytokines. In autoimmune diseases vital role played by TNF including inflammatory bowel disease, rheumatoid arthritis, systemic sclerosis, multiple sclerosis and systemic lupus erythematosus. TNF was considered as major threat for cancer development, conquering, metastasis and tumorigenesis.

Cancer-associated chronic inflammation is due to the TNF. TNF secretion was decreased by the prolong usage aspirin and significantly decrease the incidence of human colorectal colon cancer. Furthermore, in biopsy samples from human breast commonly TNF is identified, renal cancers and ovarian, also adjacent in stromal cells.

Environmental exposure to asbestos result in the formation of TNF, that enhances the progression of human malignant mesothelioma [101]. Cells or tissues were mainly affected because of the necrosis factor-alpha. TNF-α also change development of adipose tissue and also metabolism. TNF-α involved in the pathophysiology of two opposite metabolic diseases [102]. In another study, it was indicated that adipose tissue cytokine is immensely over-activated in the tissue of rats or individuals. And also obesity-linked insulin resistance that is locally generated by the TNF-α [103].

In vitro studies reported that the TNF-α is extremely affected on metabolism of lipid and adipocyte differentiation. TNF-α effects the expression of many prteions necessary for lipogensis [104,105]. By different mechanisms, TNF can also inhibit lipolysis in adipocytes [106,107]. TIARP may show as an salient enhancer of the pathological or physiological reactions of TNF-a on many feature of adipocyte physiology [108].

2.4 TNF-α Gene Polymorphism

Gene of TNF-α lies on tiny arm of chromosome 6. The gene is present inside the histocompatibility complex, whereas high TNF-α production genetic is directly associated with TNF-α loci changes in MHC. The diversity in structures observed in the TNF-α promoter [13]. A prominent polymorphism lies at nucleotide position -308. The polymorphism for TNF-α inside promoter region of gene gives two allelic structures, first is guanine allele (TNFA$*$1) and the other is rare adenosine allele (TNFA$*$2) at position -308. The second one is related to synthesis of TNF-α [13].

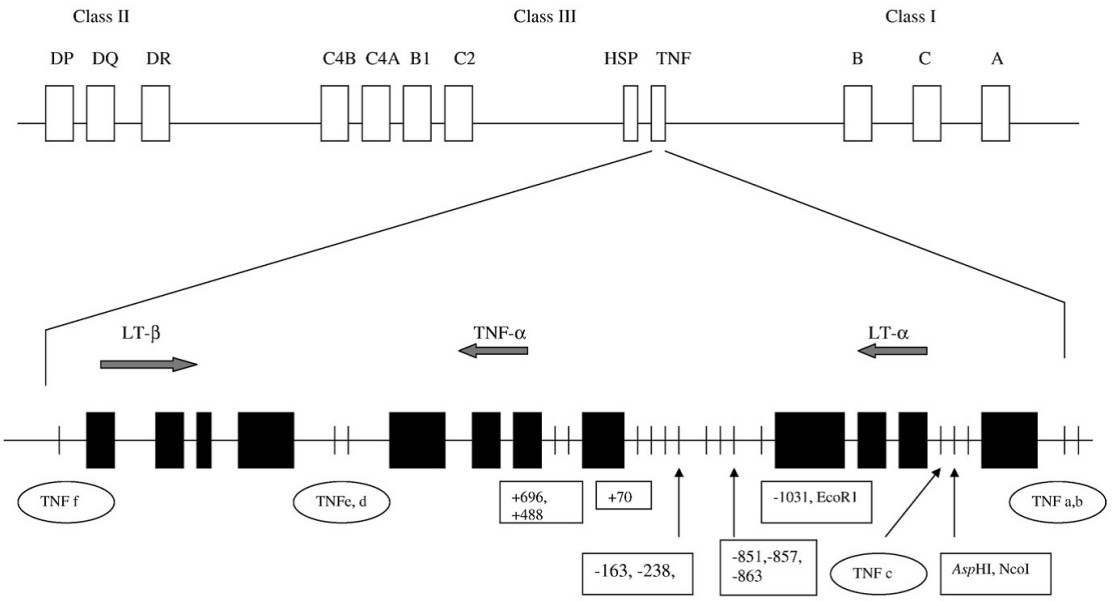

FIGURE 2.5: TNF Gene on Chromosome 6 Indicating Position of Microsatellites and SNPs [13].

TNF-α gene SNP is directly related to the functional significance of the regulating TNF-α production [109]. Though TNF-α level is a multifactorial process of regulation, so localized TNF-α is of considerable significance, that managed due to some important polymorphisms [110].

Single nucleotide polymorphism (SNP) in this region is A or G and correlates with the level of expression of this cytokine so that higher occurrence of G nucleotide is associated with decreased expression of TNF-α and higher occurrence of A nucleotide is associated with increased expression of TNF-α [111].

Human TNF-α gene polymorphism may be salient in the sensitivity or seriousness of diseases or inflammatory state that may result in many autoimmune diseases and cancers [11]. In TNF-α -308G/A gene polymorphism, A-allele contributed to increase in vitro TNF-α transcription and TNF-α level in activated human white blood cells [112]. In TNF-α -308G/A gene, A-allele has a higher transcriptional activity as compared to -308 G allele. TNF-α -308A allele marks susceptibility to many autoimmune, inflammatory diseases such as Systemic lupus erythematosus, Celiac disease and Alzheimer Disease, Rheumatoid Arthritis, Asthma, Type 2 Diabetes Mellitus etc and various cancers [113].

2.5 Autoimmune Diseases

2.5.1 Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is considered as sixth main death because that occur in the Western world, accounting for much unwholesomeness and impermanence [114] and it is roughly calculated as it increases to third-main source to year 2020 [115]. Main crucial surrounding biologic element is cigarette smoking. Anyhow, the cigarette smokers develop clinically notable airway obstruction are only 15%, host factor seem to take significant part to figure out susceptibility of an individual to catch a disease [116]. Besides cellular influx, there are increased amounts of the cytokines such as interleukin-8 and tumor necrosis factor (TNF)-α in COPD patients in their airways. Among healthy smokers, although, the TNF-α cytokine is not remarkably increased, which suggests that the indication of elevated amounts of this cytokine may determinate the inflammation in individuals with COPD because of cigarette smoking [117]. Inhalation of TNF-α by humans shows that it enhances the numbers of neutrophils in the airway [118]. Extracellular elastolytic activity increases by adherent neutrophils due to the presence of TNF-α [119]. Enhanced proteolytic activity has been observed for long time period to be crucial in the development of emphysema and also the intensification of proteolytic activity with the help of TNF-α could help in progressing the disease in COPD [120].

The patients who are exposed to cigarette smoking have abnormal production of TNF-α are more susceptible to develop COPD. Control of allele A with the increased TNF-α formation, it contributed in increased susceptibility to progression of COPD due to smoking and the development of acute/chronic infection. The patients with TNF-α -308 A polymorphism have more chances to suffer from COPD through the production of elevated amounts of TNF-α in relation with large amount of factors (e.g., any infection and cigarette smoking). The progression of COPD may be accelerated due to the presence of increased amounts of the cytokines in the airways. The outcome would be patients having polymorphism

who have more acute disease and a poor prognosis. The highly remarkable impermanacy in patients homozygous for change in structure is greatly indication of an association of the AA genotype with poor prognosis [121]. TNF-α may come up with the remodelling of airways and alteration of function of smooth muscle cell that is present in COPD [64]. Several studies has revealed the link of TNF-α -308G/A gene polymorphism to risk of COPD [122,123,124]. But in some studies, no relation was shown among them [79].

2.5.2 Osteoarthritis

This is most general form. It may be the biggest reason of ache and ailment throughout the world [125]. In western countries, 1%–2.5% of the gross national product is estimated as total economic burden for arthritis [126]. It shows symptoms like pain and stiffness, which results in decreased quality of life and a loss in movement [127]. In OA, all tissues of the synovial joint that includes cartilage and the underlying bone, nerves and muscles, may result in joint damage [128]. The main risk factors that increases the OA prevalence, is an increase in life expectancy and obesity and in the UK and some other populations throughout the world [129], making it a major issue of public health [130].

The pivotal mediators involved in enhanced catabolism and disturbed metabolism of joint tissue involved in OA are synthesized inflammatory factors. The cytokines that are vital pro-inflammatory, take part in pathophysiology of OA are TNF, IL1β and IL6 and some others factors have also been involved including IL15, IL17, IL18, IL21, chemokines and leukemia inhibitory factor (LIF). Among all the pro-inflammatory cytokine, IL1β and TNF are considered as main mediators that are involved in OA; IL1B cause cartilage demolition. TNF involved in operating the provocative cascade (Figure 2.6). Chondrocytes, osteoblasts, and mononuclear cells are involved in the formation of many catabolic factors and also some inflammatory factors that is induced by these two cytokines. The patients having OA, levels of IL1β and TNF are high in the some regions such as synovial membrane, synovial fluid, subchondral cartilage and bone [131].

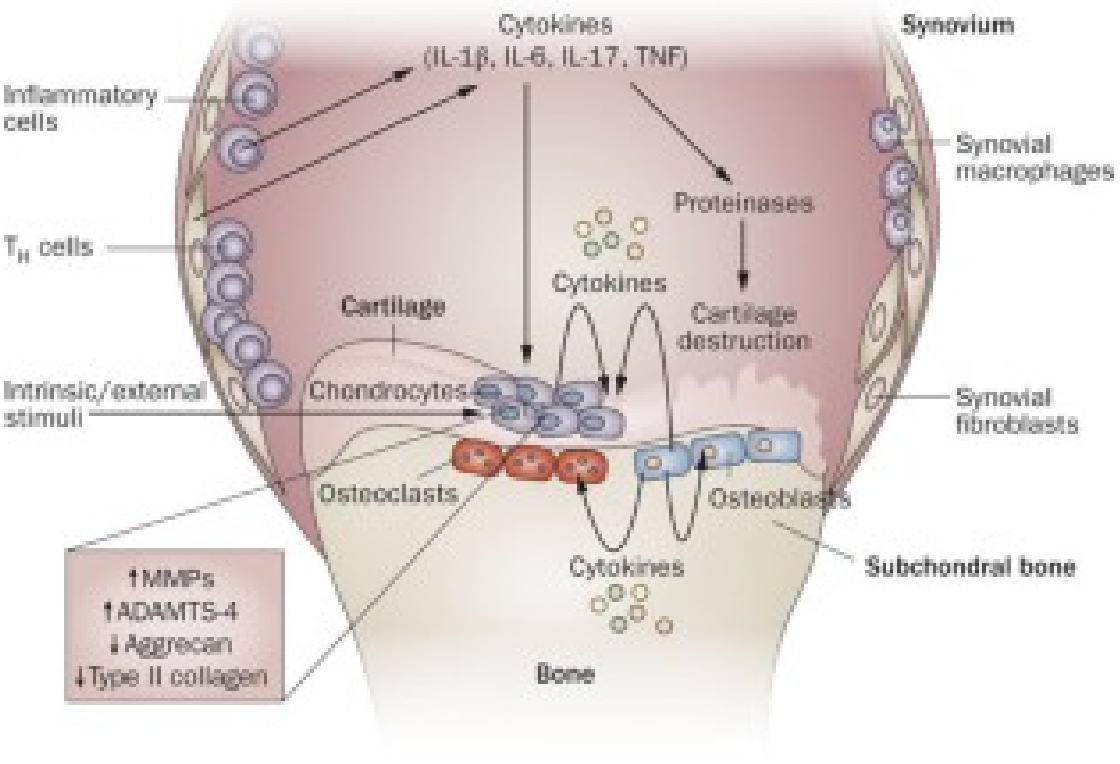

FIGURE 2.6: The Role of Proinflammatory Cytokines in the Pathophysiology of OA [132].

In Osteoarthritis synovial fibroblasts and chondrocytes, the TNFRI expression is elevated as compared to non-osteoarthritic cells. TNFRI is prominent receptor that mediated the TNF action, especially in cells of articular tissue. However, both types of receptors of TNF are recommended to take part in signal transduction and linked to distinct intracellular protein cascades [132]. IL1β and TNF raise to sustain the process of disease, causing production of other pro-inflammatory cytokines in articular cells [133]. Other mediators are also induced by IL1β and TNF that are involved in OA pathology [133]. IL1β and TNF both causes formation of reactive oxygen species (ROS) that causes degradation of cartilage [134]. In addition, IL1β and TNF down regulate the activity of the antioxidant enzymes that search ROS, which includes catalase, superoxide dismutase and glutathione peroxidase [135]. The Wnt–β catenin cascade reported as prime contributors to pathology of OA joint. In OA cartilage, the expression of β catenin and Wnt ligands is elevated [136]. Activities of TNF in OA chondrocytes include the suppression of the production of protein, proteoglycan and type II collagen [137].

The study has revealed the link of TNF-α -308G/A gene polymorphism to risk of osteoarthritis [75]. But in some studies, no linkage was shown among them [138].

2.5.3 Age-Related Macular Degeneration

It is abbreviated as AMD. It is abnormality of the central retina. It is huge cause of above-board blindness in western countries having more than 30 millions of people has been affected worldwide. This central retina, in other words macula, which is very crucial for pictorial acuity and color vision and is familiarly convoluted in pathology of AMD [139]. AMD is considered as the gradual gathering of focal or turgid druses, its size is greater than 125μm and hypo-pigmentation or hyper-pigmentation of the Retina Pigment Epithelium (RPE) [140]. Advanced form of AMD could be characerized into two forms. Firstly, it comprises of geographic atrophy (GA; dry or non-exudative AMD), that described as area of REP atrophy assessing approximately 175μm other than this and it includes exposed choroidal vessels. Other kind of this progressive illness is considered as choroidal neovascularization (CNV; wet or exudative AMD), it might include subretinal neovascular membranes; exudates, subretinal fluid and hemorrhages; subretinal/intraretinal scarring and pigment epithelial detachment (PED) [141].

Drusen are actually histological indicators of AMD that are yellow colored credits of lipids, protein, lipoprotein and remains of cells which gather in Bruch's membrane or RPE or inside the Bruch's membrane [142]. Actual AMD is one of multifactorial, late-onset human disease [143], recommending that it may involve various disease mechanisms and there are different genes accountable for different clinical subtypes [144].

Delicate, large drusen accompanying with AMD which are pigmentary abnormalities, those have been connected with a greater risk of development to advanced AMD [145]. Adding this cardiovascular harmful factors include, hypertension and hyperlipidemia have been incongruously connected with threat of AMD as well [146]. In recent times, it was suggested that dispensation of antitumor necrosis

factor-α (anti-TNF-α) agent such as infliximab, can be used for the cure of AMD. Actually, TNF-α is located inside neovascular membranes of exudative AMD [147], protein, retina and also epiretinal membrane [148].

Studies on animals as experiment have revealed that TNF-α induces the formation of new retinal vessel [149]. Furthermore, in rats and mice, this anti-TNF-α intravitreal or systemic mediators have been exposed to degenerate laser induced choroidal neovascularization [150]. The activation of endothelial cells is local effects of IL-1β and TFN-α, which is the utmost processes founded in the start of inflammation [151]. Expression of leukocyte adhesion molecules, growth factors, cytokines and HLA molecules can cause activation of endothelial cell [152]. The activation of endothelium, e.g. elevated activity of adhesion molecules and enhanced vascular permeabilization can be induced by production of pro-inflammatory factors. The wandering leukocytes intermingle with adhesion molecules those are expressed by endothelium, it slow down their speed and start gently sloping along the endothelial layer. Finally, leukocytes search the inflamed tissue where monocytes convert into dendritic cells and macrophages along with growth factors, cytokines and possible microbial components [153]. The study has indicated the relation of TNF-α -308G/A gene polymorphism to the risk of age-related macular degeneration [65]. But in some studies, no linkage was shown among TNF-α -308G/A gene polymorphism and age-related macular degeneration [154,155].

2.5.4 Asthma

This babyhood illness is common in several developed countries. Previous 25 years ago, its prevalence has been increased in the world [156]. It is specified by amplified responsiveness of the tracheobronchial tree to a large number of stimuli [157], that enhances the infiltration of various inflammatory cells like eosinophils into airway, damage of epithelial layer and also airway smooth-muscle hypertrophy [158], erratic airway obstruction, constriction usually cause inflammation in the lung's conducting airways [159] and more mucous secretion in the lung's bronchiolar walls [160]. Physiologically, it is manifested that widely diffused narrowing of

air passages and clinically by paroxysms of wheezing, cough, dyspnoea and tightness that is forced by more provokers such as airway irritants (dry air, cold, smoke etc.) and physical exertion.

Basically, it is a periodic disease with severe exacerbations dispersed with symptom-free periods. It is very complicated disease with both genetic and environmental hazard. Multiple interacting genes involved in Asthma, several shows a protective effect but others involved in disease pathogenesis [157] (Figure 2.7).

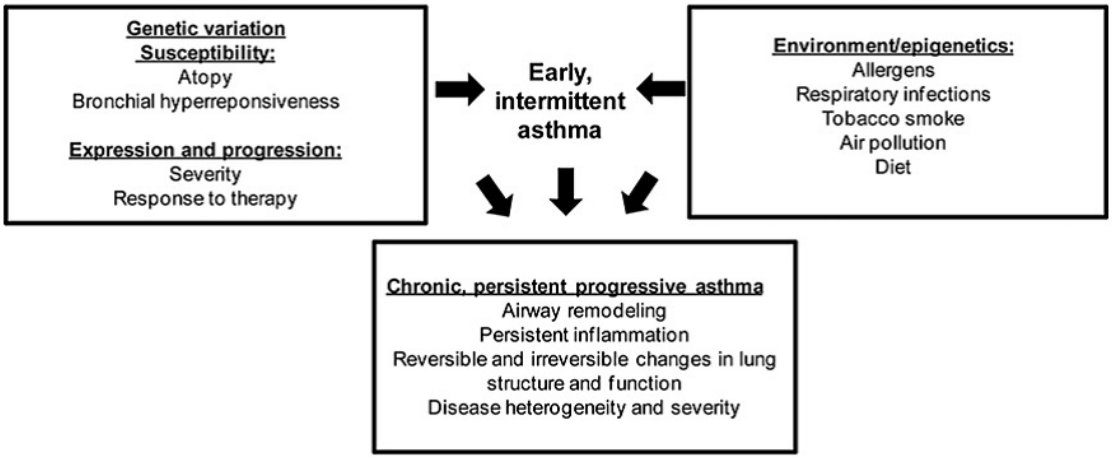

FIGURE 2.7: Gene-Environment Interactions in Asthma Severity and Susceptibility [161].

It is broadly divided in classes: one is atopic, other is nonatopic asthma and this is considered as intrinsic/extrinsic asthma and/or allergic or antiallergic and [162]. Atopic asthma concluded that the host has a genetic ability to form IgE antibodies and eosinophils, for the antigen that considered as surface markers present on allergens surface [163]. The atopic form is further classified as early onset (mild, moderate or severe), late onset (severe) and inflammation dominant, latter one represents lesser symptoms but related to heightened pulmonary remodelling or neutrophilic inflammation. Asthmic patients having more TNF-α levels in bronchoalveolar lavage fluids and for the treatment, use of anti-TNF antibody could bring symptomatic improvement. As a result, in asthma, the functional TNF-α polymorphisms were considered to be ideal entrant genetic markers [164]. Several studies has suggested the strong relation of TNF-α -308G/A gene polymorphism to risk of asthma [66,165,166].

2.5.5 Alzheimer's Disease

It is one of familiar neurodegenerative diseases in industrialized world. Objectively, it is very slow loss of intelligence functions; finally it could lead to loss of memory, then death. It is due to deposition of irregular folds of proteins, particularly aggregation of β-amyloid peptide which are extracellular feeble plaques and the hyperphosphorlylated tau (t) protein is like intracellular neurofibrillary tangles. These genetic changes are mostly occured due to rich microvascular damage that includes vascular amyloid depositions or prominent inflammation in some pompus brain areas [167]. Hereditarily, Alzheimer disease is generally classified as two kinds: (1) family cases with early-onset and (2) supposed environmental cases with fewer evident or no family clustering and of later-onset age.

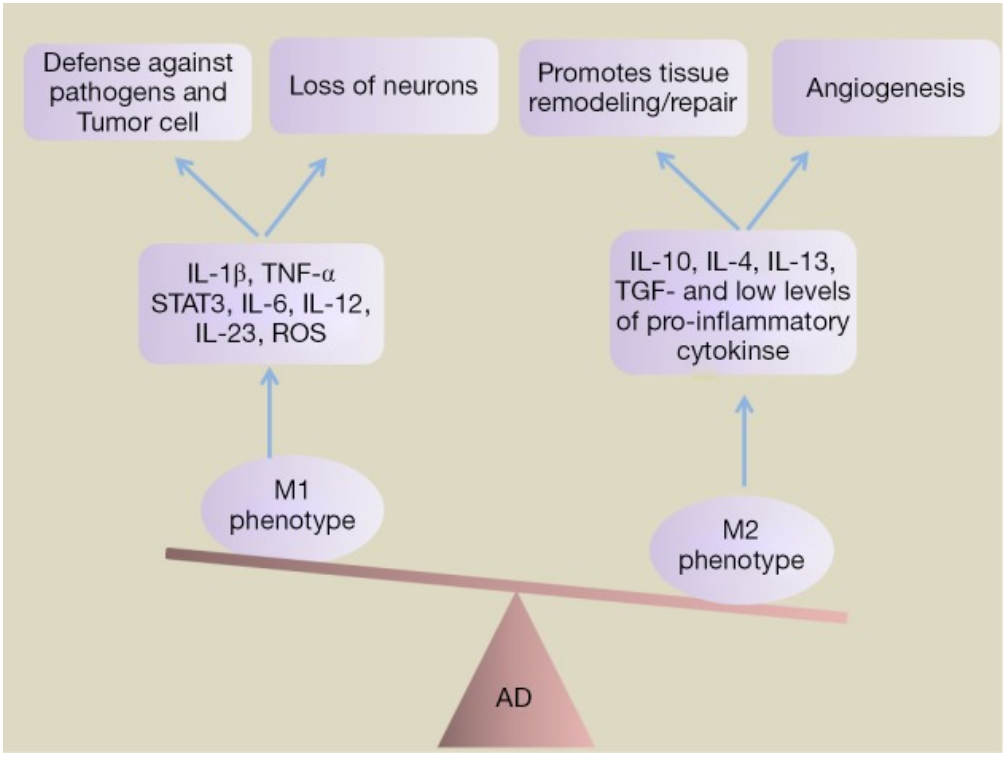

FIGURE 2.8: Different Subtypes of Microglia Produce the Different Inflammatory Cytokines That Play a Role in AD. AD, Alzheimer's Disease [37].

