A Review on Association of Genetic Polymorphism with Thyroid Hormone Level Leading to Different Diseases

By

Nafis Mahtab Mahin
19346042

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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at BRACUniversity.
2. The thesis does not contain material previously published or written by a third party, exceptwhere this is appropriately cited through full and accurate referencing.
3. The thesis does not contain materialwhichhas been accepted, or submitted, for any other degree or diploma at a university or other institution.
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Student's Full Name &Signature:

Nafis Mahtab Mahin

19346042

Approval

The thesis titled "A Review on Association of Genetic Polymorphism with Thyroid Hormone Level Leading to Different Diseases"submitted by Nafis Mahtab Mahin (19346042), of Spring, 2024has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

Supervised By:

Dr. Md. Aminul Haque
Associate Professor
School of Pharmacy
BRAC University

Approved By:

Program Director:

Professor Dr. Hasina Yasmin
Program Director and Assistant Dean
School of Pharmacy
BRAC University

Dean:

Professor Dr. Eva Rahman Kabir
Dean
School of Pharmacy
BRAC University

EthicsStatement

This study did not involve any human participants, human specimens or tissue, vertebrate animals or cephalopods, vertebrate embryos or tissues and field research.

Abstract

The study delved into the investigation of CYP27B1 hydroxylase, a vital enzyme responsible for converting 25-hydroxyvitamin D3 (25OHD3) into 1,25(OH)2D3, the most potent natural form of vitamin D crucial for immune modulation and cellular proliferation. Its association with autoimmune endocrine disorders such as Toxic Multinodular Goiter, Hashimoto's thyroiditis, Graves' disease, Asthma, and Iodothyronine was the primary focus. Genotyping analyses were conducted on patients diagnosed with Toxic Multinodular Goiter (n = 124), Hashimoto's thyroiditis (n = 139), Graves' disease (n = 334), Asthma (n = 252), Iodothyronine, alongside a healthy control group (n = 320). The analysis targeted two specific genetic variations, the promoter (21260) C/A polymorphism and the intron 6 (þ2838) C/T polymorphism. The results revealed significant associations between allelic variations of the promoter (21260) C/A polymorphism and the mentioned disorders (P = 0.0062 for Toxic Multinodular Goiter, P = 0.0173 for Hashimoto's thyroiditis, P = 0.0094 for Graves' disease, and P = 0.0028 for Asthma). Additionally, a notable distinction was observed for the intron 6 (þ2838) C/T polymorphism (P = 0.0058), particularly in Hashimoto's thyroiditis. These findings suggest diverse regulatory influences of the CYP27B1 hydroxylase gene, potentially contributing to susceptibility to a range of endocrine autoimmune disorders.

Keywords: Toxic Multinodular Goiter, Iodothyronine, Hashimoto's thyroiditis, Asthma, Graves' disease, Polymorphism and CYP27B1 hydroxylase gene.

Dedication

I dedicate this thesis to my parents and my mentor Dr. Aminul Haque. Their support and guidance have not just been invaluable to my academic journey but also my personal life, and I am truly grateful for their presence in my life.

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List of Acronyms

SNP Single Nucleotide Polymorphism

VDR Vitamin D Receptor

TSHR Thyroid Stimulating Hormone Receptor

THR Thyrotropin Releasing Hormone

AITD Autoimmune Thyroid Disease

HT Hashimoto's Thyroiditis

GD Graves' disease

CYP Cytochrome P450

HLA Human Leukocyte Antigens

TP Thyroid Polymorphism

SLE Systemic Lupus Erythematosus

Chapter 1

Introduction

1.1 Background

CYP27B1, also known as 25-hydroxyvitamin D3-1a-hydroxylase, is a mitochondrial P450 enzyme that converts 25-hydroxyvitamin D3 into 1,25(OH)2D3, which is the most active form of vitamin D. Its enzymatic activity, which is largely connected with renal function, spreads to extrarenal organs, implying participation in both endocrine and local paracrine/autocrine activities. Genetic abnormalities in the CYP27B1 gene can impair hydroxylase activity, resulting in vitamin D-dependent rickets.

