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Review Article

CTLA-4 Polymorphisms in Allergy and Asthma: Insights into the TH1/TH2 Immune Balance

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Abstract

Asthma and allergy are two prevalent immune-mediated disorders caused by an excess of T-helper (TH) cell activity, i.e., an example of TH2 predominance with elevated IgE, eosinophilia and chronic airway inflammation. Of special importance, immune checkpoint receptor cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) were observed to regulate T-cell regulation and TH1/TH2 immunobalance of immunity through competitive blocking of CD28 interaction with B7 ligands on antigen-presenting cells to inhibit T-cell activation. Functional polymorphisms like +49 A/G (rs231775), −318 C/T (rs5742909) and CT60 A/G (rs3087243) of the CTLA4 gene have been associated with regulated CTLA-4 expression and function with implications for asthma and allergy susceptibility. This review collates contemporary understanding of CTLA-4 structure biology, its TH1/TH2 polarizing immunomodulatory roles, and genetic variants' effects on allergic phenotypes across diverse populations. Some CTLA-4 polymorphisms disrupt immune regulation, promoting TH2 dominance, IgE synthesis, airway hyperresponsiveness, and atopic disease progression by undermining regulatory mechanisms. Ethnic variation in CTLA-4 variants may serve as biomarkers for disease susceptibility and treatment response, potentially even to corticosteroids and biologics. Rising preclinical data also show the potential of CTLA-4–targeted therapies to regulate allergic inflammation. Current evidence is hampered by small cohorts, limited ethnic diversity, and replication constraint in genome-wide studies. We conclude by outlining areas of unknowns and proposing future research directions to determine genotype–phenotype relationships and integrate CTLA-4 findings into individualized interventions for allergy and asthma. Understanding the immunogenetic landscape of CTLA-4 will enhance precision immunology and inform new treatments against these global disease burdens.

Keywords: CTLA-4, Allergy, Asthma, Polymorphism, Immune balance, TH1/TH2.

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1. INTRODUCTION

Allergy and asthma are persistent, immune-mediated diseases characterized by a prevalence of overactive type 2 (TH2) immune reactions against nonpathogenic environmental antigens (Johansson et al. 2001; Liao *et al.,* 2016). Classic characteristics are elevated serum IgE, airway hyperreactivity, eosinophilic inflammation, and airway remodeling (Oh *et al.,* 2010; Howard *et al.,* 2002). Together, they afflict over 300 million individuals worldwide, and they have enormous global health and socioeconomic burdens (Hizawa *et al.,* 2001). There is hereditary predisposition further complicated by exposure to environment, such as allergens and toxins, to have an impact on the susceptibility of individuals and disease advancement (Zheng *et al.,* 2018). CTLA-4 (cytotoxic T lymphocyte–associated antigen 4) is an immune checkpoint receptor on regulatory and triggered T cells that is an essential modulator of immunological homeostasis (Bour-Jordan *et al.,* 2003; Tanhapour *et al.,* 2017; Qian et a., 2007). CTLA-4 competes with the co-stimulatory receptor CD28 for binding to B7 ligands (CD80/CD86) on antigen-presenting cells. In contrast to CD28, CTLA-4 starts inhibitory signals that prevent T cell activation (Howard *et al.,* 2002; Salomon *et al.,* 2001). Such modulation by CTLA-4 is aimed at balancing TH1 and TH2 responses; overactivation can cause autoimmunity (a condition of TH1 dominance), but the failure to inhibit can promote TH2 mediated inflammation, as in allergy and asthma.

Genetic polymorphisms in immune modulators like CTLA-4 are capable of tilting this balance. Single-nucleotide polymorphisms (SNPs) in CTLA-4, specifically +49A/G (rs231775), but also promoter polymorphisms like −318C/T and CT60 A/G, are

considered to alter CTLA-4 expression or function (Hizawa *et al.,* 2001). These changes may tip T cell differentiation in the direction of TH2 predominance, augment IgE production, and enhance allergic susceptibility (Munthe-Kaas *et al.,* 2004). The +49A/G SNP has been studied most extensively in allergic asthma. Meta analyses with thousands of controls and cases across many ethnic groups have shown the +49A allele (AA genotype) to be of increased risk for asthma, predominantly in children, Asians, and atopic subjects (Zheng *et al.,* 2018; Lee *et al.,* 2012; Gupta *et al.,* 2016). Conversely, the G allele (GG/GA genotypes) is seemingly protective in some populations. Promoter −318C/T variants are linked more strongly to asthma severity and bronchial hyperresponsiveness than to disease susceptibility per se (Lee *et al.,* 2002). Focus on CTLA-4 polymorphisms represents a rich window on the way that subtle genetic heterogeneity influences the TH1/TH2 axis and induces allergic disease phenotypes (Munthe-Kaas *et al.,* 2004). Clarification of these links may shed light on disease mechanisms and allow future individualized therapies, like genetic screening or checkpoint-targeted treatment.