In AD, the systemic inflammation leads to delirium. However, this systemic inflammation in the absence of delirium, also lead to other centrally mediated symptoms, then this perception can be familiar as diseased behaviour. The systemized inflammation is specified by the structural formation of cytokines such as IL-6

and TNFα which enhances the immunity of brain transmission or progression of diseased behavior [168]. Controlling an individual risk for developing this illness, genetic factors majorly takes part in following aspect (AD) [169]. AD may be clinically characterized as neuro-inflammatory processes, that include the over-activation of microglia which causes the elevated production of proinflammatory cytokines. Moreover, neuroinflammation can also be induced by the deficiencies in anti-inflammatory system.

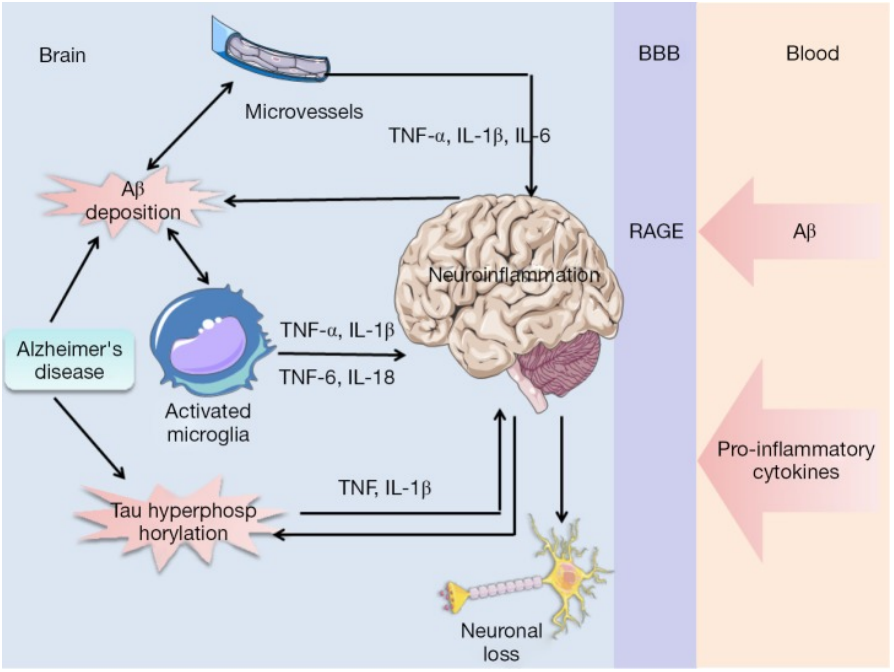

FIGURE 2.9: Speculative Model Showing the Impairment in Function of Proinflammatory Cytokines in the AD Brain [37].

TNF-α is considered as multifunctional. In animal models of AD, the role of elevated TNF-α includes inflammatory drop and also enhanced the pathology of Ab and tau [170]. While, cognition in AD patients can be improved by short-term anti-TNF-α treatment in result of relieving the Ab pathology [171]. It has also been demonstrated that in the brain of AD transgenic mice, AD-related pathology can be exacerbated by distant, nonspecific stopping of TNF-α signalling. In same way, TNF-α also induces the Ab microglial phagocytosis [172]. In return of over-activation of TNFRI, inhibition of TNFRII occur in AD brains [173]. Moreover, the TNFRI activation results in the displacement of Ab or Ab-induced neuronal death [174]. TNFRII may show some connection with the TNFRI-enhanced injury

[175]. Also communications among receptors of TNF-α may lead to some harmful effect on AD [176]. Several studies has revealed the linkage of TNF-α -308G/A gene polymorphism to the risk of AD [67,177,178].

2.5.6 Endometriosis

Endometriosis is a gynecologic sickness that affect more than 10% of the women and it is considered as a major cause of infertility and severe pain as well. It is occurring due to the implantation of functional endometrial tissue [179], outside of the uterine cavity [180].

These extrauterine endometrial tissues can be implants nearly anywhere in the body. Up to 50% of women get infertility. 5-10% of women of reproductive age can develop this disease. Various theories have been developed over time. One theory is retrograde menstruation that leads to the attachment and implantation of functional endometrial tissues, stroma and glands and stroma in places other than the cavity of uterus. Other theories to explain endometriosis include bone marrow's stem cells, lymphatic or hematogenous transport and coelomic metaplasia [180].

It occurs particularly at reproductive age, at numerous sites such as extra-peritoneal or intra-peritoneal for example peritoneum, posterior cul-de-sac, vagina, ovaries, ureters and urinary bladder. Common place of gastrointestinal endometriosis is rectosigmoid colon [181]. It has also multifactorial etiology, having possible genetic, hormonal, immunological and environmental causes [182]. The illness is characterized as a chronic when the peritoneal fluid in EM patients have high level of proinflammatory cytokines [183]. Inflammation and abnormal angiogenesis can be mediated by proinflammatory cytokines that enhances the persistence of EM [184]. Earlier findings have suggested that probable cure targets for EM includes three key pro-inflammatory cytokines that are IL-1β, IL-6 and TNF-α [185]. One study reported the elevated concentration of TNF-α in EM patients first time [186].

After that, increase in the clinical evidence that indicated the levels of TNF-α related to the succession of symptoms of EM [187]. The EM development can be reduced by anti-TNF therapy effectively [188]. TNF-α synthesized due to activated macrophages may dynamically contribute to matrix remodelling or invasion of lesions of endometriosis [189]. The pro-inflammatory cytokine's gene can convert gene transcription, so they change the biological function protein expression of cytokines due to variation in genes of cytokinesis [190]. In many studies, no linkage was shown in TNF-α -308G/A gene polymorphism with the risk of endometriosis [68,190,191].

2.5.7 Periodontal Disease

Periodontal disease adds to the global overburden of oral diseases. It has risk factors same as that of many chronic diseases. This term broadly used for inflammatory diseases that affects periodontium. Periodontium is the structure that assists the teeth. It includes gingiva, periodontal ligament, cementum and alveolar bone [192]. Against oral microbiota, an inflammatory reaction is observed. Periodontitis (PD) results in reabsorption of alveolar bone and connective tissue and also apical movement of the epithelial attachment, often lead to early tooth loss [193]. If not treated, the disease progresses over time and this is termed as Chronic periodontitis. Rapid attachment loss and bone destruction is observed in Aggressive periodontitis. Age of onset, destruction patterns, progression rates, relative amounts of plaque and calculus and inflammation signs differentiate between chronic and aggressive periodontitis. The periodontal tissue's inflammation is now considered as chronic, non-communicable disease and its associations of epidemiology and mechanism of inflammation are same as that of other systemic chronic inflammatory diseases [192]. Heritability also takes part in this disease. It determines periodontitis risk [194].

Common single base polymorphisms affects gene activity, also structural factors of the periodontium [193]. TNF-α gene housed in 6p21.3 at chromosome 6 along with region of MHC. In the promoter of this gene, eight single nucleotide polymorphisms

was recognized [195]. There can be a link between TNF-α -308 polymorphisms with disease according to researchers, due to G to A substitution on -308 position in promoter area of TNF-α, can affect synthesis of TNF-α with periodontitis [196]. In a study in Japanese population, association was reported among -1031, -863, -857 SNPs with risk of periodontitis [197]. Microbial factors and genes, both, affects AP pathogenesis [198]. TNF-α is a significant proinflammatory cytokine or modulator of immune reactions, it also seems to show a role in the pathogenesis of periodontitis. It is formed by varied types of cells comprising neutrophils, keratinocytes, fibroblasts, macrophages and B and T cells. Level of TNF-α actually adds to the pathogenesis of periodontitis [199]. Several studies indicated the relation among TNF-α -308G/A gene polymorphism and periodontal disease [69,70,200]. But in some studies, no association was shown among them [201].

2.5.8 Glaucoma

Glaucoma is a chronic and intensifying set of optic neuropathies upsetting millions of people worldwide [202]. It is linked with loss of ganglion cells in retina resultant in distinctive cupping or deterioration of the head of optic nerve and loss in peripheral vision [203]. Primary open-angle glaucoma (POAG), exfoliation glaucoma (XFG), chronic angle-closure glaucoma (ACG) are considered as widespread glaucoma's phenotypes worldwide and are the important mutual reason of glaucoma linked blindness globally. Both environmental and genetic features add to phenotypes of glaucoma [204].

Genetic studies have enhanced the invention of genes lead to glaucoma, the chief reason of permanent blindness world-wide. Glaucoma can happen at all ages, complex inheritance is commonly seen in adult-onset forms of disease [205]. Simple Mendelian genetics is followed in OPAG in children [206]. TNF-α and IL-6 are vital cytokines in the beginning and maintenance of systemic inflammation, which have been associated with the progression and rigorousness of periodontitis [207]. Furthermore, higher level of serum of these cytokines was found in periodontitis patients than in persons with healthy periodontum [208]. Leptin, adiponectin and

resistin are adipokines that are released chiefly by adipose tissues but also formed by monocytes and macrophages. It has the ability to directly affect inflammation [209]. The studies indicated the relation of TNF-α -308G/A gene polymorphism to risk of glaucoma [74,210,211].

2.5.9 Rheumatoid Arthritis

It is an autoimmune disorder in which autoantibodies (rheumatoid factors) are present which leads to chronic inflammation and tissue destruction [212]. Genetics, environment and autoimmunity are main causes of progression of rheumatoid arthritis (RA). The RA heritability has been assessed to be about 60 %, whereas up to 11–37 % of the involvement of HLA to heritability has been found. Alleles of HLA was associated with susceptibility to this disease. The association was found between genetic susceptibility and environmental factors, mainly smoking. Lastly, pharmacogenomics recognized SNPs and their association with reactions to drugs and biologics of diseases [213]. A role of cytokines as a potential factor in the synovial tissues in RA pathology was recognized [214]. It resulted in the discovery that IL-1 synthesis in these tissues was suppressed by the use of anti-TNF-α antibodies [215]. Along with previous studies, it was also reported that TNFα is the cytokine that elevates the progression of RA. For clinical trials in humans, chimeric anti-TNFα monoclonal antibodies were formed and it was observed that they considered as improving markers of RA patients [216]. Gene of TNF-α regulated or coded the TNF-α. This gene is positioned in chromosome 6, within the MHC [217]. Several studies have revealed the link of TNF-α -308G/A gene polymorphism to rheumatoid arthritis [76,218]. But in some studies, no relation was shown among TNF-α -308G/A gene polymorphism to rheumatoid arthritis [219].

2.5.10 Congenital Heart Disease

It is the common inborn anomaly in new born babies, known as congenital heart disease. The disease contains anomalies in the structure of heart that happen

sooner than birth. These defects ensue in the fetus, it is being developed during pregnancy in the uterus. In USA, about 500,000 adults affected with congenital heart disease. 1 in every 100 children has problems in their heart as a result of genetic or chromosomal alterations. Its example is Down syndrome. The following risk factors such as maternal viral infection during the first trimester of pregnancy, use of medications, extreme alcohol drinking during pregnancy, responsible for inherited heart disease in children.

And if family member has an inborn heart defect then the risk increases. Defects in heart valves, stenosis, defects in atrial and ventricular septa and a presence of hole [220], inside wall of the heart and anomaly in the heart muscle, are the reasons which results in alteration in blood circulation, heart failure and can also cause death. Genes in chromosome 1 display some defects in case of congenital heart diseases. Genetic and non-genetic categories both are considered as causes of CHD [221]. During the progression of CHD, both cytokines and chemokines were responsible for activation of the process of mitogen [222].

Tumour necrosis factor-α (TNF-α) as cell signalling protein thought to be responsible for systemic inflammation and has been recognized to enhance the progression of many forms of heart diseases, such as atrial fibrillation, CHD, myocardial fibrosis, heart failure, rheumatic heart disease and also few other cardiovascular diseases [223]. It is clinically identified in studies that greater TNF-α serum level was found in children suffering from CHD or not [224]. Some other evidences from studies also revealed the participants of TNF-α genetic variants with progression of coronary heart disease and autoimmune-associated congenital heart block [225]. The study has indicated the link of TNF-α -308G/A gene polymorphism to congenital heart disease [71,226].

2.5.11 Intracerebral Hemorrhage

When a small cranial vessel burst and blood leak into the brain parenchyma a condition arises known as spontaneous, nontraumatic intracerebral hemorrhage (ICH).

Before the hemorrhage takes place, the bursting of the vessels causes highly prevalent small vessel disease which may effect for years [227]. Another hemaorrhage stroke different from spontaneous sub dural hemorrhage and aneurysmal subarachnoid haemorrhage is a Intracerebral hemorrhage, ICH induced stroke related health and upto 50% mortality of stroke, it also constitutes upto 20% incidental strokes in USA [228]. Preeminentaly, due to the use of anticoagulation therapy in elder age and grooming life anticipation, the universality and occurrence of ICH are expected to rise in incoming years [227]. Developmental regulation of immune system and tumor proliferation are the effects of TNF. Properties of TNF-α have been shown in animal studies which include low level of water diffusion, blood brain barrier modulation, inflammatory responses and regulation of blood flow in brain, also the increase in blood cloating that may be of relevance for the pathogenesis of ICH [229]. The study has indicated the link among TNF-α -308G/A gene polymorphism and intracerebral hemorrhage [230].

2.5.12 Type 2 Diabetes Mellitus

The disease Type 2 Diabetes Mellitus (T2DM) is caused through many genes, of carbohydrate metabolism that is defined by relative impairment in insulin secretion and insulin resistance [231]. T2DM is a composite, multifactorial disease affected by both factors of environmental and genetic that are responsible for disease pathogenesis and distinct risk of individual. The relative significance of each almost changes with time and between populations, but 30 to 70% of heritability (based on family studies) decreases in the region having evident heritability indicated in patients of aged 35–60 years [232]. Extensive work has been done to identify the disease-affecting genes to better understand of the pathogenicity of disease to find new therapeutical targets and allow estimation of disease [233].

The cytokines contributed to progression of insulin resistance and T2DM due to oxidative stress or enhanced expression of few transcriptional enhancer cascades [234]. TNF-α also involved in development of tissue-specific inflammation that results in pathogenesis of T2DM [235]. TNF-α also induces the adhesion molecules

to synthesize endothelial like intracellular adhesion molecule-1 that enhances establishment in insulin resistance [236]. In T2DM pathogenesis, increased synthesis of TNF-α is also linked with the insulin resistance due to obesity in adipose tissues that results in the progression of T2DM [237]. Many studies has reported the TNF-α -308G/A gene polymorphism correlation with risk to type 2 diabetes mellitus [77,238,239]

2.5.13 Hypertension

Hypertension (HTN) is specified by high systolic blood pressure (SBP) and diastolic blood pressure (DBP). HTN occurrence has been shown to vary among ancestral groups, as proved by comparisons between Caucasian and Hispanic American as well as Caucasian and African American groups [240,241]. Numerous genetic and environmental factors may affect the more complex phenotypes such as hypertension (HTN), blood pressure (BP) and cardiovascular disease (CVD). Hypertension expands the risks of maternal/fetal vulnerability, end-organ injury and total mortality [242]. Prolonged HT can show adverse transformations in the morphology and anatomy of the heart, including left ventricular hypertrophy (LVH), atrial fibrillation (AF), myocardial infarction (MI) and congestive heart failure. High blood pressure (BP) can results in development of stroke and end-stage renal disease. 34% elevation in the probability for stroke and a 21% elevation in the possibility for coronary events is linked with increase in 5 mm Hg in DBP for long period [243]. Therefore, no single gene plays a vital role, but many genes with moderate effects reacting to environmental stimuli contribute to HTN. Genetic studies in humans give population-specific information about the variants on susceptibility to disease that affects the blood pressure due to physical activity, diverse diet and other behavioural factors and also give information about allelic heterogeneity and ancestry-specific genetic susceptibility (for example, in east Asians, the ALDH2 variants) [244]. The study reported that in pregnant rats, the arterial pressure and renal vascular resistance was significantly increased by the twofold multiplication in the plasma levels of TNF-α. Several studies in

recent years have showed that inflammation lead to development of disease. The study indicated that in diseased patients, the concentration of pro-inflammatory cytokines was elevated, this recommended that disease was associated with an immune function disorder. TNF-α enhances the production of cytokine, which elevated the activity of adhesion molecules and neutrophil. It was reported that in hypertensive patients, the serum level of TNF-α was increased in comparison to healthy controls. TNF-α protein levels were predominantly under genetic control. In recent years, sensitivity, redness and swelling plays vital function in the incidence and progression of disease with the help of cytokines. TNF-α may causes the secretion of powerful contractile vasoactive substance endothelin 1, which can results in high blood pressure. High level of TNF-α can enhances the lipid peroxidation, which can lead to destruction of the structural integrity and function of endothelial cells, results in lack of balance in endothelial cells that produce active substances. High level of secretion in endothelin due to vasodilators and vasoconstriction induces the peripheral resistance and blood pressure [245]. The studies has reported the association of TNF-α -308G/A gene polymorphism with hypertension [73,246,247].

2.5.14 Vitiligo

Vitiligo is an intricate disorder in which autoimmune destruction of melanocytes occurs within the lesions causes the formation of white patches on skin and covered hair [248]. Vitiligo is also considered as both polygenic and multifactorial indicating instantaneous endowment of many genetic risk factors and environmental stimulants [249]. Vitiligo susceptibility has also been linked to cluster of immunoregulatory genes [250]. Different genes on melanocytes also related to the progression of vitiligo [251]. So, TNF-α act as an important key factor in pigmentation because of promoting the damage of melanocyte and inhibition of melanogenesis and in same way by enhancing their survival and proper functioning of melanocytes [252]. Moreover, high level of TNF-α in vitiligo lesions is recommended as vigorous indicator for the pathogenesis [253]. An introductory report

in which anti-TNF-α agents is used as cure for global vitiligo which indicated the depigmentation stability in patients without the presence of new macules [254]. Another report suggested that the TNF-α blockers can be used on the basis of the repigmentation of vitiligo macules especially in patients of ankylosing spondylitis [255].

Gene mutations in encoding cytokines can affect their circulatory amount and thus enhances the pathogenesis of disease. TNF-α encoding gene is located within HLA gene complex present at chromosome 6 tiny arm. In the promoter region of TNF-α, many SNPs reported to alter the sites of regulation, in result effecting the TNF-α level and the expression of gene. Polymorphism at promoter region was indicated their role as accelerating the biological activity of TNF-α and disturbing their synthesis and also lead to progression of several autoimmune diseases [256]. Several studies has indicated the link of TNF-α -308G/A gene polymorphism to risk of vitiligo [78,257,258]. But in some studies, no link was shown among TNF-α -308G/A gene polymorphism and vitiligo [259].

Chapter 3

Material and Methods

3.1 Literature Search Strategy

The main sources of our search were PUBMED, Web of science, Elsevier science direct, Springer, Wiley online library, Google scholar to find out the relevant published studies about TNF-α polymorphisms.

Our research includes the following Medical Subject Headings (MeSHs) and text words:

Gene OR Polymorphism OR Genetic polymorphisms OR Genotype OR Mutation OR Variants.

Disease OR Autoimmune disease OR Inflammatory disease.

Tumor Necrosis Factor-alpha OR TNF-alpha OR TNF-α.

TNF -308 G/A OR rs1800629 or their combination.

No restriction about language of published articles was set. We read the retrieved studies to examine the link between TNF-α gene SNPs and relevant disease. We manually search the reference list of relative studies, previous meta-analysis and reviews for finding the additional and missing relevant studies. The studies were read fully and clearly to assess their suitability for inclusion in meta-analysis.

3.2 Selection Criteria

3.2.1 Inclusion Criteria

1. The outcome of study was autoimmune disease containing two comparison groups as cases and healthy controls.
2. Association between disease and TNF-α -308G/A SNP were determined.
3. Articles contained case-control studies.
4. Complete information about genotype frequency for both cases and controls.
5. Sufficient data were present in published articles to measure 95% confidence interval (CI) and odd ratios (OR).

3.2.2 Exclusion Criteria

1. Studies contain only cases; no control group were included.
2. Linkage or family based studies.
3. Sufficient published data were missing.
4. Studies included case reports, just abstracts, reviews, letter to editors and posters.
5. Current study was duplicate of previous study.
6. Studies included comparisons of laboratory methods and level of cytokines in patients.

On the basis of inclusion criteria, 120 published articles were investigated. Of which 53 irrelevant articles were excluded due to irrelevant title and abstract assessment. We excluded the 34 articles due to review, meta-analysis, case reports, evaluated cancer disease and focused on other polymorphisms of TNF-α instead of -308G/A polymorphism. 13 articles were also excluded due to the insufficient

data about genotype and alleles frequency. Finally, we selected the 20 case-control studies for this meta-analysis (Fig 3.1).