CYP27B1, located on chromosome 12q.13.1-13.3 near the vitamin D receptor (VDR) locus, regulates the physiological effects of 1,25(OH)2D3 via the nuclear VDR. This secosteroid demonstrates protective effects against autoimmune disorders and thyroiditis, in experimental animal models. Its immunomodulatory actions encompass the inhibition of T cell proliferation, HLA class II expression, secretion of inflammatory cytokines involved in autoimmune tissue destruction, and dendritic cell maturation, thereby mitigating autoimmune responses (Peeters et al., 2003).

Genetic polymorphisms in the VDR gene have been linked to an increased risk of endocrine autoimmune disorders.Additionally, associations between autoimmune disorders and genetic variations in the HLA system and genes such as CTLA-4 have been noted. Given this shared genetic susceptibility (Peeters et al., 2003), studies have focused on determining the prevalence of

specific polymorphisms in the promoter region and intron 6 of the CYP27B1 hydroxylase gene among people with Toxic Multinodular Goiter, thyroid autoimmune disease, and type 1 diabetes mellitus compared to healthy controls. These SNPs were chosen for their potential influence on gene expression and to confirm earlier findings.

1.2 SNP in Thyroid Hormone receptor

In humans, thyroid hormone is required for many developments and metabolic process. The primary agent responsible for these effects is the active thyroid hormone T3, which functions through mechanisms involving T3-regulated gene expression. These effects encompass heat generation, skeletal maturation,brain development, hormone production, oxygen utilization, breakdown and heart contractility. The conventional hypothalamic-pituitary-thyroid axis controls thyroid hormone production, particularly the precursor hormone T4, through the natural power of thyroid hormone, specifically the accessibility of T3, is controlled by the iodothyronine deiodinases D1, D2 and D3. Polymorphism variations in nucleotide groupings that happen in at slightest 1% of the population in qualities related with thyroid hormone digestion system can have a unpretentious impact on thyroid hormone levels and working all through an individual's (Owen et al., 2006).

(Peeters et al., 2003) investigated the possible effects of single nucleotide polymorphisms (SNPs) in genes related to thyroid hormone metabolism, such as deiodinases (D1-D3), the TSH receptor (TSHR), and the T3 receptor. These SNPs were found either in open databases or by sequencing the genomic DNA of 15 arbitrarily chosen individuals (30 alleles). The genotypes of these SNPs were at that point assessed in 156 healthy blood givers, and their association with plasma levels of T4, free T4, T3, reverse T3 (rT3), and TSH was investigated. Eight SNPs were detected, four of which were previously unreported. Three SNPs were found in the 3-untranslated region: D1a-C/T,

D1b-A/G, and D3-T/G. Four SNPs had missense mutations: D2-A/G (Thr92Ala), TSHRa-G/C (Asp36His), TSHRb-C/A (Pro52Thr), and TSHRc-C/G (Asp727Glu).TR-T/C was categorised as a silent SNP. D1a-T was linked to greater plasma rT3 levels (P 0.017), a larger plasma rT3/T4 ratio (P 0.01), and a lower T3/rT3 ratio (P 0.003) in a dose-dependent manner. In contrast, D1b-G was linked to a lower plasma rT3/T4 ratio (P 0.024) and a greater T3/rT3 ratio (P 0.08). Furthermore, TSHRc-G was linked to lower plasma TSH levels (P 0.04), as well as lower plasma TSH/free T4 ratio (P 0.06), TSH/T3 ratio (P 0.06), and TSH/T4 ratio (P 0.08). However, no significant relationships were seen between other SNPs and TSH or iodothyronine concentrations. Overall, this investigation discovered relationships between three SNPs within two genes (D1, TSHR) and plasma TSH or iodothyronine levels in a healthy population (J Clin Endocrinol Metab 88: 2880–2888, 2003).