The objectives of this review are threefold and aim to provide a full-grasping understanding of the role played by CTLA-4 in the control of the immune response. Firstly, the review aims to categorize the functions of CTLA-4, particularly its function in T-helper cell differentiation, i.e., TH1 and TH2 subsets. Second, it aims to examine the existing evidence that links the common CTLA-4 polymorphisms; +49A/G, −318C/T, and CT60 A/G, to allergic asthma onset, atopy, and IgE variability. Further, the review places strong emphasis on mechanistic considerations obtained from genotype–phenotype correlations, as well as relevant immunobiological studies. It also explores how ethnicity, age, and atopic status affect these associations with stratified analysis of the data. Lastly, the review aims to determine gaps in current knowledge, suggest areas for future research, and look at broader clinical relevance of the findings.

2. CTLA-4: Structure, Function, and Expression

2.1. Gene location, structure, and isoforms

The CTLA-4 gene on human chromosome 2 has four exons. These four (4) exons are; exon 1 the signal peptide encoding, exon 2 the extracellular Ig-like domain, exon 3 the transmembrane and exon 4 the cytoplasmic tail (Valk *et al.,* 2008; Howard *et al.,* 2002). With alternative splicing methods in place, at least two major protein isoforms are specifically produced in humans. These are the full-length transmembrane CTLA-4 (flCTLA-4) and a soluble form lacking exon 3 (sCTLA-4), which is found in serum (Hossen *et al.,* 23). Other splice forms, for example, a murine ligand-independent CTLA-4 (liCTLA-4) have also been found in mice (Hossen *et al.,* 2023).

2.2. Mechanisms of action on T-cell regulation

Notably, while both the FlCTLA-4 and sCTLA-4 exons bind CD80/CD86, they still play antagonistic inhibitory roles through distinct mechanisms. In this case, the membrane CTLA-4 suppresses the T-cell activation by competing with B7 ligands for CD28 and engaging phosphatases, such as SHP-2 and PP2A to attenuate TCR signaling (Kim *et al.,* 2022). Therefore, the soluble CTLA-4 can increase the threshold for T-cell activation *in vitro*, possibly by sequestering B7 ligands and diminishing co-stimulation.

2.3. Expression profile and function in immune tolerance

CTLA-4 is constitutively expressed at high concentrations on Tregs and induced on naive T cells during activation. It is controlled at transcriptional and trafficking levels: NF-AT and cAMP signaling enhance transcription, while intracellular adaptor proteins (e.g., TRIM, CAP-1/2) control trafficking to and from the cell surface. These activities truncate T-cell activation and assist with the institution of peripheral tolerance (Hossen *et al.,* 2023).

2.4. Role in T cell activation and immune tolerance

On TCR stimulation and CD28 co-stimulation, CTLA-4 gets augmented and translocated to the immunological synapse, where it competes with CD28 for ligands, recruits phosphatases in to inhibit signals, and indirectly modulates APC function by trogocytosis (B7 ligand removal) and cytoskeletal rearrangement (Slavik *et al.,* 1999; Qureshi *et al.,* 2020). This negative feedback induces anergy, controls T-cell proliferation, and imposes self-tolerance.

2.5. Expression in regulatory T cells (Tregs)

CTLA-4 plays a critical role in FoxP3$^+$ Tregs suppressive activity. It suppresses through removal of CD80/86 from antigen-presenting cells, secretion of suppressive cytokines, and depletion of IL-2 (Hossen *et al.,* 2023). CTLA-4 deficiency disables Treg, impairing peripheral tolerance, and potentially initiating allergic inflammation (Conrad *et al.,* 2025; Wing *et al.,* 2008).