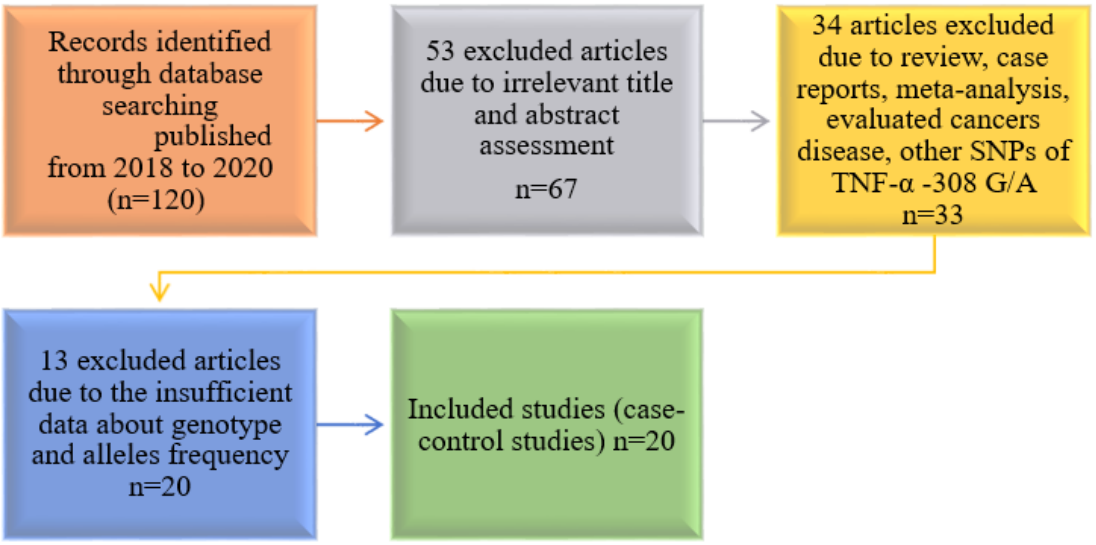

FIGURE 3.1: Flow Diagram of Selecting Eligible Studies for the Meta-Analysis.

3.3 Extraction of Data

Standard protocol was used to extract the data which meet our inclusion criteria and then save them into database. The following characteristics of study were extracted from published studies: first author's name, publication year, ethnicity (Asian, Europe and Africa), country name, total cases and controls, genotype and alleles frequency. In order to provide additional information, the authors of selected articles were contacted when necessary.

3.4 Statistical Analysis

This study is about meta-analysis based on previous articles, so no ethical approval was necessary. Our data was analysed by using Review Manager, version 5.3 (Oxford, England: The Cochrane Collaboration, 1999) as this is statistical software package for analysis and management of Cochrane Collaboration Systematic Review. The association between selected SNP of TNF-α and risk of

disease was measured by odd ratios (OR), and 95% confidence interval (CI) and also two-tailed P-values. Odd ratio is used to measure the strength of association of TNF-α with the risk of autoimmune diseases [258].

- OR>1 means increase likelihood of outcome (disease) in experimental group.
- OR<1 means decrease likelihood of outcome (disease) in experimental group.
- OR=1 means no difference in likelihood of outcome (disease) between experimental and control group.

The importance of our OR were checked out by using Z-test. Confidence Interval is the range of values within which we can be 95 percent certain, the true value lies. Width of CI indicates the precision of point estimate. Wider the interval, less the precision [260].

P-value is probability of obtaining the observed effect under a null hypothesis. Significant statistics was set at P<0.05. P-value greater than 0.05 shows no statistical significance. Two p-values shown in Review Manager software. One is related to the summary effect in meta-analysis and tell about association and it comes from Z-test of null hypothesis. Second one is related to the heterogeneity across the studies and it comes from Chi-squared test of null hypothesis [137].

Genotypic analysis was used to make certain the genetic models. We analysed the risk of five genetic models with various autoimmune diseases such as dominant model (AA genotype + AG genotype versus GG genotype), recessive model (AA genotype versus AG genotype + GG genotype); supposing both models as dominant and recessive effects of A allele, homozygous model (AA genotype versus GG genotype), heterozygous model (AG genotype versus GG genotype) and allelic model (A allele versus G allele).

Subgroup analysis based on ethnicity were also carried out to find out and to explain the variations in the results of the selected studies [165]. To figure out the null hypothesis in which shown that the effect of all the studies was same, heterogeneity test was used.

Heterogeneity in meta-analysis refers to the variation in study outcomes between the studies. Chi-Squared-Q-statistic test was used to find heterogeneity. I_2 was used to quantified the heterogeneity with the range of 0 to 100%. I_2 describes the percentage of variation across studies that seems not to be due to chance.

If the heterogeneity was significant (I_2>50% or p-value of Q test <0.1, were considered as remarkable heterogeneity), we used the random effect model. In case of less than 50% I_2, the fixed effect model was used [164].

The fixed-effects model looks attentively at only within-study variability. On the other hand, random-effects model uses the weights which comprises both the between-study and within-study variability. Because of the high heterogeneity among the populations of selected studies, we have showed the results by using random-effects model which consider as the most conservative ones [260].

Result figure of the meta-analysis represents the name of author of respective studies on the left side in alphabetical order with year of publication. Then, the frequency of genetic models in both experimental and control group, is represented in result figure. Odd ratio, confidence interval, probability and heterogeneity are also represented in the result figure [260].

Forest plot gives the visual evidence of heterogeneity and association. In the forest plot, vertical line shows the line of null effect. Horizontal lines show the 95% CI range. Size of black squares in the mid of horizontal line shows point estimate (OR) and sample size of that respective study. Diamond shape in the graph indicated the overall outcome effect. Tips or edges of diamond shows the 95% CI and top and bottom end of diamond shows the OR.

Position of diamond on left side of line of null effect represents the reduced risk of outcome in the experimental group. Position of diamond on right side of line of null effect represents the increased risk of outcome in the experimental group.

If diamond touches the line of null effect, it represents no statistical significance between experimental and control group. If diamond does not touch the line of null effect, it represents the statistical difference between both groups [260].

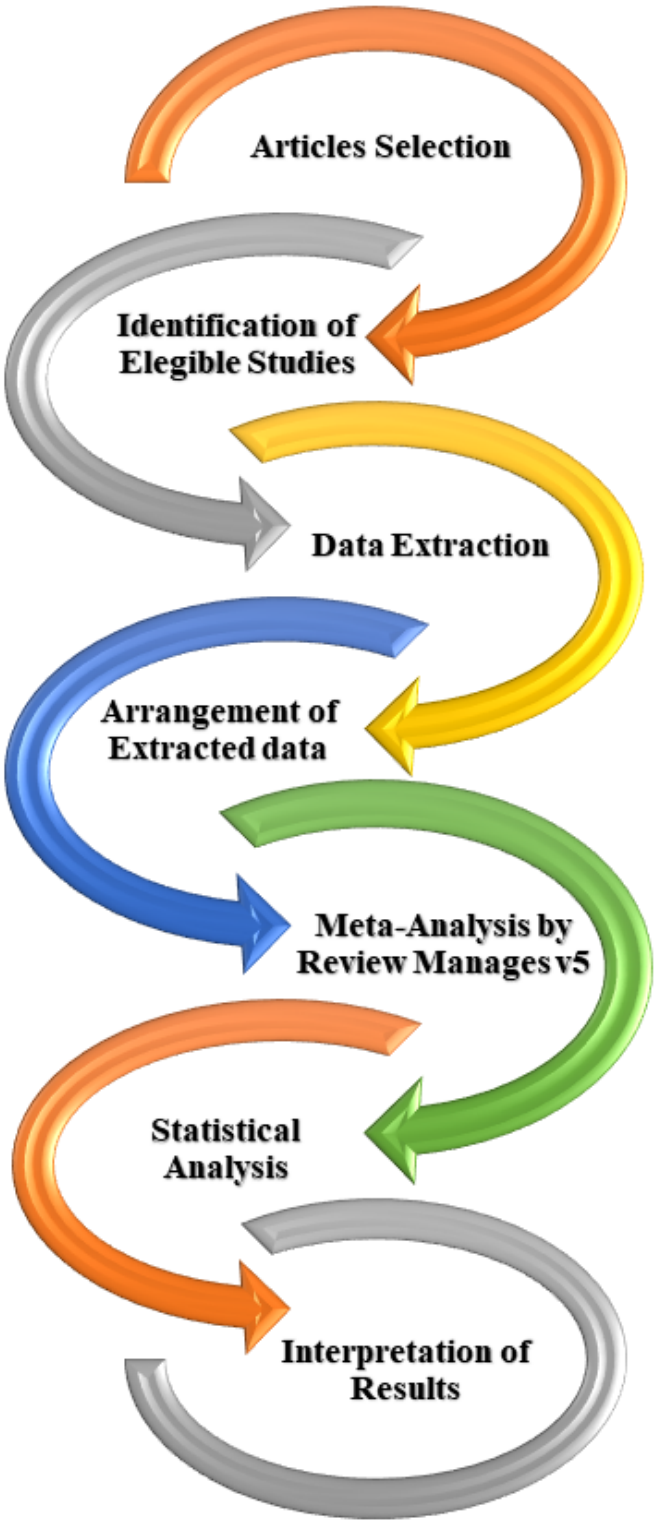

FIGURE 3.2: Flow Diagram of Methodology of the Meta-Analysis.

Chapter 4

Result and Analysis

4.1 Characteristics of Selected Articles

20 case-control studies containing 2840 cases and 3069 healthy controls selected for this meta-analysis [Table 4.1]. All the selected articles were case-control studies and published from 2018-20. Selected studies included 14 Asian case-control studies (Pakistan, Iraq, Iran, India, Bangladesh, China, Asian Russia) with 2392 cases and 2697 controls, 3 European case-control studies (Croatia and Serbia) with 288 cases and 222 controls and 3 African case-control studies (Egypt and Ethiopia) with 160 cases and 150 controls. Different techniques of PCR were used in selected studies to determine TNF-α -308G/A polymorphism. Genotype frequency of TNF-α gene in different diseases and populations [Table 4.1]. and allele frequency of TNF-α gene in different diseases and populations [Table 4.2].

4.2 Quantitative Analysis

First, we performed the meta-analysis on all subjects and then separately based on respective ethnic group. The results of meta-analysis of the association among TNF-α -308G/A gene polymorphism with autoimmune diseases are represented in Table 4.3.

TABLE 4.1: Included Studies for Meta-analyses About Association Among TNF-α rs1800629 SNP and Autoimmune Diseases and Genotype Frequency

S No.	Authors	Population	Diseases
1	Chernykh et al., 2019 [65]	Russian	Age-Related Macular Degeneration
2	Babic-Leko et al., 2020 (a) [67]	Croatian	Alzheimer disease
3	Babic-Leko et al., 2020 (b) [67]	Croatian	Mild Cognitive Impairment
4	Jalkovljevic et al., 2020 [70]	Serbian	Apical Periodontitis
5	Darweesh et al., 2019 [66]	Iraqi	Asthma
6	Majumder et al., 2018 (a) [69]	Indian	Chronic Periodontitis
7	Majumder et al., 2018 (b) [69]	Indian	Agressive Periodontitis
8	Pan et al., 2019 [71]	Chinese	Congenital Heart Disease
9	Mir et al., 2020 [79]	India	COPD
10	Tabaei et al., 2019 [72]	Iranian	Coronary Heart Disease
11	Babaabassi et al., 2019 [68]	Iranian	Endometriosis
12	Al.Awsi et al., 2019 [73]	Iraqi	Hypertension
13	Kumar et al., 2020 [230]	Indian	Intracerebral Hemorrhage
14	Naqvi et al., 2019 [75]	Pakistani	Knee Osteoarthritis

15	Passan et al., 2019 [74]	Indian	Primary Glaucoma
16	Zaghlol et al., 2019 [76]	Egyptian	Rheumatoid Arthritis
17	Fawzy et al., 2020 [219]	Egyptian	Rheumatoid Arthritis
18	Ayelign et al., 2019 [238]	Ethiopian	Type 2 Diabetes
19	Roy et al., 2019 [77]	Bangladeshi	Type 2 Diabetes
20	Rajendiran et al., 2020 [78]	Indian	Vitiligo

S	**Patients**				**Controls**			
No.	**No**	**GG**	**GA**	**AA**	**No**	**GG**	**GA**	**AA**
1	102	70	29	3	100	76	12	12
2	115	37	55	23	11	4	5	2
3	53	24	20	9	11	4	5	2
4	120	66	46	8	200	141	57	2
5	40	24	14	2	40	4	20	16
6	157	40	56	61	200	101	55	44
7	40	10	15	15	200	101	55	44
8	400	297	89	14	400	330	65	5
9	100	91	9	0	163	150	13	0
10	96	44	49	3	91	61	27	3
11	150	131	18	1	150	127	21	2
12	50	35	13	2	50	37	11	2
13	100	93	3	4	100	94	5	1
14	280	143	120	17	308	199	95	14
15	286	218	33	35	300	255	39	6
16	35	30	3	2	35	19	16	0
17	50	30	12	8	40	39	1	0

18	75	45	24	6	75	27	36	12
19	327	314	11	2	331	330	1	0
20	264	104	158	2	264	157	105	2

4.2.1 Overall Analysis

Our meta-analysis result for overall studies showed that the TNF-α -308G/A gene polymorphism was linked with increased risk of autoimmune diseases under allelic model (A vs G) based on probability value (<0.05) and position of diamond (on the right side) in the forest plot, which indicated that A allele of TNF-α -308 is associated with increased risk of autoimmune diseases.

The OR of allelic model is 1.30, 95% CI range is 0.98-1.73, P-value is 0.07 and diamond is on the right side that favors experimental group and associated with increased risk of multiple autoimmune diseases. As heterogeneity is 83% and P(het) from Q test is <0.1, the random-effects model was used for allelic model (Fig 4.1). But no statistical association was found among the TNF-α -308G/A

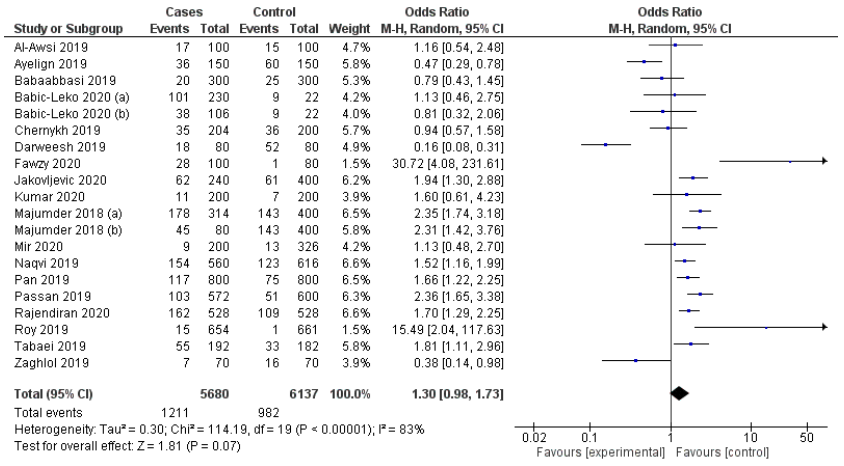

FIGURE 4.1: Meta-Analysis of 20 Case-Control Studies Represents Allelic Model (A Versus G) with the Risk of Autoimmune Diseases for Overall Analysis Using Random-Effects Model. The Odd Ratio (OD) and 95% Confidence Interval (CI) are Plotted on the Graph. Studies are Arranged Alphabetically.

gene polymorphism with various autoimmune disease in overall analysis because the probability value in remaining four genetic models is greater than 0.05 and diamond touches the line of null effect.

TABLE 4.2: Information of Distribution of Alleles of TNF-α rs1800629 for Patients and Controls

Authors	**Patients**			**Controls**			
	Freq of G	**Freq of A**	**GG+ GA**	**Freq of G**	**Freq of A**	**GA+ AA**	**GG+ GA**
Chernykh et al., 2019	169	35	99	164	36	24	88
Babic-Leko et al., 2020	129	101	92	13	09	07	09
Babic-Leko et al., 2020	68	38	44	13	09	07	09
Jalkovljevic et al., 2020	178	62	112	339	61	59	198
Darweesh et al., 2019	62	18	38	28	52	36	24
Majumder et al., 2018	136	178	96	257	143	99	156
Majumder et al., 2018	35	45	25	257	143	99	156
Pan et al., 2019	683	117	386	725	75	70	395
Mir et al., 2020	191	09	100	313	13	13	163
Tabaei et al., 2019	137	55	93	149	33	30	88
Babaabassi et al., 2019	280	20	149	275	25	23	148
Al.Awsi et al., 2019	83	17	48	85	15	13	48
Kumar et al., 2020	189	11	96	193	07	06	99
Naqvi et al., 2019	406	154	263	493	123	109	204
Passan et al., 2019	469	103	251	549	51	45	294
Zaghlol et al., 2019	63	07	33	54	16	16	35
Fawzy et al., 2020	72	28	42	79	01	01	40
Ayelign et al., 2019	114	36	69	90	60	48	63
Roy et al., 2019	639	15	325	661	01	01	330
Rajendiran et al., 2020	366	162	262	419	109	107	262

In homozygous model (AA vs GG), the association was also not found among TNF-α -308G/A gene polymorphism and autoimmune diseases in overall analysis. The OR is 1.57, 95% CI range is 0.85-2.91, P-value is 0.15 and diamond touches the line of null effect that indicated no statistical association was found among TNF-α

-308 G/A gene polymorphism and multiple autoimmune diseases. Heterogeneity is 74% and P(het) is <0.1, so again random-effects model was used (Fig 4.2).

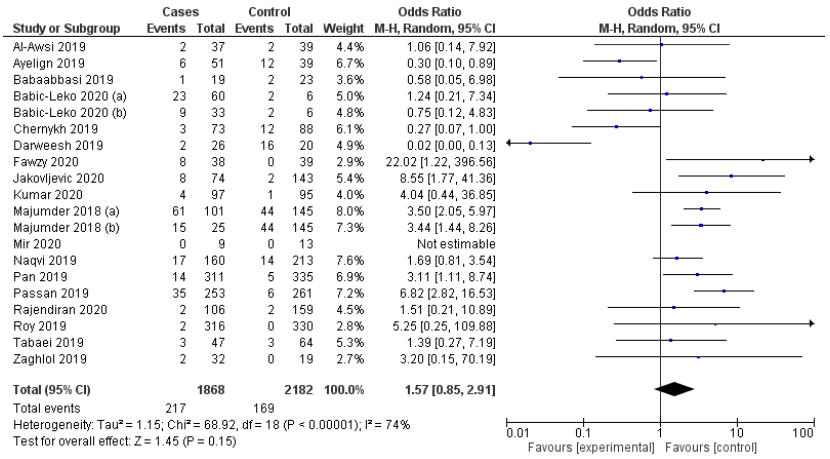

FIGURE 4.2: Meta-Analysis of 20 Case-Control Studies Represents Homozygous Model (AA Versus GG) with the Risk of Autoimmune Diseases for Overall Analysis Using Random-Effects Model. The Odd Ratio (OD) and 95% Confidence Interval (CI) are Plotted on the Graph.

In heterozygous model (AG vs GG), the association was also not found among TNF-α -308G/A gene polymorphism and autoimmune diseases in overall analysis. The OR is 1.31, 95% CI range is 0.95-1.80, P-value is 0.10 and diamond touches the line of null effect that indicated no statistical association was found among TNF-α -308 G/A gene polymorphism and multiple autoimmune diseases. Heterogeneity is 76% and P(het) is <0.1, again the random-effects model was used (Fig 4.3).

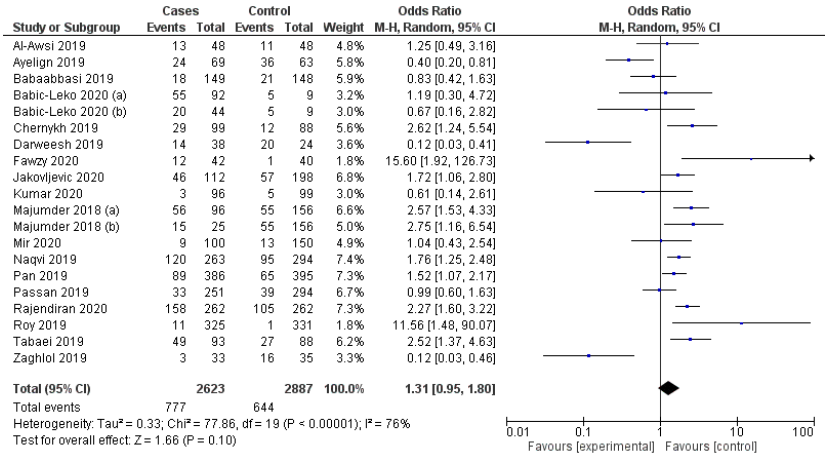

FIGURE 4.3: Meta-Analysis of 20 Case-Control Studies Represents Heterozygous Model (AG Versus GG) with the Risk of Autoimmune Diseases for Overall Analysis Using Random-Effects Model. The Odd Ratio (OD) and 95% Confidence Interval (CI) are Plotted on the Graph.

TABLE 4.3: Meta-analyses for Functional TNF- α rs1800629 Polymorphism in Autoimmune Diseases

Subgroup	**Polymorphism**	**No. of studies**	**Cases/ Controls**	**Type of model**
	A vs G	20	6891/7119	RE
	AA vs GG	20	2085/2351	RE
Total	AG vs GG	20	3400/3531	RE
	AA+AG vs GG	20	3834/3946	RE
	AA vs AG+GG	20	3057/3254	RE
Ethnicity				
	A vs G	14	5723/6219	RE
	AA vs GG	14	1741/2081	RE
Asia	AG vs GG	14	2848/3057	RE
	AA+AG vs GG	14	3170/3436	RE
	AA vs AG+GG	14	2553/2848	RE
	A vs G	3	777/523	RE
	AA vs GG	3	207/161	RE
Europe	AG vs GG	3	369/283	RE
	AA+AG vs GG	3	449/295	RE
	AA vs AG+GG	3	328/228	RE
	A vs G	3	391/377	RE
	AA vs GG	3	137/109	RE
Africa	AG vs GG	3	183/191	RE
	AA+AG vs GG	3	215/215	RE
	AA vs AG+GG	3	176/178	RE

Subgroup	**Heterogeneity Test**		**Association Test**			
	I_2	**P(het)**	**OR**	**95%CI**	**Z(test)**	**P(OR)**
	83	0.00001	1.3	0.98-1.73	1.81	0.07
	74	0.00001	1.57	0.85-2.91	1.45	0.15
Total	76	0.00001	1.31	0.95-1.80	1.66	0.1
	89	0.00001	1.14	0.75-1.75	0.63	0.53

	74	0.00001	1.2	0.69-2.12	0.65	0.52
Ethnicity						
	82	0.00001	1.41	1.05-1.89	2.29	0.02
	76	0.00001	1.52	0.75-3.06	1.17	0.24
Asia	69	0.00001	1.53	1.13-2.08	2.72	0.006
	90	0.00001	1.22	0.75-1.97	0.8	0.42
	70	0.00001	1.35	0.74-2.46	0.99	0.32
	43	0.17	1.39	0.81-2.38	1.19	0.23
	56	0.1	2.13	0.47-9.63	0.98	0.33
Europe	0	0.44	1.52	0.98-2.36	1.88	0.06
	15	0.31	1.57	0.92-2.66	1.67	0.1
	48	0.15	1.99	0.55-7.25	1.04	0.3
	90	0.00001	1.32	0.21-8.33	0.3	0.77
	80	0.007	2.22	0.11-44.10	0.52	0.6
Africa	87	0.0004	0.75	0.09-6.29	0.26	0.79
	90	0.00001	1	0.12-8.70	0	1
	83	0.003	0.59	0.06-6.13	0.44	0.66

In dominant model (AA+AG vs GG), the association was also not found among TNF-α -308G/A gene polymorphism and autoimmune diseases in overall analysis. The OR is 1.14, 95% CI range is 0.75-1.75, P-value is 0.53 and diamond touches the line of null effect that indicated no statistical association was found among TNF-α -308 G/A gene polymorphism and multiple autoimmune diseases. Heterogeneity is 89% and P(het) is <0.1, again the random-effects model was used (Fig 4.4).