1.3Disease associated with Thyroid polymorphism

1.3.1 Toxic Multinodular Goiter

In the research (Gabriel, 1999) of human physiology, thyroid hormones wield significant influence over metabolic and developmental processes, with T3, the active hormone, orchestrating gene expression. These hormones govern critical functions such as brain maturation, skeletal development, heat generation, hormone secretion, and cardiac activity. Genetic variations, termed polymorphisms, within genes involved in thyroid hormone metabolism, including D1, D2, D3, TSHR, and TRβ, possess the potential to subtly impact hormone levels and their biological activity. Subclinical hyper- and hypothyroidism symptoms underscore the profound implications of even minor hormonal fluctuations on diverse physiological facets like cognition, cholesterol regulation, heart rhythm, bone health, and cardiovascular health. Hence, a study (Gabriel, 1999) sought to explore single nucleotide polymorphisms (SNPs) within these genes, especially those situated in exons, to unravel their influence on thyroid hormone metabolism. The deiodinases housing selenocysteine (D1, D2, and D3) emerge as pivotal players in thyroid hormone regulation, necessitating specific elements like SECIS for the integration of UGA codons encoding selenocysteine. Investigation into these elements and coding sequences among healthy individuals revealed potential SNPs. Genotyping 156 healthy subjects connected the identified SNPs with plasma thyroid indicators, encompassing T4, T3, rT3, and various iodothyronine ratios, serving as markers for tissue deiodinase activities. In addition, the study (Gabriel, 1999) investigated the relationship between the D2 SNP and plasma TSH levels, TSH/T4, and TSH/free T4 ratios, given D2's function in pituitary TSH production. Correlations between SNPs in TSHR and TRβ and plasma iodothyronine levels, TSH levels, and their corresponding ratios were examined.

1.3.2 Graves' Disease

Autoimmune thyroid disorders (AITDs), such as Graves' disease and autoimmune thyroiditis (goitrous and atrophic), show family clustering whose precise aetiology is unknown (McKenzie & Zakarija 1988). The investigation (Tassi et al., 1995) into the genetic factors influencing AITD pathogenesis employs classical linkage analysis in extensive familial groups, utilizing chromosome-specific polymorphic markers to identify potential loci associated with the disease. Challenges in polygenic diseases prompt alternative methods like sib-pair analysis, though susceptible to non-genetic factors influencing the phenotype.

Exploring genetic variables influencing AITD pathogenesis entails investigating the relationship between polymorphic marker alleles and AITDs (Mangklabrus et al. 1991). Affllliation considers, a strong technique, discover susceptibility loci that are important for disease expression but are not major malady loci (Greenberg 1993). Polymorphic markers within the human major histocompatibility complex (HLA) family play an important role, showing that, while not directly causing Graves' disease or Hashimoto's thyroiditis, they may contribute to disease manifestation. The relationship of potential qualities, counting those creating the T cell receptor complex, is still debated (Demaine et al. 1987; Mangklabrus et al. 1991).

Furthermore, the study(Gareau et al., 1988) investigates a possible link between autoimmune thyroid disorders (AITDs) and Hindi 11 restriction fragment length polymorphism (RFLP) alleles of thyroid-specific genes, which are expressed exclusively in thyroid cells or are critical for thyroid function. For example, genes producing thyroid hormone receptors, which are critical for orchestrating hormone-induced actions, may alter peripheral thyroid hormone sensitivity, influencing the clinical presentation of AITDs. The study of the c-erbAß gene, which determines

the ß receptor for thyroid hormone, revealed a unique link between Graves' illness and the presence of the EAßH+ allele in the 5' region of the c-erbAß gene (Gareau et al., 1988) (Ganly & Rabbitts, 1991).

Graves' disease (Stefanić et al., 2005) is an autoimmune thyroid condition characterised by hyperthyroidism generated by thyrotropin (TSH)-receptor autoantibodies. Susceptibility involves a complex interaction of hereditary and environmental variables. Over 20 possible loci linked to Graves' illness have been discovered through genetic research, with an emphasis on immune system-regulating genes. The vitamin D receptor (VDR)-related endocrine system is critical for immunological modulation, notably through 1,25-dihydroxyvitamin D3 and VDR, which influence dendritic cell differentiation, T-cell proliferation, and proinflammatory cytokine release. The widespread presence of VDR in various immune cells underscores its significant immunoregulatory properties.