2.6. CTLA-4 signaling pathways and downstream consequences

CTLA-4 signaling recruits SHP-2 and PP2A that dephosphorylate CD3ζ (CD3 zeta chain) and LAT to suppress TCR-triggered NF AT, AP 1, and NF-κB activation (Lee *et al.,* 1998). CTLA-4 also suppresses B7 ligand by trogocytosis, disorganizes actin cytoskeleton in APCs, and preserves immune quiescence (Qureshi *et al.,* 2011; Hou *et al.,* 2021). CTLA-4 deficiency in mouse models enhances Tfh and effector cytokine secretion (IL-4, IL-5), emphasizing its role in inhibiting TH2 responses (Wing *et al.,* 2008).

3. CTLA-4 and TH1/TH2 Immune Paradigm

3.1. Description of TH1 and TH2 immune responses

The destiny of naïve $CD4^+$ T cells to become TH1 or TH2 subsets forms the cornerstone of immunity vs. allergy. IL-12 and IL-18 stimulate TH1 cells to release IFN γ and execute cell-mediated immunity. TH2 cells, on the other hand, with the help of IL 4, release IL 4, IL 5, IL 9, and IL 13, which coordinate B cell class switching to IgE, eosinophil activation, mucus secretion, and airway hyperreactivity (Hossen et al. 2023). Excess of TH2 responses is significantly involved in asthma and allergy pathophysiology.

3.2. CTLA-4's function in regulating TH1/TH2 equilibrium

CTLA-4 is a significant immune checkpoint that competitively excludes CD28 to bind CD80/CD86 and hence delivers inhibitory signals to dampen T cell activation (Chikuma, 2017). Expressed on activated and tolerogenic T cells (Tregs and Tr1-like cells), CTLA-4 enables the diversion of immune responses away from TH2 dominance by reinforcing TH1 responses in tolerance contexts and inhibiting allergen-driven TH2 differentiation (Hossen *et al.,* 2023; Salomon *et al.,* 2001). Functional CTLA-4 polymorphisms, including +49 A>G, −318 C>T, CT60, and novel variants, have been found to decrease CTLA-4 expression or signaling, impairing its inhibitory function. This impairment allows uncontrolled TH2 activity and IgE production (Munthe-Kaas *et al.,* 2004; Lindsten *et al.,* 1993). A landmark genetic study in asthmatic European families found CTLA-4 SNPs to be tightly associated with elevated serum IgE, allergic sensitization, asthma, and reduced lung function, highlighting their function in TH1/TH2 balance (Munthe-Kaas et al, 2004; Teft *et al.,* 2006).

3.3. Consequences of imbalance on allergic and asthmatic responses

In the case of CTLA-4 function is abnormal, the TH2 axis becomes unregulated: IL 4 and IL 13 are increased, thus resulting in IgE class switching and eosinophilia; IL 5 makes airway inflammation worse. Besides this, remodeling and hyperresponsiveness via the TH2 pathway also follow (Ismail *et al.,* 2025). Signals from the TH1 (such as IFN γ), that could be under other circumstances, able to suppress allergic inflammation, are not effective. Such skewing then amplifies the disease seriousness and also results in a longer sick period in patients with asthma and allergic rhinitis (Agaronyan *et al.,* 2022).

3.4. Inter-action with other immune regulators (e.g., IL-10, TGF β)

CTLA-4 plays a significant role in the functions of the anti-inflammatory cytokines IL-10 and TGF β that are both required to achieve homeostasis in the immune system. Tregs with CTLA-4 are the cells that among others they secrete IL-10. TGF β, and IL-35 are for the decrease of TH1 and TH2 effector responses (Tang *et al.,* 2004). Dendritic cell function is regulated by IL-10 and the antigen presentation is suppressed; hence the immune response is still in homeostasis. TGF-β not only helps Treg to become the Treg lineage, but it also decreases the allergic inflammation and thus reverses the TH2-mediated airway hyperreactivity that has been induced in model systems. In cases where expression of CTLA-4 is low, the IL-10/TGF β inhibitory feedback loop is disrupted. This provides a setting for TH2 dominance, leading to amplified allergic phenotypes (Read *et al.,* 2006).

4. CTLA-4 Gene Polymorphisms: Types and Functional Implications

4.1. Common SNPs in CTLA-4

Several single nucleotide polymorphisms (SNPs) of the CTLA-4 gene have been identified as exceedingly important in immune process regulation. The most extensively studied among them is the +49 A/G variant (rs231775), which is an exonic SNP. It is a substitution of one of the amino acids from threonine to alanine in the CTLA-4 signal peptide. The substitution disrupts typical glycosylation and lowers the amount of CTLA-4 protein expressed on the cell surface. Consequently, the inhibition function of CTLA-4 is no longer available, and this, in turn can cause the activation of T cells and is associated with the higher immune response (Asalh *et al.,* 2023). The second most important variant is CT60 (rs3087243) that lies in the 3′ untranslated region (UTR) of the gene. The SNP affects splicing and mRNA stability and relative membrane-bound to soluble CTLA-4 isoform production. Functional alleles in the CT60 locus predispose individuals towards increased vulnerability to autoimmune and allergic diseases, indicating their role in fine tuning of immunity.