In recessive model (AA vs AG+GG), the association was also not found among TNF-α -308G/A gene polymorphism and diseases in overall analysis. The OR is 1.20, 95% CI range is 0.69-2.12, P-value is 0.52 and diamond touches the line of null effect that indicated no statistical association was found among TNF-α -308 G/A gene polymorphism and multiple autoimmune diseases. Heterogeneity is 74% and P(het) is <0.1, again the random-effects model was used (Fig 4.5).

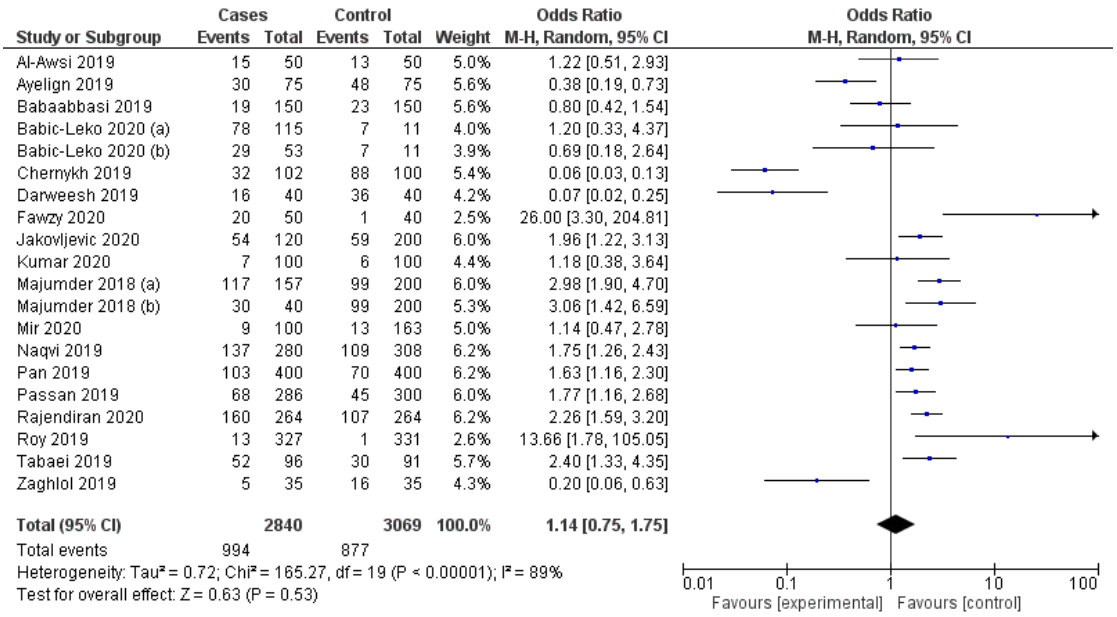

FIGURE 4.4: Meta-Analysis of 20 Case-Control Studies Represents Dominant Model (AA+AG Versus GG) with the Risk of Autoimmune Diseases for Overall Analysis Using Random-Effects Model. The Odd Ratio (OD) and 95% Confidence Interval (CI) are Plotted on the Graph.

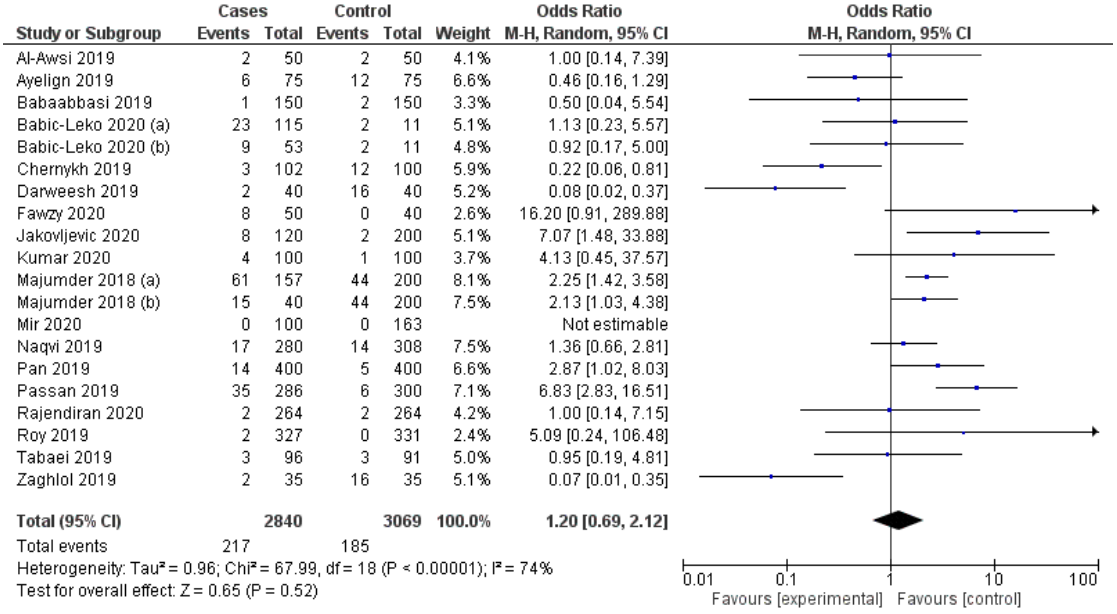

FIGURE 4.5: Meta-Analysis of 20 Case-Control Studies Represents Recessive Model (AA Versus AG+GG) with the Risk of Autoimmune Diseases for Overall Analysis Using Random-Effects Model. The Odd Ratio (OD) and 95% Confidence Interval (CI) are Plotted on the Graph.

Our meta-analysis was performed to comprehensively interpret the previous studies. Our study is the first study that was conducted to find the relation of TNF-α

-308G/A gene polymorphism with multiple autoimmune diseases in general. Our overall result indicated the significant association of TNF-α -308G/A gene polymorphism with multiple autoimmune diseases in allelic model which indicated that A allele of TNF-α -308 gene contributed to the progression of multiple autoimmune diseases.

Our results correlated with the meta-analysis conducted by Guo et al. 2019 about Type 2 Diabetes mellitus association with TNF-α -308G/A gene polymorphism. That showed the A allele of TNF-α -308 gene is risk factor for T2DM in Asians and Caucasians [239]. Our result also correlated with the Hao Sun et al., 2018 study reported that A allele of TNF-α -308 gene was significantly associated with the risk of asthma in Asians [166]. The other study also showed the strong association of A allele of TNF-α -308 gene with asthma risk [165].

But our results were inconsistent with Chen et al., 2019 study that showed reduced risk of TNF-α -308G/A gene polymorphism with Rheumatoid arthritis [261]. Sobhan et al., meta-analysis also not showed the association of TNF-α -308G/A gene polymorphism with knee osteoarthritis [138]. Yuepeng et al. 2018 was also showed no association TNF-α -308G/A gene polymorphism with CHD in Asians, but this is the result of single study. Our meta-analysis results showed the association of A allele of TNF-α -308 gene with multiple autoimmune diseases in general [262].

4.2.2 Subgroup Analysis

The subgroup analysis in our meta-analysis was performed based on ethnicity. For ethnicity, the analysis was classified into 3 subgroups (continents) i.e., Asia, Europe and Africa. Significant association of TNF-α -308G/A gene polymorphism with increased risk of multiple autoimmune diseases was observed in allelic (A vs G) and heterozygous model (AG vs GG) in Asian populations and in only heterozygous model (AG vs GG) in European populations, based on probability value <0.05 and position of diamond on right side. But no association of TNF-α -308G/A gene polymorphism with risk of multiple autoimmune diseases was

observed in homozygous, dominant and recessive models in Asian populations: allelic, homozygous, dominant and recessive models in European populations and all five genetic models (Allelic, homozygous, heterozygous, dominant and recessive models) in African populations because of probability value greater than 0.05. Random-effects model was used in all the genetic models in all population due to high heterogeneity among the selected studies.

In allelic model (A vs G) of Asian populations, the OR is 1.41, 95% CI range is 1.05-1.89, P-value is 0.02 and diamond is on the right side that favors experimental group and associated with increased risk of multiple autoimmune disease. Heterogeneity is 82% and P(het) is <0.01 (Fig 4.6).

In allelic model (A vs G) of Europe populations, the OR is 1.39, 95% CI is 0.81-2.38, P-value is 0.23 and diamond touches the line of null effect that indicated no statistical association was found among TNF-α -308 G/A gene polymorphism and multiple autoimmune diseases.

Heterogeneity is 43% and P(het) is 0.17 (Fig 4.6). In allelic model (A vs G) of African population, the OR is 1.32, 95% CI range is 0.21-8.33, P-value is 0.77 and diamond touches the line of null effect that indicated no statistical association was found among TNF-α -308 G/A gene polymorphism and multiple autoimmune diseases. Heterogeneity is 83% and P(het) is <0.1 (Fig 4.6).

In homozygous model (AA vs GG) of Asian populations, the OR is 1.52, 95% CI range is 0.75-3.06, P-value is 0.24 and diamond touches the line of null effect that indicated no statistical association was found among TNF-α -308 G/A gene polymorphism and multiple autoimmune diseases. Heterogeneity is 76% and P(het) is <0.1 (Fig 4.7).

In homozygous model (AA vs GG) of European population, the OR is 2.13, 95% CI range is 0.47-9.63, P-value is 0.33 and diamond touches the line of null effect that indicated no statistical association was found among TNF-α -308 G/A gene polymorphism and multiple autoimmune diseases. Heterogeneity is 56% and P(het) is 0.10 (Fig 4.7).

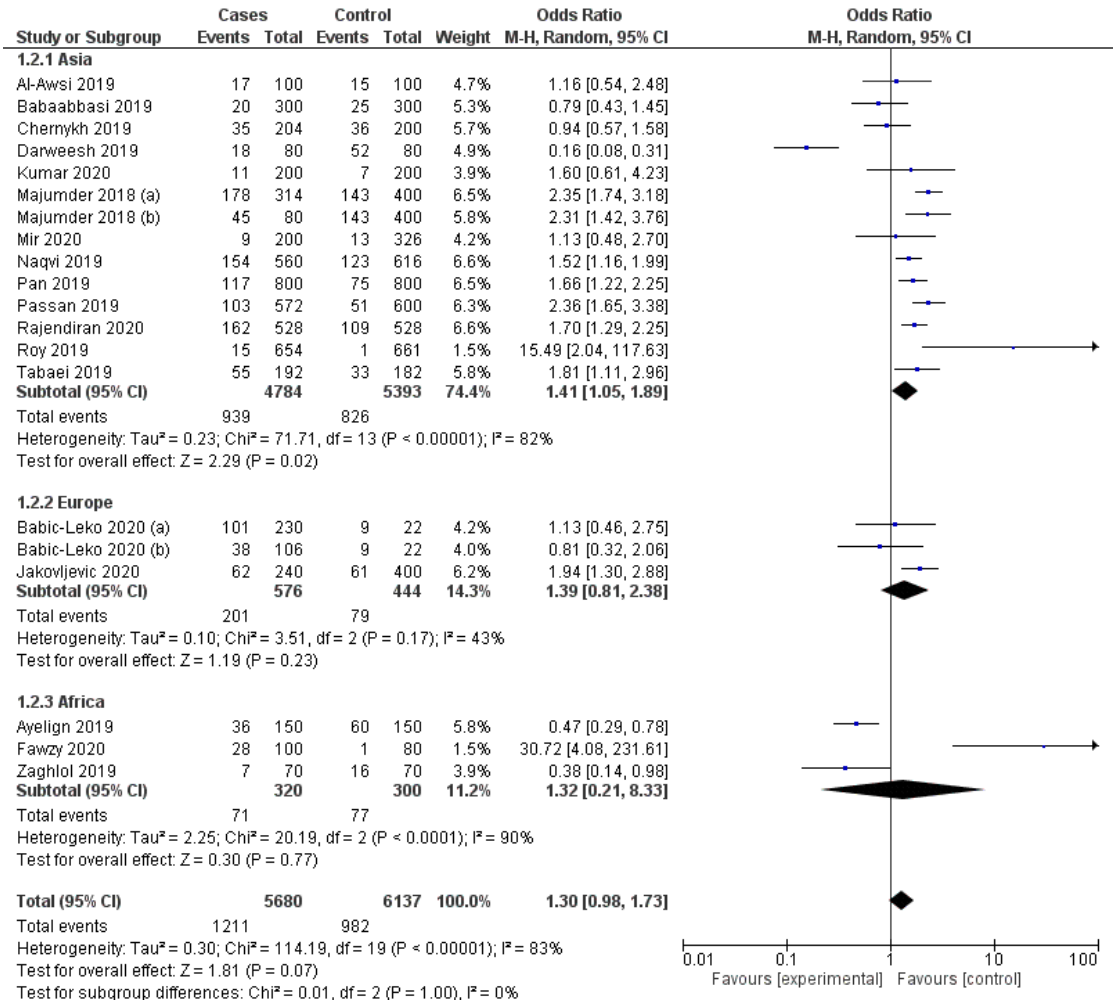

FIGURE 4.6: Meta-Analysis of 20 Case-Control Studies Represents Allelic Model (A Versus G) with the Risk of Autoimmune Diseases for Subgroup Analysis Using Random-Effects Model (14 Asian, 3 European and 3 African Populations). The Odd Ratio (OD) and 95% Confidence Interval (CI) are Plotted on the Graph.

In homozygous model (AA vs GG) of African populations, the OR is 2.22, 95% CI range is 0.11-44.10, P-value is 0.60 and diamond touches the line of null effect that indicated no statistical association was found among TNF-α -308 G/A gene polymorphism and multiple autoimmune diseases. Heterogeneity is 80% and P(het) is <0.1 (Fig 4.7).

In heterozygous model (AG vs GG) of Asian populations, the OR is 1.53, 95% CI range is 1.13-2.08, P-value is 0.006 and diamond is on the right side that favors experimental group and associated with increased risk of multiple autoimmune disease. Heterogeneity is 69% and P(het) is <0.01 (Fig 4.8).

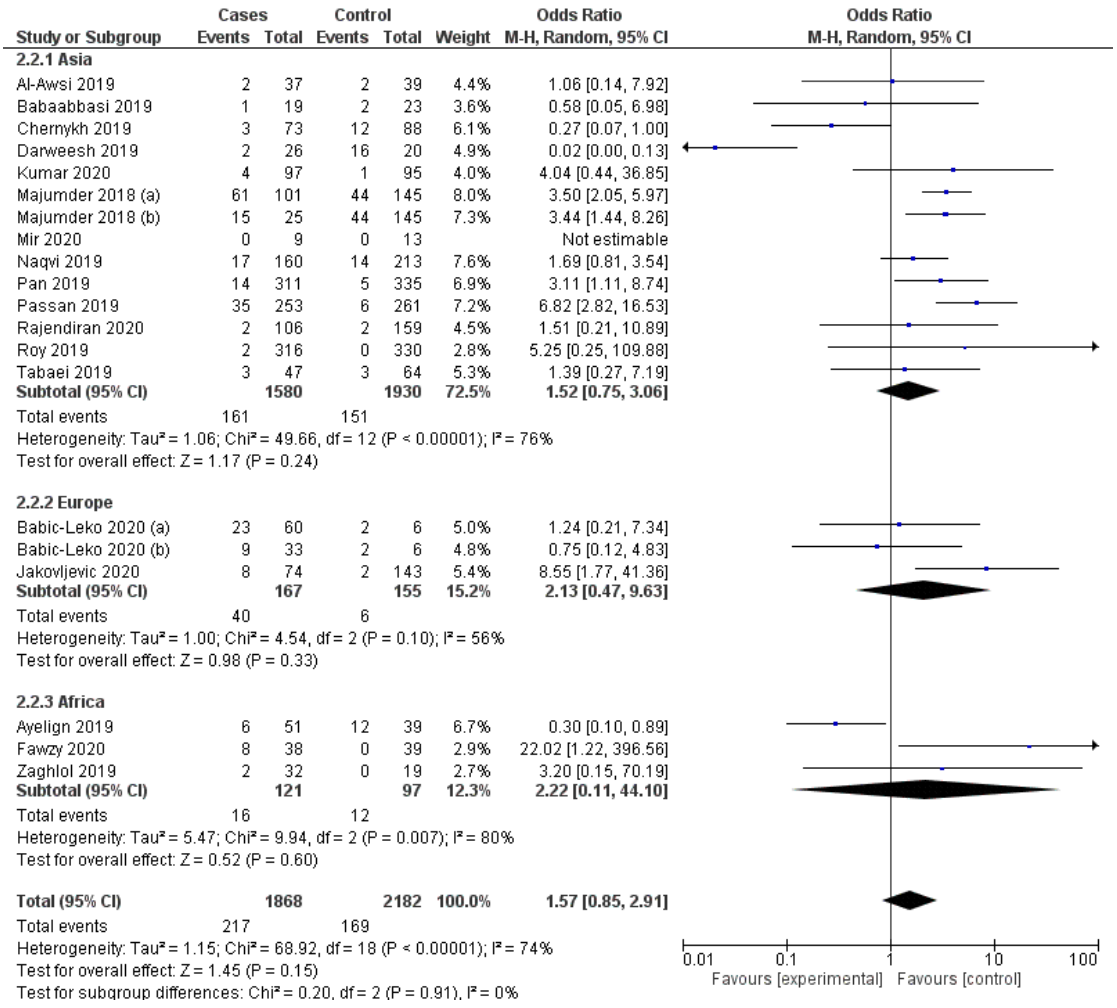

FIGURE 4.7: Meta-Analysis of 20 Case-Control Studies Represents Homozygous Model (AA Versus GG) with the Risk of Autoimmune Diseases for Subgroup Analysis Using Random-Effects Model (14 Asian, 3 European and 3 African Populations). The Odd Ratio (OD) and 95% Confidence Interval (CI) are Plotted on the Graph.

In heterozygous model (AG vs GG) of European populations, the OR is 1.52, 95% CI range is 0.98-2.36, P-value is 0.06 and diamond is on the right side that favors experimental group and associated with increased risk of multiple autoimmune disease. Heterogeneity is 0% and P(het) is 0.44 (Fig 4.8).

In heterozygous model (AG vs GG) of African population, the OR is 0.75, 95% CI range is 0.09-6.29, P-value is 0.79 and diamond touches the line of null effect that indicated no statistical association was found among TNF-α -308 G/A gene polymorphism and multiple autoimmune diseases. Heterogeneity is 87% and P(het) is $<$0.1 (Fig 4.8).

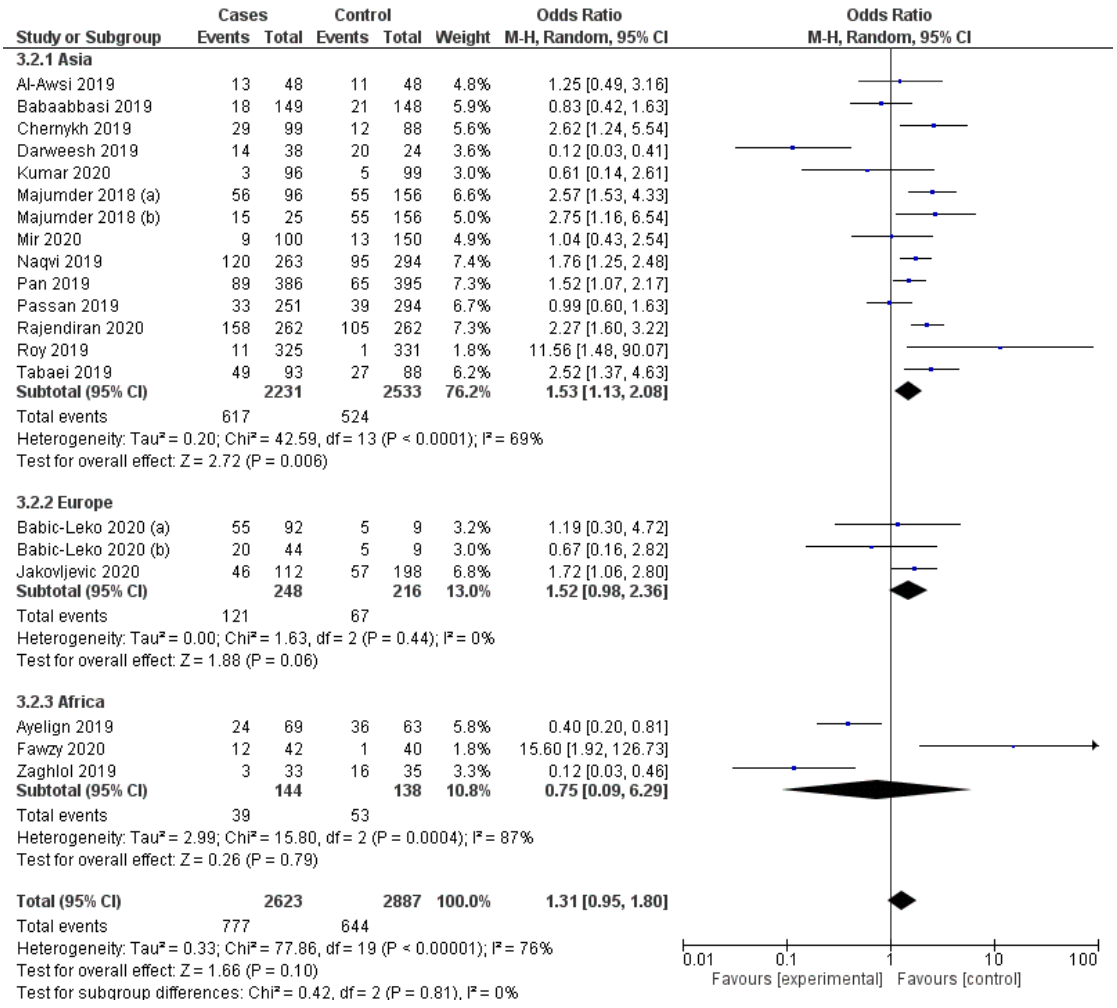

FIGURE 4.8: Meta-Analysis of 20 Case-Control Studies Represents Heterozygous Model (AG Versus GG) with the Risk of Autoimmune Diseases for Subgroup Analysis Using Random-Effects Model (14 Asian, 3 European and 3 African Populations). The Odd Ratio (OD) and 95% Confidence Interval (CI) are Plotted on the Graph.