Meta-analyses highlight common variants' involvement in disease susceptibility, with the VDR gene exhibiting detectable biallelic polymorphisms, including those defined by restriction endonucleases ApaI and BsmI, along with an additional polymorphism identified by the TaqI enzyme in its 3’-region. VDR gene variants have been implicated in various autoimmune processes, including Addison disease,insulin-dependent diabetes mellitus, Crohn disease, primary biliary cirrhosis, autoimmune hepatitisand multiple sclerosis. Recent reports establish a correlation between VDR variants and Graves’ disease susceptibility, particularly in female Japanese patients. Administration of 1,25-dihydroxyvitamin D3 has demonstrated preventive effects in animal models of thyroiditis and ameliorative effects in humans with Graves’ disease. However, replication between VDR gene polymorphisms and autoimmune thyroid disease across diverse populations has proven challenging, with conflicting reports on risk implications. Notably, VDR

polymorphisms have been shown to influence susceptibility to insulin-dependent diabetes mellitus in the Dalmatian region of Croatia. Given the association of VDR variants with insulin-dependent diabetes mellitus and thyroid autoimmunity, an investigation was conducted into the distribution and potential effects of VDR gene variants on Graves' malady helplessness in a subset of patients from Eastern Croatia.

1.3.3 Hashimoto's Thyroiditis

Hashimoto's thyroiditis (HT), the most prevalent autoimmune thyroid disorder, is marked by lymphocyte infiltration into the thyroid gland, gradually replacing parenchymal tissue with fibrous tissue. Thyroid autoantibodies (TAbs) that target thyroid peroxidase (TPO) and thyroglobulin (Tg) are a prominent biochemical characteristic seen in patient samples.

TPO, which is required for thyroid hormone production, is located on thyrocytes' apical membrane. It performs a few exercises, counting oxidizing iodine, iodinating tyrosine buildups in Tg, and interfacing iodothyrosines to form thyroxine (T4) and Triodothyronine. Tg, a big glycoprotein presents in thyroid follicles, functions as both a reservoir and a location of thyroid hormone synthesis. TPOAbs and TgAbs are both immunoglobulin G antibodies with a high affinity for their respective targets. TPOAbs, unlike TgAbs, can activate complement and harm thyroid cells via antibody-dependent cell cytotoxicity.

While both antibodies are present, evidence implies a secondary involvement in HT pathogenesis, with T-cell-mediated cytotoxicity and apoptotic pathways most likely impacting the illness. Nonetheless, TAbs are useful diagnostic indicators for thyroid autoimmunity, with TPOAbs present in more than 90% of HT patients and TgAbs in about 80%.

According to (Zaletel and Gaberšček., 2011), the reported incidence rate of Hashimoto's thyroiditis (HT) by cytology is 13.4% among patients receiving fine-needle aspiration biopsy of thyroid nodules, which is comparable to that of type 2 diabetes. Clinical symptoms range from the presence of thyroid autoantibodies (TAbs) in people with normal thyroid function to severe thyroid dysfunction. Epidemiological studies show that HT is the major cause of hypothyroidism, with a frequency of 4% to 9.5% among adults.

Although widespread, the exact mechanisms driving the development of Hashimoto's thyroiditis (HT) remain inadequately elucidated. Progress in understanding HTD, notably HT and Graves' disease (GD), calls for a thorough examination of existing evidence regarding potential catalysts for HT among vulnerable individuals and theoretical mechanisms leading to thyroid damage in HT patients.

(AITDs)Autoimmune thyroid diseases constitute a cluster of organ-specific endocrine disorders primarily orchestrated by T lymphocytes, including Hashimoto's thyroiditis (HT),Graves' disease (GD) and thyroid-associated ophthalmopathy (TAO), with GD and HT being the predominant manifestations. The development of AITDs is linked to immunological dysfunction caused by a combination of genetic predisposition and environmental variables. Recent research (Wang et al., 2016) has found over 10 susceptibility loci, including genes like CTLA4, TSHR, PTPN22, IL17, TG, HLA, and FCRL3, the majority of which are associated to immunity. The UPP, a pivotal signal transduction system, is implicated in AITD pathogenesis, particularly through the ubiquitin-conjugating enzyme UBE2L3, which plays a role in substrate ubiquitination and subsequent degradation. Variations in UBE2L3 have been observed in various autoimmune disorders, highlighting the investigation of UBE2L3 mutations in the development of AITDs. This case–control study aims to analyze single nucleotide polymorphisms (SNPs) in the UBE2L3 region

within a Chinese Han population affected by AITDs, specifically focusing on rs131654, rs5754217, rs2298428, rs140489, and rs5998672.