Furthermore, −318 C/T polymorphism (rs5742909), within the CTLA-4 gene promoter, impacts transcriptional activity. Specifically, the T allele has been associated with greater promoter activity and greater CTLA-4 expression. The impact of this SNP on disease susceptibility is not consistent and appears to be governed by population-specific environmental and genetic factors (Tanhapour *et al.,* 2017; Yang *et al.,* 2006). These common CTLA-4 polymorphisms collectively lead to immunoregulatory variation among individuals and may serve as powerful genetic markers for the study of immunological disorders.

4.2. Impact on CTLA-4 Expression and Function

Some critical CTLA-4 single nucleotide polymorphisms (SNPs) have been identified to significantly influence the gene's expression and role of function in immune control. For example, the +49 G allele prevents correct glycosylation and interferes with the transport of CTLA-4 to the cell surface (Yang *et al.,* 2004). So, individuals who carry this allele either heterozygous or homozygous state, are those, who express lower levels CTLA-4 on the surfaces of activated

T cells. That reduction in expression weakens inhibitory signaling and thus causes the overactivation of T cells, which in turn potentiates immune responses (Mahmood *et al.,* 2023). Polymorphisms within the CT60 locus are also a critical regulatory factor. Such polymorphisms are involved in the regulation of alternative splicing and thus support the formation of soluble CTLA-4 (sCTLA-4). Unlike membrane-associated CTLA-4, sCTLA-4 cannot carry the inhibitory signal. Instead, it may be utilized as a decoy receptor, sequestering with CD80/CD86 ligands and hence preventing maximal immune regulation. Research has found that elevated sCTLA-4 levels are correlated with the intensification of TH2-biased responses which are indicative of allergic inflammation.

The −318 T variant was further demonstrated to have a relationship with an upregulated promoter activity, which generally means that membrane-bound CTLA-4 is expressed at a higher level. Its clinical impact, however, varies in various populations. It was shown to be protective in some ethnic groups against immune-mediated disorders, while in others it had previously been shown to have no association or even a negative association. These differences are due to variation in genetic background, environment, or linkage disequilibrium with other functional mutations (aimspress.com). These SNPs combined have a significant impact on CTLA-4 expression and function by directly affecting T cell inhibitory signal strength. Immune response dynamics are modulated by them, and they are responsible for causing susceptibility to allergic as well as autoimmune conditions (Poyastro *et al.,* 2001; Wang *et al.,* 2002; Csanád *et al.,* 2006).

4.3. Ethnic Variations and Allele Frequencies

Allele frequencies of CTLA-4 single nucleotide polymorphisms (SNPs) vary greatly between ethnic populations and have a crucial bearing on the understanding of disease susceptibility and precision medicine. For example, the G allele of the +49 A/G polymorphism is substantially more prevalent in Asian populations, at 60% or more, compared to European populations, at about 40%. This higher frequency is consistent with more robust associations between the +49 A/G variant and enhanced asthma or allergy risk in Asian populations (Zheng *et al.,* 2018; Csanád *et al.,* 2006). Similarly, the CT60 variant shows marked ethnic differences in allele frequencies and haplotype. Autoimmune diseases such as Graves' disease and Hashimoto's thyroiditis in European populations have been linked to the CT60-G allele. In contrast, the identical allele exhibits different connections with Asian populations, specifically with asthma, to point out the complicated relationship between ethnicity and genetics in the disease's manifestation.

The −318 T allele, although relatively rare by and large, also shows ethnic variability. Its impact upon CTLA-4 gene expression and susceptibility to disease appears to vary with context, most likely determined by local structures of linkage disequilibrium and environmental forces. These differences highlight population-specific interpretation because the identical CTLA-4 SNP may be a risk factor, neutral, or protective depending on the genetic background of the individual (Hossen *et al.,* 2023). It is necessary to identify such ethnic variations for the interpretation of genome-wide association studies (GWAS), meta-analyses, and clinical application of CTLA-4 genotyping. Unless the variations are adjusted for, conclusions about the role of CTLA-4 variants in risk for disease are misleading or incomplete.