In dominant model (AA+AG vs GG) of Asian populations, the OR is 1.22, 95% CI range is 0.75-1.97, P-value is 0.42 and diamond touches the line of null effect that indicated no statistical association was found among TNF-α -308 G/A gene polymorphism and multiple autoimmune diseases. Heterogeneity is 90% and P(het) is <0.1. In dominant model (AA+AG vs GG) of European populations, the OR is 1.57, 95% CI range is 0.92-2.66, P-value is 0.10 and diamond touches the line of null effect that indicated no statistical association was found among TNF-α -308 G/A gene polymorphism and multiple autoimmune diseases. Heterogeneity is 15% and P(het) is 0.31 (Fig 4.9). In dominant model (AA+AG vs GG) of African population, the OR is 1.00, 95% CI range is 0.12-8.70, P-value is 1.00

and diamond touches the line of null effect that indicated no statistical association was found among TNF-α -308 G/A gene polymorphism and multiple autoimmune diseases. Heterogeneity is 90% and P(het) is <0.1 (Fig 4.9).

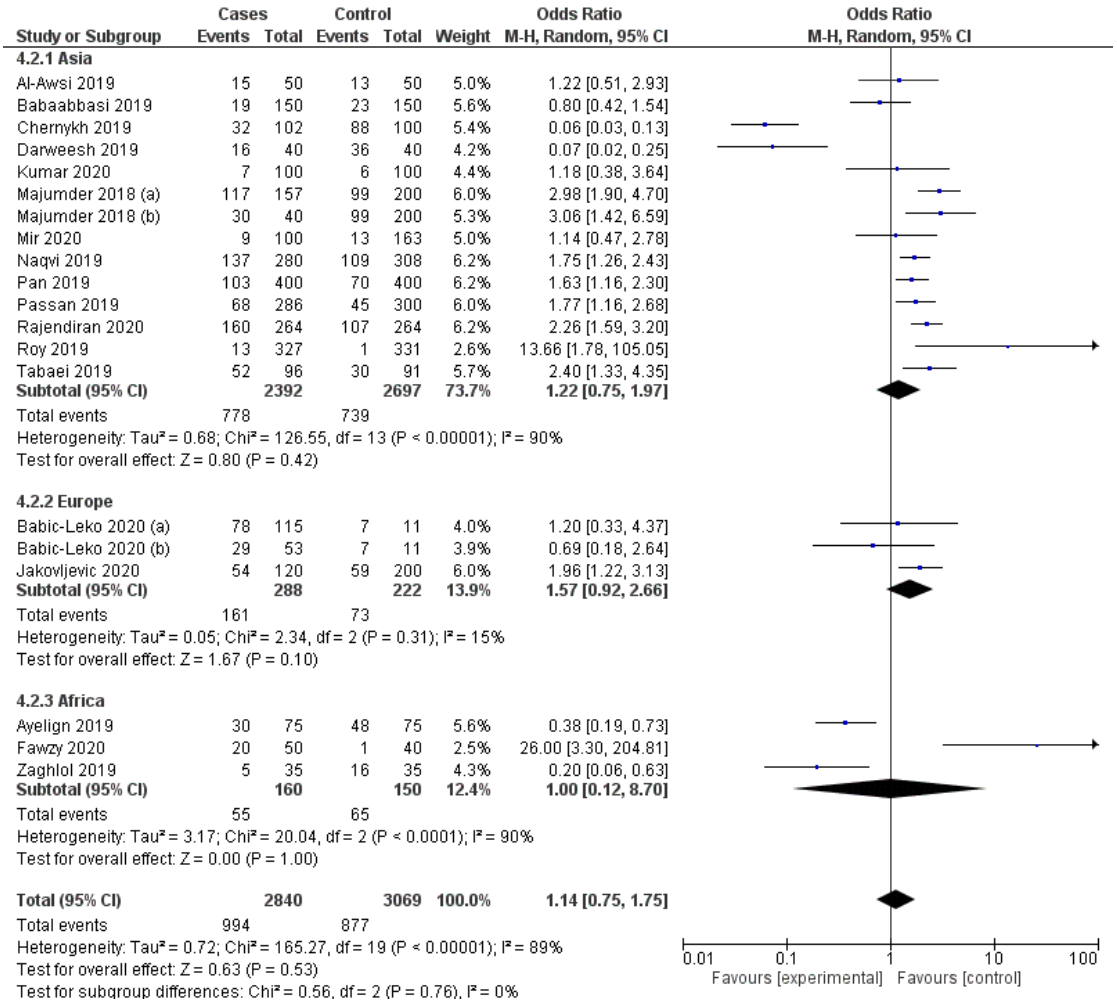

FIGURE 4.9: Meta-Analysis of 20 Case-Control Studies Represents Dominant Model (AA+AG Versus GG) with the Risk of Autoimmune Diseases for Subgroup Analysis Using Random-Effects Model (14 Asian, 3 European and 3 African Populations). The Odd Ratio (OD) and 95% Confidence Interval (CI) are Plotted on the Graph.

In recessive model (AA vs AG+GG) of Asian populations, the OR is 1.35, 95% CI range is 0.74-2.46, P-value is 0.32 and diamond touches the line of null effect that indicated no statistical association was found among TNF-α -308 G/A gene polymorphism and multiple autoimmune diseases. Heterogeneity is 70% and P(het) is <0.1. In recessive model (AA vs AG+GG) of European populations, the OR is 1.99, 95% CI range is 0.55-7.25, P-value is 0.30 and diamond touches the line of null effect that indicated no statistical association was found among TNF-α -308

G/A gene polymorphism and multiple autoimmune diseases. Heterogeneity is 48% and P(het) is 0.15. In recessive model (AA vs AG+GG) of African populations, the OR is 0.59, 95% CI range is 0.06-6.13, P-value is 0.66 and diamond touches the line of null effect that indicated no statistical association was found among TNF-α -308 G/A gene polymorphism and multiple autoimmune diseases. Heterogeneity is 83% and P(het) is <0.1 (Fig 4.10)

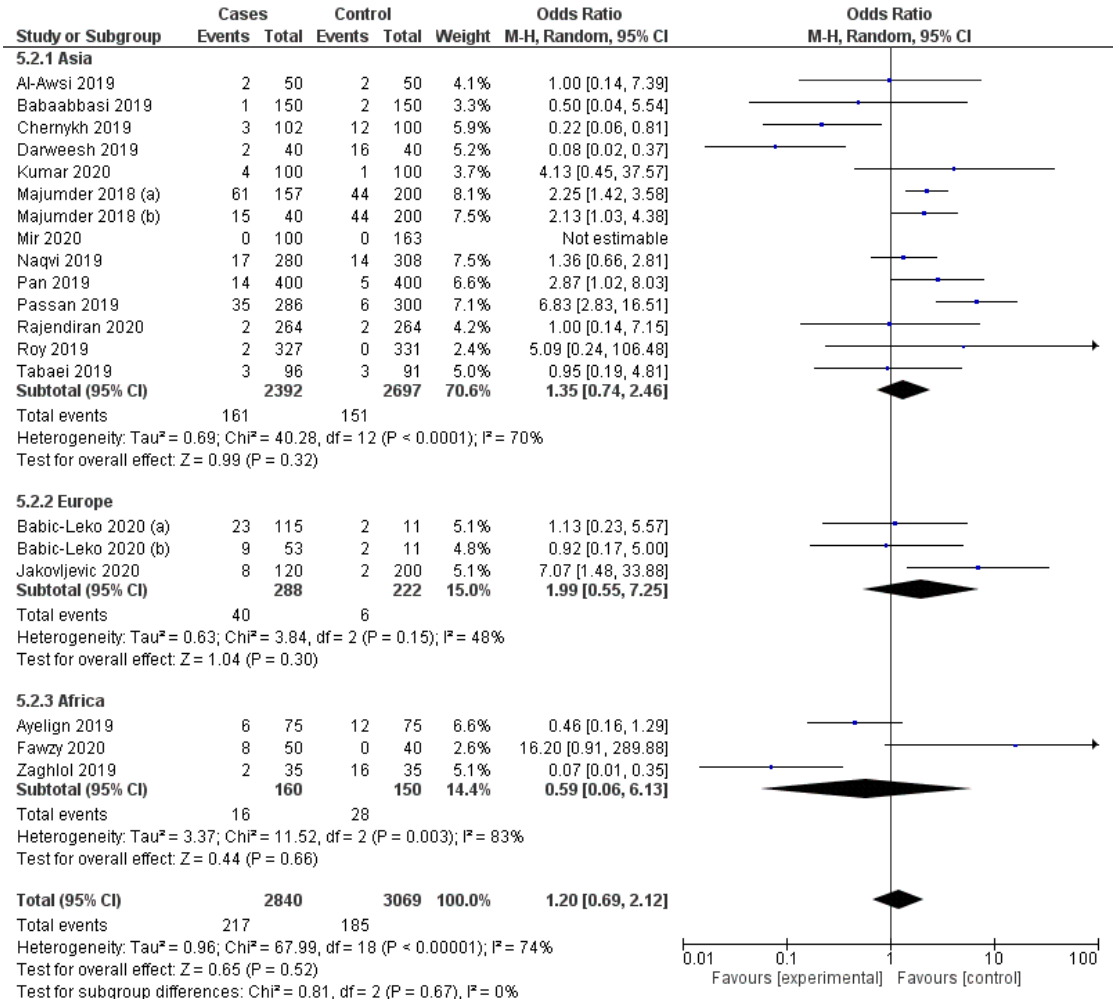

FIGURE 4.10: Meta-Analysis of 20 Case-Control Studies Represents Recessive Model (AA Versus AG+GG) with the Risk of Autoimmune Diseases for Subgroup Analysis Using Random-Effects Model (14 Asian, 3 European and 3 African Populations). The Odd Ratio (OD) and 95% Confidence Interval (CI) are Plotted on the Graph.

After subgroup analysis, the statistical significant association of TNF-α -308G/A gene polymorphism was found in allelic and heterozygous models in Asian populations and only in heterozygous model in European populations but no association of TNF-α -308G/A gene polymorphism with found in homozygous, dominant and

recessive model in Asian populations; allelic, homozygous, dominant and recessive models in European populations and all five genetic models in African populations suggest that different samples size and genetic background may be responsible for these differences. Clinical heterogeneity can also prove this difference among patients and controls. Our results also matched with other finding of the study showing the association of A allele of TNF-α -308 gene with Alzheimer's disease in Chinese (Asia) [263]. Our results also correlated with the findings of the study that indicated that no statistical association was found among the TNF-α with Alzheimer's disease in homozygous, dominant and recessive model [264]. Our results also correlated with the study that indicated the significant association of A allele of TNF-α gene with the increased risk of asthma [165].

This result correlated with the meta-analysis conducted by Song et al., 2013 that showed no association of A allele of TNF-α -308 gene with risk of periodontitis in Europeans [265]. But our result did not match with the meta-analysis conducted by Salles et al., 2017 in Brazil. Their results showed an association between genotype distribution of TNF-α -308G/A gene polymorphism with apical periodontitis [200]. TNF-α -308G/A gene polymorphism showed different role in different ethnic group of periodontal disease. It need to be explained why TNF-α -308G/A gene polymorphism shows no association with periodontitis in Europeans.

Our result in Europeans also correlated with the updated meta-analysis conducted by Wang, 2015 indicated that TNF-α -308G/A gene polymorphism not showed the significant protective effect for Alzheimer's disease in southern Europeans [263]. This study also correlated with the meta-analysis about Alzheimer's disease that showed no association with TNF-α -308G/A gene polymorphism [266].

Chapter 5

Conclusions and Recommendations

This meta-analysis was performed to find out the association of TNF-α -308G/A gene polymorphism with the risk of autoimmune diseases in Asian, Africans and Europeans population. Twenty studies were included for TNF-α rs1800629 with 2840 cases and 3069 controls focused on TNF-α -308G/A gene polymorphism. Meta-analysis was done by the Review Manager v5 software.

In summary, the results of our meta-analysis showed significant association of TNF-α -308G/A with increased risk of multiple autoimmune diseases, which indicated that A allele of TNF-α gene participate in the pathophysiology of many illnesses. Our results also indicated the significant association of TNF-α -308G/A gene polymorphism with increased risk of multiple autoimmune diseases, was observed in allelic (A vs G) and heterozygous model (AG vs GG) in Asian populations and in only heterozygous model (AG vs GG) in European populations, based on probability value <0.05 and position of diamond on right side. It enhances the idea of potential role for the anti-TNF therapy to maintain the physiological evidence of TNF-α. But no association of TNF-α -308G/A gene polymorphism with risk of multiple autoimmune diseases was observed in homozygous, dominant and recessive models in Asian populations: allelic, homozygous, dominant and recessive

models in European populations and all five genetic models (Allelic, homozygous, heterozygous, dominant and recessive models) in African populations because of probability value greater than 0.05.

This meta-analysis has some limitations. First, publication bias has not been done in our meta-analysis, so there is need to find the publication bias overall and within subgroups. Second, meta-analysis can also be performed on the basis of some other factors such as age, type of disease, country. Third, our meta-analysis included limited numbers of studies in the subgroup analysis. More studies can be selected to find out more evident results. Fourth, our meta-analysis was conducted on autoimmune diseases. This can be done on different cancers type. Fifth, our meta-analysis was conducted on the basis of only Asians, Europeans and Africans. This can be done on the basis of some other ethnic subgroups.

Bibliography

[1]. W. M. Chu, "Tumor necrosis factor", *Cancer letters*, vol. 328, no. 2, pp. 222-225, 2013.

[2]. E. Carswell, L. J. Old, R. Kassel, S. Green, N. Fiore, and B. Williamson, "An endotoxin-induced serum factor that causes necrosis of tumors", *Proceedings of the National Academy of Sciences*, vol. 72, no. 9, pp. 3666-3670, 1975.

[3]. D. J. MacEwan, "TNF receptor subtype signalling: differences and cellular consequences", *Cellular signalling*, vol. 14, no. 6, pp. 477-492, 2002.

[4]. U. Roy, "3D Modeling of Tumor Necrosis Factor Receptor and Tumor Necrosis Factor-bound Receptor Systems", *Molecular informatics*, vol. 38, no. 5, pp. 1800011, 2019.

[5]. G. Chen, and D. V. Goeddel, "TNF-R1 signaling: a beautiful pathway", *Science*, vol. 296, no. 5573, pp. 1634-1635, 2002.

[6]. E. Jones, D. Stuart, and N. Walker, "Structure of tumour necrosis factor", *Nature*, vol. 338, no. 6212, pp. 225-228, 1989.

[7]. E. Jones, D. Stuart, and N. Walker, "The structure of tumour necrosis factor-implications for biological function", *Journal of Cell Science*, vol. 1990, no. Supplement 13, pp. 11-18, 1990.

[8]. K. Tsukamoto, N. Ohta, Y. Shirai, and M. Emi, "A highly polymorphic CA repeat marker at the human tumor necrosis factor alpha (TNF-α) locus", *Journal of human genetics*, vol. 43, no. 4, pp. 278-279, 1998.

[9]. A. Wilson, F. Di Giovine, A. Blakemore, and G. Duff, "Single base polymorphism in the human tumour necrosis factor alpha (TNFα) gene detectable by Ncol restriction of PCR product", *Human molecular genetics*, vol. 1, no. 5, pp. 353-353, 1992.

[10]. N. J. Makhatadze, "Tumor necrosis factor locus: genetic organisation and biological implications", *Human immunology*, vol. 59, no. 9, pp. 571-579, 1998.

[11]. M. M. Elahi, K. Asotra, B. M. Matata, and S. S. Mastana, "Tumor necrosis factor alpha- 308 gene locus promoter polymorphism: an analysis of association with health and disease", *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*, vol. 1792, no. 3, pp. 163-172, 2009.

[12]. S. D'Alfonso, G. Colombo, S. D. Bella, R. Scorza, and P. Momigliano-Richiardi, "Association between polymorphisms in the TNF region and systemic lupus erythematosus in the Italian population", *Tissue Antigens*, vol. 47, no. 6, pp. 551-555, 1996.

[13]. M. Aidoo, P. D. McElroy, M. S. Kolczak, D. J. Terlouw, F. O. ter Kuile, B. Nahlen, A. A. Lal, and V. Udhayakumar, "Tumor necrosis factor-α promoter variant 2 (TNF2) is associated with pre-term delivery, infant mortality, and malaria morbidity in western Kenya: Asembo Bay Cohort Project IX", *Genetic Epidemiology: The Official Publication of the International Genetic Epidemiology Society*, vol. 21, no. 3, pp. 201-211, 2001.

[14]. J. P. Mira, A. Cariou, F. Grall, C. Delclaux, M. R. Losser, F. Heshmati, C. Cheval, M. Monchi, J. L. Teboul, and F. Riché, "Association of TNF2, a TNF-α promoter polymorphism, with septic shock susceptibility and mortality: a multicenter study", *Jama*, vol. 282, no. 6, pp. 561-568, 1999.

[15]. F. C. Kull, S. Jacobs, and P. Cuatrecasas, "Cellular receptor for 125I-labeled tumor necrosis factor: specific binding, affinity labeling, and relationship to sensitivity", *Proceedings of the National Academy of Sciences*, vol. 82, no. 17, pp. 5756-5760, 1985.

[16]. N. H. Ruddle, "Tumor necrosis factor and related cytotoxins", *Elsevier Current Trends*, 1987.

[17]. J. Mestan, W. Digel, S. Mittnacht, H. Hillen, D. Blohm, A. Möller, H. Jacobsen, and H. Kirchner, "Antiviral effects of recombinant tumour necrosis factor in vitro", *Nature*, vol. 323, no. 6091, pp. 816-819, 1986.

[18]. J. Playfair, and J. Taverne, "Tumour Necrosis Factor and Related Cytotoxins". pp. 192, 1987.

[19]. B. Beutler, and A. Cerami, "Tumor necrosis, cachexia, shock, and inflammation: a common mediator", *Annual review of biochemistry*, vol. 57, no. 1, pp. 505-518, 1988.

[20]. F. Wollheim, D. Heinegard, M. Palladino, T. Saxne, and N. Talal, "Tumour necrosis factor α in synovial fluid: difference between rheumatoid arthritis and reactive arthritis", *Arthritis Rheum*, vol. 30, no. suppl 4, pp. S129, 1987.

[21]. G. H. Wong, and D. V. Goeddel, "Tumour necrosis factors α and β inhibit virus replication and synergize with interferons", *Nature*, vol. 323, no. 6091, pp. 819-822, 1986.

[22]. K. Frei, C. Siepl, P. Groscurth, S. Bodmer, C. Schwerdel, and A. Fontana, "Antigen presentation and tumor cytotoxicity by interferon-γ-treated microglial cells", *European journal of immunology*, vol. 17, no. 9, pp. 1271-1278, 1987.

[23]. M. Sawada, N. Kondo, A. Suzumura, and T. Marunouchi, "Production of tumor necrosis factor-alpha by microglia and astrocytes in culture", *Brain research*, vol. 491, no. 2, pp. 394-397, 1989.

[24]. A. Millar, M. Singer, A. Meager, N. Foley, N. M. Johnson, and G. Rook, "Tumour necrosis factor in bronchopulmonary secretions of patients with adult respiratory distress syndrome", *The Lancet*, vol. 334, no. 8665, pp. 712-714, 1989.

[25]. A. H. Hajeer, and I. V. Hutchinson, "TNF-α gene polymorphism: Clinical and biological implications", *Microscopy research and technique*, vol. 50, no. 3, pp. 216-228, 2000.

[26]. V. Bernard, X. Pillois, I. Dubus, D. Benchimol, J. P. Labouyrie, T. Couffinhal, P. Coste, and J. Bonnet, "The –308 G/A tumor necrosis factor-α gene dimorphism: a risk factor for unstable angina", *Clinical Chemistry and Laboratory Medicine (CCLM)*, vol. 41, no. 4, pp. 511-516, 2003.

[27]. J. Fonseca, T. Carvalho, M. Cruz, P. Nero, M. Sobral, A. Mourao, J. Cavaleiro, D. Ligeiro, I. Abreu, and M. Carmo-Fonseca, "Polymorphism at position –308 of the tumour necrosis factor-α gene and rheumatoid arthritis pharmacogenetics", *Annals of the Rheumatic Diseases*, vol. 64, no. 5, pp. 793-794, 2005.

[28]. S. Gupta, "Tumor necrosis factor-α-induced apoptosis in T cells from aged humans: a role of TNFR-I and downstream signaling molecules", *Experimental gerontology*, vol. 37, no. 2-3, pp. 293-299, 2002.

[29]. A. A. Lobito, T. L. Gabriel, J. P. Medema, and F. C. Kimberley, "Disease causing mutations in the TNF and TNFR superfamilies: Focus on molecular mechanisms driving disease", *Trends in molecular medicine*, vol. 17, no. 9, pp. 494-505, 2011.

[30]. M. D. Turner, B. Nedjai, T. Hurst, and D. J. Pennington, "Cytokines and chemokines: at the crossroads of cell signalling and inflammatory disease", *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research*, vol. 1843, no. 11, pp. 2563-2582, 2014.