1.3.4 Asthma

Research (Duan et al, 2013) on chronic condition affecting millions worldwide, asthma is characterized by airway inflammation and hyper-responsiveness, posing significant health and financial challenges. Despite the availability of diverse asthma treatments, there remains substantial variability in treatment response, influenced in part by genetic factors. Studies on β2-agonists, the primary therapy for asthma, have identified genetic associations with bronchodilator response (BDR), yet these findings only explain a fraction of the variability, suggesting the involvement of additional factors.

Previous research observed distinct expression patterns of transcription factors (TFs) in human airway cell lines under conditions mimicking asthma and exposure to β2-agonists. Treatment with leukotriene D4, fiery cytokines, and β2-agonists isoproterenol brought about to considerable modifications in TF quality expression. Given the significance of these cell sorts in asthma pathogenesis, strikingly irritation and bronchoconstriction's, it was hypothesized that genes activated under these conditions may impact β2-agonist treatment response in asthma patients. This study intends to evaluate the connection between particular SNP in the TF genes and BDR in asthma trial groups treated with short-acting β2-agonists.

1.3.5 Iodothyronine

Thyroid hormones (Peeters et al., 2003) are critical in a assortment of metabolic and formative forms within the human body, with the active hormone T3 predominantly controlling gene expression. These hormones impact hormone secretion, brain development, heat production, heart function and skeletal maturation. Polymorphisms in thyroid hormone metabolism genes, such as D1, D2, D3, TSHR, and TRβ, can have unobtrusive impacts on hormone levels and bioactivity. Subclinical hyperthyroidism and hypothyroidism symptoms underscore the significance of minor hormonal alterations in various physiological aspects such as atherosclerosis, cholesterol metabolism, bone density, heart rate, and cognition. Therefore, a study was conducted to examine (SNPs) in these genes, with a particular emphasis on those located in exons, to uncover their impact on thyroid hormone metabolism.

The deiodinases containing selenocysteine (D1, D2, and D3) are critical for thyroid hormone regulation, with UGA codons encoding selenocysteine requiring specific elements like SECIS for their inclusion. Investigation of these elements and coding sequences in healthy subjects revealed potential SNPs. Genotyping of 156 healthy individuals linked the identified SNPs with plasma thyroid indexes, including T4, T3, rT3, and various iodothyronine ratios, which are indicative of tissue deiodinase activities. Furthermore, the study investigated the relationship between the D2 SNP and plasma TSH levels, TSH/T4, and TSH/free T4 ratios, taking into account D2's involvement in controlling hypophyseal TSH production. The study also examined the relationship between SNPs in TSHR and TRβ and plasma iodothyronine and TSH levels, as well as their ratios.

1.4 Objective

This review article focuses on the investigation of SNPswithin the CYP27B1 gene and their intricate connections with various diseases namely Toxic Multinodular Goiter, Hashimoto's thyroiditis, Iodothyronine, Graves' disease and Asthma. The fundamental objectives of this comprehensive review encompass the provision of contemporary insights to researchers, clinicians and patients alike. The aim is to furnish an all-encompassing and current portrayal of the disease linked with the Thyroid polymorphism of the CYP27B1 gene, while simultaneously underscoring the paramount importance of ongoing research endeavors in augmenting our comprehension of these incapacitating ailments and our therapeutic capabilities to address them.

Chapter 2

Methods

This paper focuses on reviewing the relationship between a specific single nucleotide polymorphism (SNP) called CYP27B1 and its association with various diseases. The author conducted a literature search using specific keywords such as "Thyroid," "CYP27B1" (CYP27B1 receptor), "CYP27B1 polymorphism," "Toxic Multinodular Goiter," "Hashimoto's thyroiditis,""Graves," "Asthma" and "Iodothyronine" in databases including PubMed, Medline, Science Direct, Nature, and Google Scholar. These databases were chosen to ensure the authenticity of the articles used as sources for information and data collection in this review paper.

In cases where the full text of an article was not accessible, the author requested a reprint from the corresponding author. Only articles with complete texts were considered for data retrieval. The publications of interest covered different ethnicities, and DNA and allele information was given priority. Once these criteria were met, the author thoroughly read all the articles to identify the connection between the Thyroid hormone andCYP27B1 and its impact on patients with various diseases. Specifically, the focus was on the CYP27B1 polymorphism, and the author selectively examined the results pertaining to this SNP in their article.