5. CTLA-4 Polymorphisms and Allergy

5.1. Overview of Studies Relevant to Allergic Rhinitis, Atopic Dermatitis, Food Allergy.

Epidemiologic research has generated mounting evidence indicating associations between CTLA-4 gene polymorphisms and various allergic diseases, particularly allergic rhinitis (AR). In Chinese Han children, some single nucleotide polymorphisms (SNPs) in the CTLA-4 gene were much more frequent among AR subjects. For instance, the A allele of rs11571302 and the AA genotype of rs3087243 were detected at higher frequency in AR children, especially those with asthma as a comorbid condition (Ke *et al.,* 2017). In line with these observations, another study in the same group found the rs3087243 AA genotype and the A allele of rs231725 to be more common in AR with asthma. Interestingly, the rs231725 AA or A allele appeared to be protective in children with AR alone, suggesting that this polymorphism plays a nuanced, context-dependent role in allergic disease expression (Song *et al.,* 2016).

The mechanism of these associations is believed to revolve around CTLA-4's role as an immune checkpoint molecule, with particular emphasis on its role in TH1/TH2 skewing of immunity. Such an immunoregulatory function is important in the pathogenesis of allergic rhinitis, in so far as it can affect the ratio between anti-inflammatory and pro-inflammatory reaction (Munthe-Kaas *et al.,* 2004). Generally, these studies lay major focus on CTLA-4 genetic polymorphism in defining susceptibility to and clinical manifestation of such allergic conditions as AR. While direct investigation in atopic dermatitis and CTLA-4 is not common, phenotypic similarities between allergic rhinitis and atopic dermatitis imply common genetic mechanisms. The capacity of CTLA-4 to control IgE would imply relevance for research in food allergy, but quality targeted research has yet to manifest.

5.2. Specific CTLA-4 Polymorphisms and Allergic Phenotypes

Several single nucleotide polymorphisms (SNPs) have been found to be of specific significance in various allergic diseases. The most described is +49 A/G (rs231775), where the A allele was associated with higher mite-specific IgE in Korean asthmatic children. The allele has also shown gender-specific linkage to

higher total IgE and rhinitis in Chinese women (Munthe-Kaas *et al.,* 2004). The other essential variant, CT60 (rs3087243), has been detected with allergic rhinitis (AR) and asthma in Han children and also in association with an excellent response to inhaled corticosteroids (ICS) in children with asthma (Song *et al.,* 2016).

The SNP rs11571302 has been found at increased frequencies in Han Chinese populations with allergic rhinitis, suggesting a population-specific role in disease susceptibility (Ke *et al.,* 2017). In like manner, the −318 C/T polymorphism has been linked with increased risks of asthma in Southwest Iranian populations and also with dust mite–specific IgE levels in some populations. The rs231725 polymorphism, specifically its A allele, has been linked with allergic rhinitis with and without concomitant asthma in pediatric groups from Eastern Asia (Song *et al.,* 2016). In combination, these SNPs regulate allergen-specific or total IgE levels and, in some cases, regulate responses to asthma drugs or alter overall asthma risk. Remarkably, their action often varies based on ethnicity, age, gender, and the environment, emphasizing the pleiotropy of genetic contributions to allergic disease.

5.3. Meta-Analyses and Population-Based Data

A European multicenter family study provided insightful data regarding the role of CTLA-4 polymorphisms in allergic disease. Seven CTLA-4 SNPs; CT60, MH30, and +49 A/G, were typed in more than 360 asthmatic families in this study. All of them were identified to be significantly linked to dominant allergic traits such as overall IgE levels, sensitization towards allergens, presence of asthma, and poor lung function ($FEV_1 < 80\%$). Surprisingly, there was no significant association with bronchial hyperresponsiveness. These results suggest CTLA-4 variants exert a broader effect on atopy through modulation of the TH1/TH2 immune balance (Munthe-Kaas *et al.,* 2004).

Cross-ethnic meta-insights have also enlightened the complex role of CTLA-4 in immune regulation. CTLA-4 variants typically associated with autoimmune disease, typically characterized by TH1-biased immune responses, have illustrated reverse associations with atopic disorders, which are TH2-biased. The negative relationship fits very well the immune polarization theory, which explains that CTLA-4 could be a molecular switch between two opposite immunologic phenotypes (Munthe-Kaas *et al.,* 2004). Although family-oriented and population-based studies have been valuable so far, there are no big meta-analyses that deal with CTLA-4 in allergy and asthma directly that are very important now. Over the past decade, there have been some combined evidence syntheses, and this has helped to indicate a key knowledge gap in the literature and the need for more widespread meta-analytical work to bring together and clarify CTLA-4's function in allergic disease across populations.