[31]. A. Ercolini, and S. D. Miller, "The role of infections in autoimmune disease", *Clinical & Experimental Immunology*, vol. 155, no. 1, pp. 1-15, 2009.

[32]. P. Marrack, J. Kappler, and B. L. Kotzin, "Autoimmune disease: why and where it occurs", *Nature medicine*, vol. 7, no. 8, pp. 899-905, 2001.

[33]. M. M. DeAngelis, L. A. Owen, M. A. Morrison, D. J. Morgan, M. Li, A. Shakoor, A. Vitale, S. Iyengar, D. Stambolian, and I. K. Kim, "Genetics of age-related macular degeneration (AMD)", *Human molecular genetics*, vol. 26, no. R1, pp. R45-R50, 2017.

[34]. G. I. N. A. (GINA). "Global stratetgy for asthma management and prevention 2009" 3 August, 2020; http://www.ginasthma.org.

[35]. R. J. Klein, C. Zeiss, E. Y. Chew, J. Y. Tsai, R. S. Sackler, C. Haynes, A. K. Henning, J. P. SanGiovanni, S. M. Mane, and S. T. Mayne, "Complement factor H polymorphism in age-related macular degeneration", *Science*, vol. 308, no. 5720, pp. 385-389, 2005.

[36]. L. Akhabir, and A. J. Sandford, "Genome-wide association studies for discovery of genes involved in asthma", *Respirology*, vol. 16, no. 3, pp. 396-406, 2011.

[37]. W. Y. Wang, M. S. Tan, J. T. Yu, and L. Tan, "Role of pro-inflammatory cytokines released from microglia in Alzheimer's disease", *Annals of translational medicine*, vol. 3, no. 10, 2015.

[38]. E. H. Corder, A. M. Saunders, W. J. Strittmatter, D. E. Schmechel, P. C. Gaskell, G. Small, A. Roses, J. Haines, and M. A. Pericak-Vance, "Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families", *Science*, vol. 261, no. 5123, pp. 921-923, 1993.

[39]. E. C. Dun, R. N. Taylor, and F. Wieser, "Advances in the genetics of endometriosis", *Genome medicine*, vol. 2, no. 10, pp. 75, 2010.

[40]. P. Koninckx, "The physiopathology of endometriosis: pollution and dioxin", *Gynecologic and obstetric investigation*, vol. 47, no. Suppl. 1, pp. 47-50, 1999.

[41]. A. Augoulea, A. Alexandrou, M. Creatsa, N. Vrachnis, and I. Lambrinoudaki, "Pathogenesis of endometriosis: the role of genetics, inflammation and oxidative stress", *Archives of gynecology and obstetrics*, vol. 286, no. 1, pp. 99-103, 2012.

[42]. M. L. Laine, W. Crielaard, and B. G. Loos, "Genetic susceptibility to periodontitis", *Periodontology*, vol. 58, no. 1, pp. 37-68, 2012.

[43]. T. C. Jakobs, R. T. Libby, Y. Ben, S. W. John, and R. H. Masland, "Retinal ganglion cell degeneration is topological but not cell type specific in DBA/2J mice", *The Journal of cell biology*, vol. 171, no. 2, pp. 313-325, 2005.

[44]. H. A. Quigley, and E. M. Addicks, "Regional differences in the structure of the lamina cribrosa and their relation to glaucomatous optic nerve damage", *Archives of ophthalmology*, vol. 99, no. 1, pp. 137-143, 1981.

[45]. M. Takamoto, and M. Araie, "Genetics of primary open angle glaucoma", *Japanese journal of ophthalmology*, vol. 58, no. 1, pp. 1-15, 2014.

[46]. A. J. Silman, and J. E. Pearson, "Epidemiology and genetics of rheumatoid arthritis", *Arthritis Res*, vol. 4, no. Suppl 3, pp. S265-72, 2002.

[47]. J. B. Imboden, "The immunopathogenesis of rheumatoid arthritis", *Annual Review of Pathology: Mechanisms of Disease*, vol. 4, pp. 417-434, 2009.

[48]. I. Muntean, R. Togănel, and T. Benedek, "Genetics of congenital heart disease: past and present", *Biochemical genetics*, vol. 55, no. 2, pp. 105-123, 2017.

[49]. J. I. Hoffman, and S. Kaplan, "The incidence of congenital heart disease", *Journal of the American college of cardiology*, vol. 39, no. 12, pp. 1890-1900, 2002.

[50]. G. Cervellin, and G. Lippi, "Of MIs and men-a historical perspective on the diagnostics of acute myocardial infarction". pp. 535-543, 2014.

[51]. S. Blankenberg, G. Luc, P. Ducimetière, D. Arveiler, J. Ferrières, P. Amouyel, A. Evans, F. o. Cambien, and L. Tiret, "Interleukin-18 and the risk of coronary heart disease in European men: the Prospective Epidemiological Study of Myocardial Infarction (PRIME)", *Circulation*, vol. 108, no. 20, pp. 2453-2459, 2003.

[52]. P. Welsh, P. Whincup, O. Papacosta, S. Wannamethee, L. Lennon, A. Thomson, A. Rumley, and G. Lowe, "Serum matrix metalloproteinase-9 and coronary heart disease: a prospective study in middle-aged men", *QJM: An International Journal of Medicine*, vol. 101, no. 10, pp. 785-791, 2008.

[53]. B. Jefferis, P. Whincup, P. Welsh, S. Wannamethee, A. Rumley, D. Lawlor, S. Ebrahim, and G. Lowe, "Prospective study of circulating soluble CD40 ligand concentrations and the incidence of cardiovascular disease in a nested prospective case–control study of older men and women", *Journal of Thrombosis and Haemostasis*, vol. 9, no. 8, pp. 1452-1459, 2011.

[54]. M. Woodward, P. Welsh, A. Rumley, H. Tunstall-Pedoe, and G. D. Lowe, "Do inflammatory biomarkers add to the discrimination of cardiovascular disease after allowing for social deprivation? Results from a 10-year cohort study in Glasgow, Scotland", *European heart journal*, vol. 31, no. 21, pp. 2669-2675, 2010.

[55]. N. E. Lane, and M. C. Nevitt, "Osteoarthritis, bone mass, and fractures: how are they related?", *Arthritis & Rheumatism*, vol. 46, no. 1, pp. 1-4, 2002.

[56]. D. M. Salter, S. L. Su, and H. S. Lee, "Epidemiology and genetics of osteoarthritis", *Journal of Medical Sciences*, vol. 34, no. 6, pp. 252, 2014.

[57]. J. Elliott, and M. Smith, "The acute management of intracerebral hemorrhage: a clinical review", *Anesthesia & Analgesia*, vol. 110, no. 5, pp. 1419-1427, 2010.

[58]. D. Woo, G. J. Falcone, W. J. Devan, W. M. Brown, A. Biffi, T. D. Howard, C. D. Anderson, H. B. Brouwers, V. Valant, and T. W. Battey, "Meta-analysis of genome-wide association studies identifies 1q22 as a susceptibility locus for intracerebral hemorrhage", *The American Journal of Human Genetics*, vol. 94, no. 4, pp. 511-521, 2014.

[59]. M. Stumvoll, B. J. Goldstein, and T. W. Van Haeften, "Type 2 diabetes: principles of pathogenesis and therapy", *The Lancet*, vol. 365, no. 9467, pp. 1333-1346, 2005.

[60]. M. S. H. Akash, K. Rehman, and A. Liaqat, "Tumor necrosis factor-alpha: role in development of insulin resistance and pathogenesis of type 2 diabetes mellitus", *Journal of cellular biochemistry*, vol. 119, no. 1, pp. 105-110, 2018.

[61]. R. Czajkowski, Meci nska-Jundziłł, K, "Current aspects of vitiligo genetics". *Postepy Dermatol. Alergol*, vol. 31, pp. 247-255, 2014.

[62]. M. S. Islam, "Hypertension: from basic research to clinical practice", *Hypertension: from basic research to clinical practice*, pp. 1-2: Springer, 2016.

[63]. G. Snider, "Defining chronic obstructive pulmonary disease", *Chronic obstructive pulmonary disease*, pp. 1-8: Springer, 1995.

[64]. M. Higham, N. Pride, A. Alikhan, and N. Morrell, "Tumour necrosis factor-alpha gene promoter polymorphism in chronic obstructive pulmonary disease", *European Respiratory Journal*, vol. 15, no. 2, pp. 281-284, 2000.

[65]. V. Chernykh, A. Shevchenko, V. Konenkov, V. Prokofiev, A. Eremina, and A. Trunov, "TNF-α gene polymorphisms: association with age-related macular degeneration in Russian population", *International Journal of Ophthalmology*, vol. 12, no. 1, pp. 25, 2019.

[66]. M. F. Darweesh, and E. J. Kadhem, "The Impact of Genetic variation at TNF-α -308G/A on their serum production and severity of Asthma disease". p. 062050, 2019.

[67]. M. Babić Leko, M. Nikolac Perković, N. Klepac, D. Š. Štrac, F. Borovečki, N. Pivac, P. R. Hof, and G. Šimić, "IL-1β, IL-6, IL-10 and TNF α Single Nucleotide Polymorphisms in Human Influence the Susceptibility to Alzheimer's Disease Pathology", *Journal of Alzheimer's Disease*, no. Preprint, pp. 1-19, 2020.

[68]. B. Babaabasi, A. Ahani, F. Sadeghi, H. Bashizade-Fakhar, and H. R. K. Khorshid, "The association between TNF-alpha gene polymorphisms and endometriosis in an Iranian population", *International Journal of Fertility & Sterility*, vol. 13, no. 1, pp. 6, 2019.

[69]. P. Majumder, K. Thou, M. Bhattacharya, V. Nair, S. Ghosh, and S. K. Dey, "Association of tumor necrosis factor-α (TNF-α) gene promoter polymorphisms with aggressive and chronic periodontitis in the eastern Indian population", *Bioscience Reports*, vol. 38, no. 4, 2018.

[70]. A. Jakovljevic, N. Nikolic, J. Carkic, K. Beljic-Ivanovic, I. Soldatovic, M. Miletic, M. Andric, and J. Milasin, "Association of polymorphisms in TNF-α, IL-1β, GSTM and GSTT genes with apical periodontitis: is there a link with herpesviral infection?", *International Endodontic Journal*, 2020.

[71]. J. Pan, J. Hu, X. Qi, and L. Xu, "Association study of a functional variant of TNF-α gene and serum TNF-α level with the susceptibility of congenital heart disease in a Chinese population", *Postgraduate medical journal*, pp. postgradmedj-2019-136621, 2019.

[72]. S. Tabaei, H. Mehrad-Majd, M. Soori, and S. Tabaee, "The effect of tumor necrosis factor-alpha (-308G/A) and interferon gamma (+874T/C) polymorphisms on susceptibility to coronary heart disease", *Nucleosides, Nucleotides and Nucleic Acids*, vol. 38, no. 10, pp. 701-712, 2019.

[73]. G. R. L. Al-Awsi, E. D. C. Al-garawi, and H. H. Abdulhussein, "Investigation of Tumor Necrosis Factor-Alpha (TNF-α) Gene Polymorphism in Patients with Hypertension in Al-Diwaniyah City, Iraq", *Journal of Global Pharma Technology*, vol. 10, no. 2S, pp. 144-148, 2019.

[74]. S. Passan, S. Goyal, M. A. Bhat, D. Singh, and V. Vanita, "Association of TNF-α gene alterations (c.-238G>A, c.-308G>A, c.-857C>T, c.-863G>A) with primary glaucoma in north Indian cohort", *Gene*, vol. 709, pp. 25-35, 2019.

[75]. S. K. B. Naqvi, M. Bibi, I. Murtaza, and Q. Javed, "Interleukin-6 (-572) and tumor necrosis factor α (-308 and -238) polymorphisms and risk of knee osteoarthritis in a Pakistani population: a case–control study", *Iranian Journal of Science and Technology, Transactions A: Science*, vol. 43, no. 4, pp. 1485-1490, 2019.

[76]. H. M. Zaghlol, S. Abdelshafy, R. A. Mohamed, and E. A. Abdelaleem, "Tumour necrosis factor gene polymorphisms in Egyptian patients with rheumatoid arthritis and their relation to disease activity and severity", *Central-european Journal of Immunology*, vol. 44, no. 3, pp. 277, 2019.

[77]. D. Roy, M. Ullah, B. Basak, M. Hasan, M. Tanzim, and A. Haque, "Identification of TNF-α -308G/A (rsl800629) polymorphism in Bangladeshi population related to type-2 diabetes", *J Appl Biol Biotech*, vol. 7, no. 06, pp. 25-30, 2019.

[78]. K. S. Rajendiran, M. Rajappa, L. Chandrashekar, D. M. Thappa, and P. Devaraju, "Association Analysis of Tumor Necrosis Factor Alpha Promoter Polymorphisms and Vitiligo Susceptibility in South Indian Tamils", *Dermatology*, pp. 1-11, Feb 19, 2020.

[79]. H. Mir, P. A. Koul, D. Bhat, and Z. A. Shah, "A case–control study of tumor necrosis factor-alpha promoter polymorphism and its serum levels in patients with chronic obstructive pulmonary disease in Kashmir, North India", *Lung India*, vol. 37, no. 3, pp. 204, 2020.

[80]. A. Cerami, "Inflammatory cytokines, Clinical immunology and immunopathology", vol. 62, no. 1, pp. S3-S10, 1992.

[81]. L. Wang, F. S. Wang, and M. E. Gershwin, "Human autoimmune diseases: a comprehensive update", *Journal of internal medicine*, vol. 278, no. 4, pp. 369-395, 2015.

[82]. L. Hang, R. M. Nakamura, and R. Tubbs, "Current concepts and advances in clinical laboratory testing for autoimmune diseases", *Critical reviews in clinical laboratory sciences*, vol. 34, no. 3, pp. 275-311, 1997.

[83]. S. Panda, and J. L. Ding, "Natural antibodies bridge innate and adaptive immunity", *The journal of immunology*, vol. 194, no. 1, pp. 13-20, 2015.

[84]. K. Nagamine, P. Peterson, H. S. Scott, J. Kudoh, S. Minoshima, M. Heino, K. J. Krohn, M. D. Lalioti, P. E. Mullis, and S. E. Antonarakis, "Positional cloning of the APECED gene", *Nature genetics*, vol. 17, no. 4, pp. 393-398, 1997.

[85]. S. Shah, E. Wu, V. K. Rao, and T. K. Tarrant, "Autoimmune lymphoproliferative syndrome: an update and review of the literature", *Current allergy and asthma reports*, vol. 14, no. 9, pp. 1-5, 2014.

[86]. L. M. Sollid, W. Pos, and K. W. Wucherpfennig, "Molecular mechanisms for contribution of MHC molecules to autoimmune diseases", *Current opinion in immunology*, vol. 31, pp. 24-30, 2014.

[87]. L. C. Kottyan, E. E. Zoller, J. Bene, X. Lu, J. A. Kelly, A. M. Rupert, C. J. Lessard, S. E. Vaughn, M. Marion, and M. T. Weirauch, "The IRF5–TNPO3 association with systemic lupus erythematosus has two components that other autoimmune disorders variably share", *Human molecular genetics*, vol. 24, no. 2, pp. 582-596, 2015.

[88]. A. Muto, S. Tashiro, O. Nakajima, H. Hoshino, S. Takahashi, E. Sakoda, D. Ikebe, M. Yamamoto, and K. Igarashi, "The transcriptional programme of antibody class switching involves the repressor Bach2", *Nature*, vol. 429, no. 6991, pp. 566-571, 2004.

[89]. A. Itoh-Nakadai, R. Hikota, A. Muto, K. Kometani, M. Watanabe-Matsui, Y. Sato, M. Kobayashi, A. Nakamura, Y. Miura, and Y. Yano, "The transcription repressors Bach2 and Bach1 promote B cell development by repressing the myeloid program", *Nature immunology*, vol. 15, no. 12, pp. 1171-1180, 2014.

[90]. R. Roychoudhuri, K. Hirahara, K. Mousavi, D. Clever, C. A. Klebanoff, M. Bonelli, G. Sciumè, H. Zare, G. Vahedi, and B. Dema, "BACH2 represses effector programs to stabilize T reg-mediated immune homeostasis", *Nature*, vol. 498, no. 7455, pp. 506-510, 2013.

[91]. A. Zhernakova, S. Withoff, and C. Wijmenga, "Clinical implications of shared genetics and pathogenesis in autoimmune diseases", *Nature Reviews Endocrinology*, vol. 9, no. 11, pp. 646-659, 2013.

[92]. P. Quintero-Ronderos, and G. Montoya-Ortiz, "Epigenetics and autoimmune diseases", *Autoimmune diseases*, vol. 2012, 2012.

[93]. D. Fradin, S. Le Fur, C. Mille, N. Naoui, C. Groves, D. Zelenika, M. I. McCarthy, M. Lathrop, and P. Bougneres, "Association of the CpG methylation pattern of the proximal insulin gene promoter with type 1 diabetes", *PloS one*, vol. 7, no. 5, pp. e362-78, 2012.

[94]. S. Colafrancesco, C. Perricone, R. Priori, G. Valesini, and Y. Shoenfeld, "Sjögren's syndrome: another facet of the autoimmune/inflammatory syndrome induced by adjuvants (ASIA)", *Journal of autoimmunity*, vol. 51, pp. 10-16, 2014.

[95]. S. Kivity, M. T. Arango, M. Ehrenfeld, O. Tehori, Y. Shoenfeld, J.-M. Anaya, and N. Agmon-Levin, "Infection and autoimmunity in Sjogren's syndrome: a clinical study and comprehensive review", *Journal of autoimmunity*, vol. 51, pp. 17-22, 2014.

[96]. D. P. Bogdanos, D. S. Smyk, P. Invernizzi, E. I. Rigopoulou, M. Blank, S. Pouria, and Y. Shoenfeld, "Infectome: a platform to trace infectious triggers of autoimmunity", *Autoimmunity reviews*, vol. 12, no. 7, pp. 726-740, 2013.

[97]. L. Guilherme, S. E. Oshiro, K. C. Faé, E. Cunha-Neto, G. Renesto, A. C. Goldberg, A. C. Tanaka, P. M. Pomerantzeff, M. H. Kiss, and C. Silva, "T-cell reactivity against streptococcal antigens in the periphery mirrors reactivity of heart-infiltrating T lymphocytes in rheumatic heart disease patients", *Infection and Immunity*, vol. 69, no. 9, pp. 5345-5351, 2001.

[98]. M. Blank, O. Barzilai, and Y. Shoenfeld, "Molecular mimicry and autoimmunity", *Clinical reviews in allergy & immunology*, vol. 32, no. 1, pp. 111-118, 2007.

[99]. B. B. Aggarwal, "Structure of tumor necrosis factor and its receptor", *Biotherapy*, vol. 3, no. 2, pp. 113-120, 1991.

[100]. J. Rothe, G. Gehr, H. Loetscher, and W. Lesslauer, "Tumor necrosis factor receptors-structure and function", *Immunologic research*, vol. 11, no. 2, pp. 81-90, 1992.

[101]. M. Carbone, B. H. Ly, R. F. Dodson, I. Pagano, P. T. Morris, U. A. Dogan, A. F. Gazdar, H. I. Pass, and H. Yang, "Malignant mesothelioma: facts, myths, and hypotheses", *Journal of cellular physiology*, vol. 227, no. 1, pp. 44-58, 2012.

[102]. J. M. Argilés, J. López-Soriano, S. Busquets, and F. J. López-Soriano, "Journey from cachexia to obesity by TNF", *The FASEB journal*, vol. 11, no. 10, pp. 743-751, 1997.

[103]. D. E. Moller, "Potential role of TNF-α in the pathogenesis of insulin resistance and type 2 diabetes", *Trends in Endocrinology & Metabolism*, vol. 11, no. 6, pp. 212-217, 2000.

[104]. M. Kawakami, P. H. Pekala, M. D. Lane, and A. Cerami, "Lipoprotein lipase suppression in 3T3-L1 cells by an endotoxin-induced mediator from exudate cells", *Proceedings of the National Academy of Sciences*, vol. 79, no. 3, pp. 912-916, 1982.

[105]. P. Pekala, M. Kawakami, W. Vine, M. D. Lane, and A. Cerami, "Studies of insulin resistance in adipocytes induced by macrophage mediator", *The Journal of experimental medicine*, vol. 157, no. 4, pp. 1360-1365, 1983.

[106]. J. M. Stephens, and P. Pekala, "Transcriptional repression of the GLUT4 and C/EBP genes in 3T3-L1 adipocytes by tumor necrosis factor-alpha", *Journal of Biological Chemistry*, vol. 266, no. 32, pp. 21839-21845, 1991.

[107]. S. C. Souza, L. M. de Vargas, M. T. Yamamoto, P. Lien, M. D. Franciosa, L. G. Moss, and A. S. Greenberg, "Overexpression of perilipin A and B blocks the ability of tumor necrosis factor α to increase lipolysis in 3T3-L1 adipocytes", *Journal of Biological Chemistry*, vol. 273, no. 38, pp. 24665-24669, 1998.

[108]. M. Moldes, F. Lasnier, X. Gauthereau, C. Klein, J. Pairault, B. Fève, and A.-M. Chambaut-Guérin, "Tumor necrosis factor-α-induced adipose-related protein (TIARP), a cell-surface protein that is highly induced by tumor necrosis factor-α and adipose conversion", *Journal of Biological Chemistry*, vol. 276, no. 36, pp. 33938-33946, 2001.

[109]. A. G. Wilson, J. A. Symons, T. L. McDowell, H. O. McDevitt, and G. W. Duff, "Effects of a polymorphism in the human tumor necrosis factor α promoter on transcriptional activation", *Proceedings of the National Academy of Sciences*, vol. 94, no. 7, pp. 3195-3199, 1997.

[110]. T. Kubota, D. M. McNamara, J. J. Wang, M. Trost, C. F. McTiernan, D. L. Mann, and A. M. Feldman, "Effects of tumor necrosis factor gene polymorphisms on patients with congestive heart failure", *Circulation*, vol. 97, no. 25, pp. 2499-2501, 1998.