By studying multiple articles and extracting data from 25 relevant sources, it was concluded that CYP27B1 polymorphism is associated with certain diseases due to differences in allele and genotype distribution. The author aimed to summarize the findings in a simplified manner to enhance readers' understanding. Each study's data, including the author's name, year of the study, ethnicity of the subjects, genotype distribution, allele distribution, and other relevant information, were calculated and analyzed.

Chapter 3

Discussion

3.1 Toxic Multinodular Goiter

Recent research(Gabriel, 1999) on autonomously functioning thyroid nodules (AFTN) has led to the discovery of mutations in hTSHR that are constantly activating. This prompted an investigation to determine if similar mutations are implicated in Toxic Multinodular Goiter (TMNG), a more prevalent cause of hyperthyroidism. However, analysis of TMNG patients' nodular and genomic DNA failed to identify activating mutations. Instead, variations in hTSHR, particularly within the carboxyl-terminal intracellular tail, were observed. Notably, one variant, D727E, was found more frequently in TMNG patients compared to controls. Although this variant did not display constant activation, it exhibited altered response to TSH, suggesting potential involvement in TMNG development. Unlike mutations seen in AFTN, these variations were genomic and likely contributed subtly to thyroid function and growth over time.

While the D727E variant was linked to TMNG, its presence alone was insufficient to cause the condition, as it was also present in approximately 10% of normal individuals. However, it may predispose individuals to abnormal thyroid growth and function when combined with other genetic or environmental factors. The precise mechanisms underlying this association remain unclear, but could involve intracellular signaling, transcription factors, growth factor response, or environmental factors like iodine exposure. Moreover, while mutations in hTSHR were rare in examined AFTN patients, further investigations are necessary to explore the role of the identified variations in euthyroid goiter and their potential contributions to the disorder.

3.2 Association of Graves' Disease

The research(Heward et al., 2006) examined the relationship between five tag SNPs inside the PTPN22 gene and the rs2476601 SNP, already related with rheumatoid arthritis, in a case-control cohort of people with Graves' disease (GD). Using Haploview's aggressive tagging option, the coverage of these six SNPs was evaluated, capturing a substantial portion of known common variation in the gene. Despite sufficient statistical power, none of the individual SNPs displayed an association with GD, nor did any SNP correlate with specific clinical phenotypes, indicating no contribution to the disorder or its clinical subtypes.

Analysis of linkage disequilibrium (LD) revealed strong correlation among all SNPs, forming a single LD block. Haplotype analysis identified both predisposing and protective haplotypes. While the rs2476601 SNP and the predisposing haplotype were linked to GD, the protective haplotype did not show any excess transmission, likely due to its rarity. Conditional analyses confirmed that the effect of the predisposing haplotype was solely attributed to the rs2476601 variant, while the mechanism underlying the protective haplotype remained unidentified.

Comparisons with RA data sets revealed differing haplotype associations, potentially influenced by geographical origins and varying LD patterns between populations. Although PTPN22 appears to function as a general autoimmunity locus, differences in SNP associations and haplotypes between RA and GD suggest disease-specific mechanisms. Further investigation is necessary to understand how PTPN22 variants affect autoimmune diseases and their pathways, potentially through the differential expression of LYP isoforms and their binding affinities with adaptor molecules. Detailed LD mapping and functional investigations are needed to determine the specific involvement of PTPN22 in GD and other autoimmune disorders.

3.3 Association of Hashimoto’s thyroiditis

This research (Abdullah et al., 2021) marks the inaugural investigation in Iraq into the relationship between IRGM genotypes and Hashimoto's thyroiditis (HT) disease. In line with previous findings by Yao et al., it indicates that three SNPs within the IRGM gene do not exhibit a connection with HT but exhibit a strong association with Graves' disease (GD). The implications of IRGM genetic variations extend beyond autoimmune thyroid diseases (AITD), as demonstrated by studies by Glas et al. and Pranculienė et al., linking IRGM SNPs to Crohn’s disease and inflammatory bowel disease, respectively. Additionally, IRGM polymorphisms have been tied to gastric carcinoma, systemic lupus erythematosus (SLE), as well as several bacterial and viral infections.