[111]. M. Karimi, L. C. Goldie, M. N. Cruickshank, E. K. Moses, and L. J. Abraham, "A critical assessment of the factors affecting reporter gene assays for promoter SNP function: a reassessment of -308 TNF polymorphism function using a novel integrated reporter system", *European journal of human genetics*, vol. 17, no. 11, pp. 1454-1462, 2009.

[112]. Y. L. Lee, R. McConnell, K. Berhane, and F. Gilliland, "Ambient ozone modifies the effect of tumor necrosis factor -G308A on bronchitic symptoms among children with asthma", *Allergy*, vol. 64, no. 9, pp. 1342-1348, 2009.

[113]. A. Wilson, N. De Vries, F. d. Pociot, F. Di Giovine, L. Van der Putte, and G. Duff, "An allelic polymorphism within the human tumor necrosis factor alpha promoter region is strongly associated with HLA A1, B8, and DR3 alleles", *The Journal of experimental medicine*, vol. 177, no. 2, pp. 557-560, 1993.

[114]. C. J. Murray, and A. D. Lopez, "Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study", *The lancet*, vol. 349, no. 9064, pp. 1498-1504, 1997.

[115]. J. Manfreda, Y. Mao, and W. Litven, "Morbidity and Mortality from Chronic Obstructive Pulmonary Disease1, 2", *Am Rev Respir Dis*, vol. 140, pp. S19-S26, 1989.

[116]. A. B. Thompson, D. Daughton, R. A. Robbins, M. A. Ghafouri, M. Oehlerking, and S. I. Rennard, "Intraluminal airway inflammation in chronic bronchitis", *Am Rev Respir Dis*, vol. 140, no. 6, pp. 1527-1537, 1989.

[117]. V. M. Keatings, P. D. Collins, D. M. Scott, and P. J. Barnes, "Differences in interleukin-8 and tumor necrosis factor-alpha in induced sputum from patients with chronic obstructive pulmonary disease or asthma", *American journal of respiratory and critical care medicine*, vol. 153, no. 2, pp. 530-534, 1996.

[118]. P. S. Thomas, D. H. Yates, and P. J. Barnes, "Tumor necrosis factor-alpha increases airway responsiveness and sputum neutrophilia in normal human subjects", *American journal of respiratory and critical care medicine*, vol. 152, no. 1, pp. 76-80, 1995.

[119]. A. Chamba, S. C. Afford, R. A. Stockley, and D. Burnett, "Extracellular proteolysis of fibronectin by neutrophils: characterization and the effects of

recombinant cytokines", *Am J Respir Cell Mol Biol*, vol. 4, no. 4, pp. 330-337, 1991.

[120]. T. Tetley, "New perspectives on basic mechanisms in lung disease. 6. Proteinase imbalance: its role in lung disease", *Thorax*, vol. 48, no. 5, pp. 560-565, 1993.

[121]. V. M. Keatings, S. J. Cave, M. J. Henry, K. Morgan, C. M. O'Connor, M. X. FitzGerald, and N. Kalsheker, "A polymorphism in the tumor necrosis factor-α gene promoter region may predispose to a poor prognosis in COPD", *Chest*, vol. 118, no. 4, pp. 971-975, 2000.

[122]. R. K. Shukla, S. Kant, S. Bhattacharya, and B. Mittal, "Association of cytokine gene polymorphisms in patients with chronic obstructive pulmonary disease", *Oman Medical Journal*, vol. 27, no. 4, pp. 285, 2012.

[123]. C. Shi, and H. Zhao, "Association between Tumor Necrosis Factor-308 G/A Polymorphism and Chronic Obstructive Pulmonary Disease Risk in Chinese Population: Evidence from a Meta-Analysis", *Clinical laboratory*, vol. 65, no. 10, 2019.

[124]. M. S. Asl, A. Ahmadi, J. Salimian, S. Shohani, S. A. Jamalkandi, and M. Ghanei, "TNF-α -308G/A variant and susceptibility to chronic obstructive pulmonary disease: A systematic review and meta-analysis", *Cytokine*, vol. 123, pp. 154763, 2019.

[125]. S. C. Warner, and A. M. Valdes, "The genetics of osteoarthritis: A review", *Journal of Functional Morphology and Kinesiology*, vol. 1, no. 1, pp. 140-153, 2016.

[126]. R. Bitton, "The economic burden of osteoarthritis", *The American journal of managed care*, vol. 15, no. 8 Suppl, pp. S230-5, 2009.

[127]. A. M. Valdes, S. A. Doherty, W. Zhang, K. R. Muir, R. A. Maciewicz, and M. Doherty, "Inverse relationship between preoperative radiographic severity and postoperative pain in patients with osteoarthritis who have undergone

total joint arthroplasty": *InSeminars in arthritis snd rheumatism*, vol. 41, no. 4, pp. 568-575, 2012.

[128]. C. Baugé, N. Girard, E. Lhuissier, C. Bazille, and K. Boumediene, "Regulation and role of TGFβ signaling pathway in aging and osteoarthritis joints", *Aging and disease*, vol. 5, no. 6, pp. 394, 2014.

[129]. K. Chapman, and A. M. Valdes, "Genetic factors in OA pathogenesis", *Bone*, vol. 51, no. 2, pp. 258-264, 2012.

[130]. Y. Miyamoto, D. Shi, M. Nakajima, K. Ozaki, A. Sudo, A. Kotani, A. Uchida, T. Tanaka, N. Fukui, and T. Tsunoda, "Common variants in DVWA on chromosome 3p24.3 are associated with susceptibility to knee osteoarthritis", *Nature genetics*, vol. 40, no. 8, pp. 994-998, 2008.

[131]. J. Martel-Pelletier, D. Lajeunesse, and J.-P. Pelletier, "Etiopathogenesis of osteoarthritis, Arthritis and Allied Conditions": *A Textbook of Rheumatology*, vol. 15, pp. 2199-2226, 2005.

[132]. N. Alaaeddine, J. DiBattista, J. Pelletier, J. Cloutier, K. Kiansa, M. Dupuis, and J. Martel-Pelletier, "Osteoarthritic synovial fibroblasts possess an increased level of tumor necrosis factor-receptor 55 (TNF-R55) that mediates biological activation by TNF-alpha", *The Journal of rheumatology*, vol. 24, no. 10, pp. 1985-1994, 1997.

[133]. M. Lotz, R. Terkeltaub, and P. Villiger, "Cartilage and joint inflammation. Regulation of IL-8 expression by human articular chondrocytes", *The Journal of Immunology*, vol. 148, no. 2, pp. 466-473, 1992.

[134]. V. Afonso, R. Champy, D. Mitrovic, P. Collin, and A. Lomri, "Reactive oxygen species and superoxide dismutases: role in joint diseases", *Joint bone spine*, vol. 74, no. 4, pp. 324-329, 2007.

[135]. J. L. Scott, C. Gabrielides, R. K. Davidson, T. E. Swingler, I. M. Clark, G. A. Wallis, R. P. Boot-Handford, T. B. Kirkwood, R. W. Talyor, and D. A. Young, "Superoxide dismutase downregulation in osteoarthritis progression

and end-stage disease", *Annals of the rheumatic diseases*, vol. 69, no. 8, pp. 1502-1510, 2010.

[136]. A. B. Blom, S. M. Brockbank, P. L. van Lent, H. M. van Beuningen, J. Geurts, N. Takahashi, P. M. van der Kraan, F. A. van de Loo, B. W. Schreurs, and K. Clements, "Involvement of the Wnt signaling pathway in experimental and human osteoarthritis: prominent role of Wnt-induced signaling protein 1", *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology*, vol. 60, no. 2, pp. 501-512, 2009.

[137]. J. Saklatvala, "Tumour necrosis factor α stimulates resorption and inhibits synthesis of proteoglycan in cartilage", *Nature*, vol. 322, no. 6079, pp. 547-549, 1986.

[138]. M. R. Sobhan, M. Mahdinezhad-Yazdi, K. Aghili, M. Zare-Shehneh, S. Rastegar, J. Sadeghizadeh-Yazdi, and H. Neamatzadeh, "Association of TNF-α -308G/A and -238G/A polymorphisms with knee osteoarthritis risk: a case-control study and meta-analysis", *Journal of orthopaedics*, vol. 15, no. 3, pp. 747-753, 2018.

[139]. F. Grassmann, S. Fauser, and B. H. Weber, "The genetics of age-related macular degeneration (AMD)–Novel targets for designing treatment options?", *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 95, pp. 194-202, 2015.

[140]. Y. Chen, M. Bedell, and K. Zhang, "Age-related macular degeneration: genetic and environmental factors of disease", *Molecular interventions*, vol. 10, no. 5, pp. 271, 2010.

[141]. N. M. Bressler, "Early detection and treatment of neovascular age-related macular degeneration", *The Journal of the American Board of Family Practice*, vol. 15, no. 2, pp. 142-152, 2002.

[142]. S. Dithmar, N. A. Sharara, C. A. Curcio, N. A. Le, Y. Zhang, S. Brown, and H. E. Grossniklaus, "Murine high-fat diet and laser photochemical model

of basal deposits in Bruch membrane", *Archives of ophthalmology*, vol. 119, no. 11, pp. 1643-1649, 2001.

[143]. L. G. Fritsche, R. N. Fariss, D. Stambolian, G. R. Abecasis, C. A. Curcio, and A. Swaroop, "Age-related macular degeneration: genetics and biology coming together", *Annual review of genomics and human genetics*, vol. 15, pp. 151-171, 2014.

[144]. M. M. DeAngelis, A. C. Silveira, E. A. Carr, and I. K. Kim, "Genetics of age-related macular degeneration: current concepts, future directions": *In-Saminars in opthalmology*, vol. 26, no. 3, pp. 77-93, 2011.

[145]. T. Clemons, R. C. Milton, R. Klein, and J. Seddon, "Risk factors for the incidence of advanced age-related macular degeneration in the Age-Related Eye Disease Study (AREDS) AREDS report no. 19", *Ophthalmology*, vol. 112, no. 4, pp. 533-539, 2005.

[146]. I. C. Munch, A. Linneberg, and M. Larsen, "Precursors of age-related macular degeneration: associations with physical activity, obesity, and serum lipids in the inter99 eye study", *Investigative ophthalmology & visual science*, vol. 54, no. 6, pp. 3932-3940, 2013.

[147]. H. Oh, H. Takagi, C. Takagi, K. Suzuma, A. Otani, K. Ishida, M. Matsumura, Y. Ogura, and Y. Honda, "The potential angiogenic role of macrophages in the formation of choroidal neovascular membranes", *Investigative ophthalmology & visual science*, vol. 40, no. 9, pp. 1891-1898, 1999.

[148]. D. Armstrong, A. J. Augustin, R. Spengler, A. Al-Jada, T. Nickola, F. Grus, and F. Koch, "Detection of vascular endothelial growth factor and tumor necrosis factor alpha in epiretinal membranes of proliferative diabetic retinopathy, proliferative vitreoretinopathy and macular pucker", *Ophthalmologica*, vol. 212, no. 6, pp. 410-414, 1998.

[149]. S. Majka, P. G. McGuire, and A. Das, "Regulation of matrix metalloproteinase expression by tumor necrosis factor in a murine model of retinal

neovascularization", *Investigative ophthalmology & visual science*, vol. 43, no. 1, pp. 260-266, 2002.

[150]. J. L. Olson, R. J. Courtney, and N. Mandava, "Intravitreal infliximab and choroidal neovascularization in an animal model", *Archives of Ophthalmology*, vol. 125, no. 9, pp. 1221-1224, 2007.

[151]. A. B. Lentsch, and P. A. Ward, "Regulation of inflammatory vascular damage", *The Journal of pathology*, vol. 190, no. 3, pp. 343-348, 2000.

[152]. A. Blann, "Endothelial cell activation, injury, damage and dysfunction: separate entities or mutual terms?", *Blood coagulation & fibrinolysis*, vol. 11, no. 7, pp. 623-630, 2000.

[153]. C. Shi, and E. G. Pamer, "Monocyte recruitment during infection and inflammation", *Nature reviews immunology*, vol. 11, no. 11, pp. 762-774, 2011.

[154]. M. H. J. Bonyadi, M. Bonyadi, H. Ahmadieh, N. Fotuhi, N. Shoeibi, S. Saadat, and Z. Yagubi, "Tumor necrosis factor gene polymorphisms in advanced non-exudative age-related macular degeneration", *Journal of ophthalmic & vision research*, vol. 10, no. 2, pp. 155, 2015.

[155]. Z. S. Ulhaq, "Genetic polymorphisms associated with Age-related macular degeneration", *International Journal of Retina*, vol. 3, no. 1, 2020.

[156]. M. Bijanzadeh, P. Mahesh, and N. Ramachandra, "An understanding of the genetic basis of asthma", The *Indian journal of medical research*, vol. 133, no. 2, pp. 149-161, 2011.

[157]. Y. Lee, K. Cheon, H. Lee, W. Kim, Y. Rhee, and D. Kim, "Gene polymorphisms of endothelial nitric oxide synthase and angiotensin-converting enzyme in patients with asthma", *Allergy*, vol. 55, no. 10, pp. 959-963, 2000.

[158]. X. Xu, Z. Fang, B. Wang, C. Chen, W. Guang, Y. Jin, J. Yang, S. Lewitzky, A. Aelony, and A. Parker, "A genomewide search for quantitative-trait loci

underlying asthma", *The American Journal of Human Genetics*, vol. 69, no. 6, pp. 1271-1277, 2001.

[159]. H. Los, G. Koppelman, and D. Postma, "The importance of genetic influences in asthma", *European Respiratory Journal*, vol. 14, no. 5, pp. 1210-1227, 1999.

[160]. S. J. Lin, L. Y. Chang, D. C. Yan, Y. J. Huang, T. J. Lin, and T. Y. Lin, "Decreased intercellular adhesion molecule-1 (CD54) and L-selectin (CD62L) expression on peripheral blood natural killer cells in asthmatic children with acute exacerbation", *Allergy*, vol. 58, no. 1, pp. 67-71, 2003.

[161]. R. E. Slager, G. A. Hawkins, X. Li, D. S. Postma, D. A. Meyers, and E. R. Bleecker, "Genetics of asthma susceptibility and severity", *Clinics in chest medicine*, vol. 33, no. 3, pp. 431-443, 2012.

[162]. N. Hernandez-Pacheco, M. Pino-Yanes, and C. Flores, "Genomic predictors of asthma phenotypes and treatment response", *Frontiers in pediatrics*, vol. 7, pp. 6, 2019.

[163]. J. R. Mammen, and K. Arcoleo, "Understanding the genetics of asthma and implications for clinical practice", *Journal of the American Association of Nurse Practitioners*, vol. 31, no. 7, pp. 384-387, 2019.

[164]. M. Hirose, and T. Horiguchi, "Asthma phenotypes", *Journal of General and Family Medicine*, vol. 18, no. 5, pp. 189-194, 2017.

[165]. S. W. Kang, S. K. Kim, Y. R. Han, D. Hong, J. Chon, J.-H. Chung, S.-J. Hong, M.-S. Park, and J. Y. Ban, "Promoter Polymorphism (-308G/A) of Tumor Necrosis Factor-Alpha (TNF-α) Gene and Asthma Risk: An Updated Meta-Analysis", *Genetic testing and molecular biomarkers*, vol. 23, no. 6, pp. 363-372, 2019.

[166]. H. Sun, Q. Li, Y. Jin, and H. Qiao, "Associations of tumor necrosis factor-α polymorphisms with the risk of asthma: a meta-analysis", *Experimental and Molecular Pathology*, vol. 105, no. 3, pp. 411-416, 2018.

[167]. L. Bertram, C. M. Lill, and R. E. Tanzi, "The genetics of Alzheimer disease: back to the future", *Neuron*, vol. 68, no. 2, pp. 270-281, 2010.

[168]. C. Holmes, C. Cunningham, E. Zotova, D. Culliford, and V. Perry, "Proinflammatory cytokines, sickness behavior and Alzheimer disease", *Neurology*, vol. 77, no. 3, pp. 212-218, 2011.

[169]. L. Bertram, and R. E. Tanzi, "The genetics of Alzheimer's disease", *Progress in molecular biology and translational science*, vol. 107, pp. 79-100: Elsevier, 2012.

[170]. M. C. Janelsins, M. A. Mastrangelo, K. M. Park, K. L. Sudol, W. C. Narrow, S. Oddo, F. M. LaFerla, L. M. Callahan, H. J. Federoff, and W. J. Bowers, "Chronic neuron-specific tumor necrosis factor-alpha expression enhances the local inflammatory environment ultimately leading to neuronal death in 3xTg-AD mice", *The American journal of pathology*, vol. 173, no. 6, pp. 1768-1782, 2008.

[171]. F. E. McAlpine, J.-K. Lee, A. S. Harms, K. A. Ruhn, M. Blurton-Jones, J. Hong, P. Das, T. E. Golde, F. M. LaFerla, and S. Oddo, "Inhibition of soluble TNF signaling in a mouse model of Alzheimer's disease prevents pre-plaque amyloid-associated neuropathology", *Neurobiology of disease*, vol. 34, no. 1, pp. 163-177, 2009.

[172]. S. L. Montgomery, M. A. Mastrangelo, D. Habib, W. C. Narrow, S. A. Knowlden, T. W. Wright, and W. J. Bowers, "Ablation of TNF-RI/RII expression in Alzheimer's disease mice leads to an unexpected enhancement of pathology: implications for chronic pan-TNF-α suppressive therapeutic strategies in the brain", *The American journal of pathology*, vol. 179, no. 4, pp. 2053-2070, 2011.

[173]. X. Cheng, L. Yang, P. He, R. Li, and Y. Shen, "Differential activation of tumor necrosis factor receptors distinguishes between brains from Alzheimer's disease and non-demented patients", *Journal of Alzheimer's Disease*, vol. 19, no. 2, pp. 621-630, 2010.

[174]. P. He, Z. Zhong, K. Lindholm, L. Berning, W. Lee, C. Lemere, M. Staufenbiel, R. Li, and Y. Shen, "Deletion of tumor necrosis factor death receptor inhibits amyloid β generation and prevents learning and memory deficits in Alzheimer's mice", *The Journal of cell biology*, vol. 178, no. 5, pp. 829-841, 2007.

[175]. S. L. Montgomery, W. C. Narrow, M. A. Mastrangelo, J. A. Olschowka, M. K. O'Banion, and W. J. Bowers, "Chronic neuron-and age-selective down-regulation of TNF receptor expression in triple-transgenic Alzheimer disease mice leads to significant modulation of amyloid-and Tau-related pathologies", *The American journal of pathology*, vol. 182, no. 6, pp. 2285-2297, 2013.

[176]. F. Su, F. Bai, and Z. Zhang, "Inflammatory cytokines and Alzheimer's disease: a review from the perspective of genetic polymorphisms", *Neuroscience bulletin*, vol. 32, no. 5, pp. 469-480, 2016.

[177]. Y. H. Lee, S. J. Choi, J. D. Ji, and G. G. Song, "Association between TNF-α promoter -308A/G polymorphism and Alzheimer's disease: a meta-analysis", *Neurological Sciences*, vol. 36, no. 6, pp. 825-832, 2015.

[178]. M. Zheng, B. Chang, L. Tian, C. Shan, H. Chen, Y. Gao, G. Huang, and M. Zhang, "Relationship between inflammatory markers and mild cognitive impairment in Chinese patients with type 2 diabetes: a case-control study", *BMC endocrine disorders*, vol. 19, no. 1, pp. 73, 2019.

[179]. B. Borghese, K. T. Zondervan, M. S. Abrao, C. Chapron, and D. Vaiman, "Recent insights on the genetics and epigenetics of endometriosis", *Clinical genetics*, vol. 91, no. 2, pp. 254-264, 2017.

[180]. K. Krishnamoorthy, and A. H. Decherney, "Genetics of endometriosis", *Clinical Obstetrics and Gynecology*, vol. 60, no. 3, pp. 531-538, 2017.

[181]. M. S. Abrao, S. Podgaec, J. A. Dias Jr, M. Averbach, R. Garry, L. F. F. Silva, and F. M. Carvalho, "Deeply infiltrating endometriosis affecting the

rectum and lymph nodes", *Fertility and sterility*, vol. 86, no. 3, pp. 543-547, 2006.

[182]. D. Deiana, S. Gessa, M. Anardu, A. Daniilidis, L. Nappi, M. N. D'Alterio, A. Pontis, and S. Angioni, "Genetics of endometriosis: a comprehensive review", *Gynecological Endocrinology*, vol. 35, no. 7, pp. 553-558, 2019.

[183]. W. P. Dmowski, and D. P. Braun, "Immunology of endometriosis", Best Practice & Research Clinical *Obstetrics & Gynaecology*, vol. 18, no. 2, pp. 245-263, 2004.

[184]. M. Hickey, Ballard K, Farquhar C. "Endometriosis". *BMJ*, vol. 348, pp. 1752, 2014.

[185]. A. M. Malutan, T. Drugan, N. Costin, R. Ciortea, C. Bucuri, M. P. Rada, and D. Mihu, "Pro-inflammatory cytokines for evaluation of inflammatory status in endometriosis", *Central-European journal of immunology*, vol. 40, no. 1, pp. 96, 2015.

[186]. J. Eisermann, M. J. Gast, J. Pineda, R. R. Odem, and J. L. Collins, "Tumor necrosis factor in peritoneal fluid of women undergoing laparoscopic surgery", *Fertility and sterility*, vol. 50, no. 4, pp. 573-579, 1988.

[187]. J. A. Keenan, T. T. Chen, N. L. Chadwell, D. S. Torry, and M. R. Caudle, "IL-1β, TNF-α, and IL-2 in peritoneal fluid and macrophage-conditioned media of women with endometriosis", *American Journal of Reproductive Immunology*, vol. 34, no. 6, pp. 381-385, 1995.

[188]. E. Zulfikaroglu, S. Kılıc, M. Islimye, M. Aydin, S. Zergeroglu, and S. Batioglu, "Efficacy of anti-tumor necrosis factor therapy on endometriosis in an experimental rat model", *Archives of gynecology and obstetrics*, vol. 283, no. 4, pp. 799-804, 2011.

[189]. S. Kilic, M. Evsen, N. Tasdemir, N. Yilmaz, B. Yuksel, M. Dogan, and S. Batioglu, "Follicular fluid vascular endothelial growth factor and tumour

necrosis factor α concentrations in patients with endometriosis undergoing ICSI", *Reproductive biomedicine online*, vol. 15, no. 3, pp. 316-320, 2007.

[190]. X. L. Cao, J. Chai, Y. Y. Yu, X. Tian, J. Y. Zhao, L. Y. Yu, and Z. G. Sun, "Association of TNF-α gene T-1031C polymorphism with endometriosis: A meta-analysis", *American Journal of Reproductive Immunology*, pp. e13305, 2020.

[191]. Y. Y. Hsieh, C. C. Chang, F. J. Tsai, Y. Hsu, H. D. Tsai, and C. H. Tsai, "Polymorphisms for interleukin-4 (IL-4) –590 promoter, IL-4 intron3, and tumor necrosis factor alpha –308 promoter: Non-association with endometriosis", *Journal of clinical laboratory analysis*, vol. 16, no. 3, pp. 121-126, 2002.

[192]. E. M. Cardoso, C. Reis, and M. C. Manzanares-Céspedes, "Chronic periodontitis, inflammatory cytokines, and interrelationship with other chronic diseases", *Postgraduate medicine*, vol. 130, no. 1, pp. 98-104, 2018.

[193]. L. Nibali, A. Di Iorio, Y. K. Tu, and A. R. Vieira, "Host genetics role in the pathogenesis of periodontal disease and caries", *Journal of clinical periodontology*, vol. 44, pp. S52-S78, 2017.

[194]. P. N. Baer, "The case for periodontosis as a clinical entity", *Journal of periodontology*, vol. 42, no. 8, pp. 516-520, 1971.

[195]. W. T. Loo, C. B. Fan, L. J. Bai, Y. Yue, Y. D. Dou, M. Wang, H. Liang, M. N. Cheung, L. W. Chow, and Y. Tian, "Gene polymorphism and protein of human pro-and anti-inflammatory cytokines in Chinese healthy subjects and chronic periodontitis patients": *InJournal of translational medicine*, vol. 10, no. Supplement 1, pp. S8, 2012.

[196]. A. Fassmann, L. I. Holla, D. Buckova, A. Vasku, V. Znojil, and J. Vanek, "Polymorphisms in the +252 (A/G) lymphotoxin-alpha and the -308 (A/G) tumor necrosis factor-alpha genes and susceptibility to chronic periodontitis

in a Czech population", *Journal of periodontal research*, vol. 38, no. 4, pp. 394-399, 2003.

[197]. M. Endo, H. Tai, K. Tabeta, T. Kobayashi, K. Yamazaki, and H. Yoshie, "Analysis of single nucleotide polymorphisms in the 5'-flanking region of tumor necrosis factor-alpha gene in Japanese patients with early-onset periodontitis", *Journal of periodontology*, vol. 72, no. 11, pp. 1554-1559, 2001.

[198]. E. C. Küchler, J. F. Mazzi-Chaves, L. S. Antunes, C. Kirschneck, F. Baratto-Filho, and M. D. Sousa-Neto, "Current trends of genetics in apical periodontitis research", *Brazilian oral research*, vol. 32, 2018.

[199]. R. Górska, H. Gregorek, J. Kowalski, A. Laskus-Perendyk, M. Syczewska, and K. Madaliński, "Relationship between clinical parameters and cytokine profiles in inflamed gingival tissue and serum samples from patients with chronic periodontitis", *Journal of clinical periodontology*, vol. 30, no. 12, pp. 1046-1052, 2003.

[200]. A. G. Salles, L. A. A. Antunes, P. A. Carvalho, E. C. Küchler, and L. S. Antunes, "Association between apical periodontitis and TNF-α -308G/A gene polymorphism: a systematic review and meta-analysis", *Brazilian Dental Journal*, vol. 28, no. 5, pp. 535-542, 2017.

[201]. S. Solhjoo, S. H. Mahmoudzadeh, Z. Heidari, M. Hashemi, and L. M. Rigi, "Association between TNF-α (–308 G→A) gene polymorphism and chronic periodontitis", 2014.

[202]. H. A. Quigley, and A. T. Broman, "The number of people with glaucoma worldwide in 2010 and 2020", *British journal of ophthalmology*, vol. 90, no. 3, pp. 262-267, 2006.

[203]. Y. H. Kwon, J. H. Fingert, M. H. Kuehn, and W. L. Alward, "Primary open-angle glaucoma", *New England Journal of Medicine*, vol. 360, no. 11, pp. 1113-1124, 2009.

[204]. Y. Liu, and R. R. Allingham, "Molecular genetics in glaucoma", *Experimental eye research*, vol. 93, no. 4, pp. 331-339, 2011.

[205]. J. L. Wiggs, and L. R. Pasquale, "Genetics of glaucoma", *Human molecular genetics*, vol. 26, no. R1, pp. R21-R27, 2017.

[206]. A. O. Khan, "Genetics of primary glaucoma", *Current opinion in ophthalmology*, vol. 22, no. 5, pp. 347-355, 2011.

[207]. A. L. Ejeil, F. Gaultier, S. Igondjo-Tchen, K. Senni, B. Pellat, G. Godeau, and B. Gogly, "Are cytokines linked to collagen breakdown during periodontal disease progression?", *Journal of periodontology*, vol. 74, no. 2, pp. 196-201, 2003.

[208]. T. Nakajima, T. Honda, H. Domon, T. Okui, K. Kajita, H. Ito, N. Takahashi, T. Maekawa, K. Tabeta, and K. Yamazaki, "Periodontitis-associated up-regulation of systemic inflammatory mediator level may increase the risk of coronary heart disease", *Journal of periodontal research*, vol. 45, no. 1, pp. 116-122, 2010.

[209]. G. Fantuzzi, "Adipose tissue, adipokines, and inflammation", *Journal of Allergy and Clinical Immunology*, vol. 115, no. 5, pp. 911-919, 2005.

[210]. M. A. Hamid, L. Moemen, H. Labib, H. Helmy, and T. Elsergany, "Risk of open angle glaucoma due to tumor necrosis factor alpha gene polymorphisms", *Electronic physician*, vol. 8, no. 2, pp. 1978, 2016.

[211]. R. Simionescu, A. P. Cherecheanu, L. Voinea, and R. Sfrenț-Cornățeanu, "TNF-α Gene Polymorphisms and Primary Open Angle Glaucoma in Romanian Population/Polimorfisme ale genei TNF-α în populația română cu glaucom primar cu unghi deschis", *Revista Romana de Medicina de Laborator*, vol. 23, no. 1, pp. 47-58, 2015.

[212]. M. Feldmann, and R. N. Maini, "Anti-TNF therapy, from rationale to standard of care: what lessons has it taught us?", *The Journal of Immunology*, vol. 185, no. 2, pp. 791-794, 2010.

[213]. J. Kurkó, T. Besenyei, J. Laki, T. T. Glant, K. Mikecz, and Z. Szekanecz, "Genetics of rheumatoid arthritis—a comprehensive review", *Clinical reviews in allergy & immunology*, vol. 45, no. 2, pp. 170-179, 2013.

[214]. G. Buchan, K. Barrett, M. Turner, D. Chantry, R. Maini, and M. Feldmann, "Interleukin-1 and tumour necrosis factor mRNA expression in rheumatoid arthritis: prolonged production of IL-1 alpha", *Clinical and experimental immunology*, vol. 73, no. 3, pp. 449, 1988.

[215]. F. Brennan, A. Jackson, D. Chantry, R. Maini, and M. Feldmann, "Inhibitory effect of TNFα antibodies on synovial cell interleukin-1 production in rheumatoid arthritis", *The Lancet*, vol. 334, no. 8657, pp. 244-247, 1989.

[216]. M. J. Elliott, R. N. Maini, M. Feldmann, J. R. Kalden, C. Antoni, J. S. Smolen, B. Leeb, F. C. Breedveld, J. D. Macfarlane, and J. Bijl, "Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor α (cA2) versus placebo in rheumatoid arthritis", *The Lancet*, vol. 344, no. 8930, pp. 1105-1110, 1994.

[217]. H. Kreft, and W. Jetz, "Global patterns and determinants of vascular plant diversity", *Proceedings of the National Academy of Sciences*, vol. 104, no. 14, pp. 5925-5930, 2007.

[218]. Y. H. Lee, J. D. Ji, and G. G. Song, "Tumor necrosis factor-alpha promoter -308A/G polymorphism and rheumatoid arthritis susceptibility: a metaanalysis", *The Journal of rheumatology*, vol. 34, no. 1, pp. 43-49, 2007.

[219]. R. M. Fawzy, G. A. Hammad, S. E. Egila, A. N. Elkasas, and N. A. Fouad, "Association of tumor necrosis factor-α (TNF-α) -308A/G (rs1800629) gene polymorphism with carotid artery atherosclerosis in rheumatoid arthritis patients", *The Egyptian Rheumatologist*, 2020.

[220]. R. Sun, M. Liu, L. Lu, Y. Zheng, and P. Zhang, "Congenital heart disease: causes, diagnosis, symptoms, and treatments", *Cell biochemistry and biophysics*, vol. 72, no. 3, pp. 857-860, 2015.

[221]. G. Spinetti, O. Fortunato, A. Caporali, S. Shantikumar, M. Marchetti, M. Meloni, B. Descamps, I. Floris, E. Sangalli, and R. Vono, "MicroRNA-15a and microRNA-16 impair human circulating proangiogenic cell functions and are increased in the proangiogenic cells and serum of patients with critical limb ischemia", *Circulation research*, vol. 112, no. 2, pp. 335-346, 2013.

[222]. R. Sharma, A. P. Bolger, W. Li, P. A. Davlouros, H. D. Volk, P. A. Poole-Wilson, A. J. Coats, M. A. Gatzoulis, and S. D. Anker, "Elevated circulating levels of inflammatory cytokines and bacterial endotoxin in adults with congenital heart disease", *The American journal of cardiology*, vol. 92, no. 2, pp. 188-193, 2003.

[223]. F. Franco, G. D. Thomas, B. Giroir, D. Bryant, M. C. Bullock, M. C. Chwialkowski, R. G. Victor, and R. M. Peshock, "Magnetic resonance imaging and invasive evaluation of development of heart failure in transgenic mice with myocardial expression of tumor necrosis factor-α", *Circulation*, vol. 99, no. 3, pp. 448-454, 1999.

[224]. D. Wang, J. Fang, R. Wang, D. Sun, K. Xia, W. Yin, S. Zhang, and L. Sun, "Elevated serum ghrelin, tumor necrosis factor-α and interleukin-6 in congenital heart disease", *Pediatrics International*, vol. 58, no. 4, pp. 259-264, 2016.

[225]. C. S. Carvalho, "Integrated probability of coronary heart disease subject to the- 308 tumor necrosis factor-alpha SNP: a Bayesian meta-analysis", *PeerJ*, vol. 3, pp. e1236, 2015.

[226]. R. M. Clancy, C. B. Backer, X. Yin, R. P. Kapur, Y. Molad, and J. P. Buyon, "Cytokine polymorphisms and histologic expression in autopsy studies: contribution of TNF-α and TGF-β1 to the pathogenesis of autoimmune-associated congenital heart block", *The Journal of Immunology*, vol. 171, no. 6, pp. 3253-3261, 2003.

[227]. A. I. Qureshi, A. D. Mendelow, and D. F. Hanley, "Intracerebral haemorrhage", *The Lancet*, vol. 373, no. 9675, pp. 1632-1644, 2009.

[228]. A. I. Qureshi, S. Tuhrim, J. P. Broderick, H. H. Batjer, H. Hondo, and D. F. Hanley, "Spontaneous intracerebral hemorrhage", *New England Journal of Medicine*, vol. 344, no. 19, pp. 1450-1460, 2001.

[229]. N. R. Sibson, A. M. Blamire, V. H. Perry, J. Gauldie, P. Styles, and D. C. Anthony, "TNF-α reduces cerebral blood volume and disrupts tissue homeostasis via an endothelin-and TNFR2-dependent pathway", *Brain*, vol. 125, no. 11, pp. 2446-2459, 2002.

[230]. P. Kumar, S. Misra, A. Kumar, M. Faruq, S. Vivekanandhan, A. K. Srivastava, and K. Prasad, "The Relationship Between Tumor Necrosis Factor-Alpha (-308G/A, +488G/A, -857C/T and -1031T/C) Gene Polymorphisms and Risk of Intracerebral Hemorrhage in the North Indian Population: A Hospital-Based Case-Control Study", *Neurology India*, vol. 68, no. 1, pp. 78, 2020.

[231]. O. Gill-Carey, and A. T. Hattersley, "Genetics and type 2 diabetes in youth", *Pediatric diabetes*, vol. 8, pp. 42-47, 2007.

[232]. P. Almgren, M. Lehtovirta, B. Isomaa, L. Sarelin, M.-R. Taskinen, V. Lyssenko, T. Tuomi, L. Groop, and B. S. Group, "Heritability and familiality of type 2 diabetes and related quantitative traits in the Botnia Study", *Diabetologia*, vol. 54, no. 11, pp. 2811, 2011.

[233]. E. Ahlqvist, T. S. Ahluwalia, and L. Groop, "Genetics of type 2 diabetes", *Clinical chemistry*, vol. 57, no. 2, pp. 241-254, 2011.

[234]. J. Tuomilehto, J. Lindström, J. G. Eriksson, T. T. Valle, H. Hämäläinen, P. Ilanne-Parikka, S. Keinänen-Kiukaanniemi, M. Laakso, A. Louheranta, and M. Rastas, "Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance", *New England Journal of Medicine*, vol. 344, no. 18, pp. 1343-1350, 2001.

[235]. K. Rehman, and M. S. H. Akash, "Mechanisms of inflammatory responses and development of insulin resistance: how are they interlinked?", *Journal of biomedical science*, vol. 23, no. 1, pp. 1-18, 2016.

[236]. F. B. Hu, J. B. Meigs, T. Y. Li, N. Rifai, and J. E. Manson, "Inflammatory markers and risk of developing type 2 diabetes in women", *Diabetes*, vol. 53, no. 3, pp. 693-700, 2004.

[237]. D. Rajarajeswari, K. Ramalingam, and J. Naidu, "Tumor necrosis factor–alpha in the development of insulin resistance in type 2 diabetes mellitus", 2011.

[238]. B. Ayelign, M. Genetu, T. Wondmagegn, G. Adane, M. Negash, and N. Berhane, "TNF-α (-308) Gene Polymorphism and Type 2 Diabetes Mellitus in Ethiopian Diabetes Patients", *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, vol. 12, pp. 2453, 2019.

[239]. X. Guo, C. Li, J. Wu, Q. Mei, C. Liu, W. Sun, L. Xu, and S. Fu, "The association of TNF-α -308G/A and -238G/A polymorphisms with type 2 diabetes mellitus: a meta-analysis", *Bioscience Reports*, vol. 39, no. 12, 2019.

[240]. S. M. Haffner, B. D. Mitchell, R. A. Valåez, H. P. Hazuåa, P. A. Morales, and M. P. Stern, "Eight-year incidence of hypertension in Mexican-Americans and non-Hispanic whites: the San Antonio Heart Study", *American journal of hypertension*, vol. 5, no. 3, pp. 147-153, 1992.

[241]. H. Snieder, G. A. Harshfield, and F. A. Treiber, "Heritability of blood pressure and hemodynamics in African-and European-American youth", *Hypertension*, vol. 41, no. 6, pp. 1196-1201, 2003.

[242]. M. S. Islam, "Ambulatory blood pressure monitoring in the diagnosis and treatment of hypertension", *Hypertension: from basic research to clinical practice*, pp. 109-116: Springer, 2016.

[243]. S. MacMahon, R. Peto, R. Collins, J. Godwin, J. Cutler, P. Sorlie, R. Abbott, J. Neaton, A. Dyer, and J. Stamler, "Blood pressure, stroke, and coronary heart disease: part 1, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias", *The Lancet*, vol. 335, no. 8692, pp. 765-774, 1990.

[244]. N. Franceschini, and T. H. Le, "Genetics of hypertension: discoveries from the bench to human populations", *American Journal of Physiology-Renal Physiology*, vol. 306, no. 1, pp. F1-F11, 2014.

[245]. J. F. Navarro-Gonzalez, and C. Mora-Fernandez, "The role of inflammatory cytokines in diabetic nephropathy", *Journal of the American Society of Nephrology*, vol. 19, no. 3, pp. 433-442, 2008.

[246]. Y. Y. Li, "Tumor necrosis factor-alpha G308A gene polymorphism and essential hypertension: a meta-analysis involving 2244 participants", *PLoS One*, vol. 7, no. 4, pp. e35408, 2012.

[247]. Y. S. Yao, W. W. Chang, and Y. L. Jin, "Association between TNF-α promoter -308G/A polymorphism and essential hypertension in the Asian population: A meta-analysis", *Journal of the Renin-Angiotensin-Aldosterone System*, vol. 18, no. 4, pp. 1470320317741066, 2017.

[248]. R. A. Spritz, "Modern vitiligo genetics sheds new light on an ancient disease", *The Journal of dermatology*, vol. 40, no. 5, pp. 310-318, 2013.

[249]. R. A. Spritz, and G. H. Andersen, "Genetics of vitiligo", *Dermatologic clinics*, vol. 35, no. 2, pp. 245-255, 2017.

[250]. C. Shen, J. Gao, Y. Sheng, J. Dou, F. Zhou, X. Zheng, R. Ko, X. Tang, C. Zhu, and X. Yin, "Genetic susceptibility to vitiligo: GWAS approaches for identifying vitiligo susceptibility genes and loci", *Frontiers in genetics*, vol. 7, pp. 3, 2016.

[251]. R. Speeckaert, and N. van Geel, "Vitiligo: an update on pathophysiology and treatment options", *American journal of clinical dermatology*, vol. 18, no. 6, pp. 733-744, 2017.

[252]. M. Martínez-Esparza, C. Jiménez-Cervantes, F. Solano, J. A. Lozano, and J. C. García-Borrón, "Mechanisms of melanogenesis inhibition by tumor necrosis factor-α in B16/F10 mouse melanoma cells", *European journal of biochemistry*, vol. 255, no. 1, pp. 139-146, 1998.

[253]. N. H. Kim, D. Torchia, P. Rouhani, B. Roberts, and P. Romanelli, "Tumor necrosis factor-α in vitiligo: direct correlation between tissue levels and clinical parameters, Cutaneous and ocular toxicology", vol. 30, no. 3, pp. 225-227, 2011.

[254]. K. M. AlGhamdi, H. Khurrum, A. Taieb, and K. Ezzedine, "Treatment of generalized vitiligo with anti-TNF-α agents", *J Drugs Dermatol*, vol. 11, no. 4, pp. 534-39, 2012.

[255]. J. A. Simón, and R. Burgos-Vargas, "Vitiligo improvement in a patient with ankylosing spondylitis treated with infliximab", *Dermatology*, vol. 216, no. 3, pp. 234-235, 2008.

[256]. L. J. Abraham, and K. M. Kroeger, "Impact of the -308 TNF promoter polymorphism on the transcriptional regulation of the TNF gene: relevance to disease", *Journal of leukocyte biology*, vol. 66, no. 4, pp. 562-566, 1999.

[257]. A. M. Namian, S. Shahbaz, R. Salmanpoor, M. R. Namazi, F. Dehghani, and E. Kamali-Sarvestani, "Association of interferon-gamma and tumor necrosis factor alpha polymorphisms with susceptibility to vitiligo in Iranian patients", *Archives of dermatological research*, vol. 301, no. 1, pp. 21-25, 2009.

[258]. Y. H. Lee, and S. Bae, "Associations between TNF-α polymorphisms and susceptibility to rheumatoid arthritis and vitiligo: a meta-analysis", *Genet Mol Res*, vol. 14, no. 2, pp. 5548-59, 2015.

[259]. G. Nie, J. Qi, C. Huang, T. Yang, N. Shi, and Y. Chen, "Meta-analysis of the TNF-α -308G/A polymorphism and vitiligo risk", *Genet Mol Res*, vol. 14, no. 4, pp. 17296-304, 2015.

[260]. Cochrane Colaboration, "Tutorial: How to read a forest plot": 25 August 2020, https://s4be.cochrane.org/blog/2016/07/11/tutorial-read-forest-plot/.

[261]. L. Chen, Z. Huang, Y. Liao, B. Yang, and J. Zhang, "Association between tumor necrosis factor polymorphisms and rheumatoid arthritis as well as systemic lupus erythematosus: a meta-analysis", *Brazilian Journal of Medical and Biological Research*, vol. 52, no. 3, 2019.

[262]. J. Yuepeng, X. Zhao, Y. Zhao, and L. Li, "Gene polymorphism associated with TNF-α (G308A), IL-6 (C174G) and susceptibility to coronary atherosclerotic heart disease: A meta-analysis", *Medicine*, vol. 98, no. 2, 2019.

[263]. T. Wang, "TNF-alpha G308A polymorphism and the susceptibility to Alzheimer's disease: an updated meta-analysis", *Archives of medical research*, vol. 46, no. 1, pp. 24-30, 2015.

[264]. D. Di Bona, G. Candore, C. Franceschi, F. Licastro, G. Colonna-Romano, C. Cammà, D. Lio, and C. Caruso, "Systematic review by meta-analyses on the possible role of TNF-α polymorphisms in association with Alzheimer's disease", *Brain research reviews*, vol. 61, no. 2, pp. 60-68, 2009.

[265]. G. G. Song, S. J. Choi, J. D. Ji, and Y. H. Lee, "Association between tumor necrosis factor-α promoter -308A/G, -238A/G, interleukin-6 -174G/C and -572G/C polymorphisms and periodontal disease: a meta-analysis", *Molecular biology reports*, vol. 40, no. 8, pp. 5191-5203, 2013.

[266]. A. Ng, W. W. Tam, M. W. Zhang, C. S. Ho, S. F. Husain, R. S. McIntyre, and R. C. Ho, "IL-1β, IL-6, TNF-α and CRP in elderly patients with depression or Alzheimer's disease: systematic review and meta-analysis", *Scientific reports*, vol. 8, no. 1, pp. 1-12, 2018.