Associations between IRGM SNPs and tuberculosis (TB) have been identified by (Song et al. and Lu et al.), with specific variants offering protection against latent TB progression. Furthermore, IRGM polymorphisms have been implicated in leprosy and Candida infections. Recent investigations have established links between IRGM SNPs and Helicobacter pylori (H. pylori)-related inflammation, suggesting that certain genotypes may mitigate inflammation in the gastric mucosa during H. pylori infection, thereby reducing the risk of gastric cancer. Other genetic polymorphisms, such as those within the CXCL9, IL-27, and thyroglobulin genes, have been associated with susceptibility to AITD across diverse populations. Similarly, variants of the inositol hexaphosphate kinase 3 gene have been found to decrease the risk of HT in Algerian individuals, while no notable disparities in the PD-L1 gene genotype frequency were observed between AITD patients and healthy controls.

Differences in findings across genetic studies may arise from variations in study populations, environmental factors, dietary habits, methodological approaches, and sociodemographic characteristics of participants. However, the study's limitation due to the small number of participants highlights the need for future research with larger sample sizes to provide more robust insights.

3.4 Association of Asthma

(Duan et al., 2013) found that the THRB gene, located on chromosome 3p24.2, encodes the β subunit of the thyroid hormone receptor, which regulates transcription. Genetic differences in THRB may influence lung development and smooth muscle function, thereby leading to airway inflammation and constriction. A non-coding SNP (rs892940) near THRB has been associated to the responsiveness to β2-agonists in asthma populations, indicating its importance in treatment effectiveness. More research is needed to understand how this gene regulates bronchodilator responsiveness, which holds promise for personalized asthma care.However, constraints like as sample sizes and biases in replication populations should be recognized. Furthermore, numerous SNPs across genes were modestly linked with bronchodilator responsiveness, maybe because to linkage disequilibrium. Discovering transcription factors that regulate bronchodilator responsiveness opens up new treatment pathways for asthma management, however targeting TFs directly creates hurdles in terms of avoiding side effects. More study is needed to optimize the administration of such medications and gain a better knowledge of genetic influences on asthma treatment results.

3.5 Association of Iodothyronine

This research (Peeters et al., 2003) examines polymorphisms within genes involved in the thyroid hormone pathway, including TSHR, TRβ and D1, D2, D3. It identifies four novels, eight polymorphisms and four previously documented. The D1a-C/T polymorphism was linked to higher plasma rT3 levels, whereas the D1b-A/G polymorphism was linked to variations in the rT3/T4 and T3/rT3 ratios. Haplotype analysis revealed a range of impacts on plasma iodothyronine levels. However, the D2-Thr92Ala polymorphism had no significant effect on plasma TSH levels, while the D3-T/G polymorphism had no effect on plasma iodothyronine. The TSHRc-Asp727Glu variation was associated to lower plasma TSH levels, indicating functional significance. A silent variation in the TRβ gene did not show significant correlation with plasma TSH or iodothyronine levels. In conclusion, this work offers insight on the significance of certain polymorphisms in thyroid hormone regulation, emphasizing the need for more research, particularly on the incidence of certain SNPs in the community.

Chapter 4

Conclusion

Thyroid hormone exerts a significant influence on the function of the immune system, primarily mediated through its interaction with the CYP27B1 gene. Variations in the CYP27B1 gene have the potential to impact the immune response, potentially leading to conditions such as Toxic Multinodular Goiter, Iodothyronine, Hashimoto's thyroiditis, Graves' disease, and Asthma. Interestingly, individuals with Hashimoto's thyroiditis and Graves' disease often imbalance thyroid hormone, suggesting its potential involvement in disease progression. However, the exact mechanisms are not fully understood.

Despite the connection between the CYP27B1 gene and various disease communities, there are other factors at play that remain incompletely understood and may contribute to the development of these disorders in specific populations. Furthermore, the diverse and scattered nature of the available data indicates that the CYP27B1 gene effects may vary depending on an individual's ethnic background. The susceptibility to these diseases cannot be generalized across different populations. As a result, further study is needed to establish a definitive link between CYP27B1 and the disorders indicated above. Population diversity, age, gender, and other variables all need to be taken into account. The link between CYP27B1 and these disorders has been proven in numerous populations.

Future Aspect

CYP27B1 gene has shown connections in various groups, additional research is required to validate its role in different diseases and gain a comprehensive understanding of the topic.

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