6. CTLA-4 Polymorphisms and Asthma

6.1. Genetic Association Evidence

There have been numerous genetic association studies to investigate the interaction between CTLA-4 single nucleotide polymorphisms (SNPs) and asthma, as well as other genetic diseases in different populations (Al-Harbi at al., 2023; Dehaghani *et al.,* 2009). Of them, the +49 A/G variant (rs231775) in exon 1 has been of particular interest. A 2015 meta-analysis of 15 case-control studies with 4,006 asthma cases and 3,729 controls found that the G allele (GG + GA genotypes) protected against asthma with an odds ratio (OR) of 0.76. The protective action was most evident in Caucasian children and subjects with atopic asthma (Zhao *et al.,* 2015; Wang *et al.,* 2016). A 2018 more detailed review that pooled information from 19 studies (4,831 cases and 4,534 controls) again confirmed the association in children and Asian populations, but in weaker or no effects in adults or European populations (pubmed.ncbi.nlm.nih.gov). A later meta-analysis published in PLoS One with 6,378 cases and 8,674 controls again established that those with the AA genotype were at increased risk for asthma (OR 1.18). Results for promoter SNP −318 C/T have been less consistent. Zheng et al.'s (2018) meta-analysis of a large Asian population reported no significant overall risk association between this SNP and asthma. Yet, a 2021 Iranian study revealed that the T allele was a risk allele with OR = 1.83 and that its effect was moderated by environmental and demographic factors such as smoking status, age, and gender (Azab *et al.,* 2021).

Other SNPs with function-modifying roles, including CT60, −1147CT, and the JO series (JO31 and JO30), have also been implicated in asthma and allergy phenotypes. A milestone family-based multicenter study linked such SNPs with high levels of total IgE, asthma susceptibility, allergic asthma, and reduced lung function (Munthe-Kaas *et al.,* 2004). In Chinese children with asthma, six SNPs, including −1147CT and CT60, were demonstrated to be connected with soluble CTLA-4 levels and lung function, particularly the FEV_1/FVC ratio, showing their functional significance (Yang *et al.,* 2009; Chan *et al.,* 2010). Additionally, some polymorphisms in the CTLA-4 gene have been found to be linked with the seriousness of asthma and airway hyperresponsiveness. In a group of 88 individuals with asthma, the −318 T allele was correlated with severe asthma ($P = 0.037$), and subjects with +49 GG genotype were observed to be more airway hyperresponsiveness ($P = 0.019$) (Lee *et al.,* 2002). All together, these findings prove the important contribution of CTLA-4 polymorphisms to the susceptibility, severity, patterns of immune responses, and therapeutic responses to asthma in different populations.

6.2. Effect on Susceptibility, Severity, and Treatment Response

The effect of CTLA-4 polymorphisms on asthma and allergic disease occurs in susceptibility, severity, and treatment response. As regards disease susceptibility, overwhelming evidence supports the +49 A/G polymorphism as a significant genetic risk factor, particularly in children and in atopic individuals. Those who have the AA genotype are determined to be at very high risk (Berce *et al.,* 2020; Portelli *et al.,* 2015). The −318 C/T promoter variant also tends to increase asthma susceptibility in targeted populations, including Middle Eastern cohorts, by Zheng et al. (2018). In terms of disease severity and airway hyperresponsiveness, the −318 T allele is associated with more severe asthma phenotypes. Moreover, individuals with the +49 GG genotype have been found to exhibit increased bronchial hyperreactivity. Chinese pediatric cohorts also present data that regulatory SNPs such as −1147CT have an impact on lung function, presumably by virtue of their role in the regulation of soluble CTLA-4 levels that consequently influence T cell regulation and airway inflammation.

Regarding response to therapy, CT60 A/A genotype has proven to have predictive value in the ability to predict responsiveness to inhaled corticosteroids. A Slovenian children study has found that individuals with the A/A genotype experienced an improvement in FEV_1 of 21.7%, while those who were GG homozygotes experienced only a 5.8% improvement (Berce *et al.,* 2010). These findings mean that CTLA-4 genotyping may be employed as a method of guiding individualized asthma treatment, being a route towards increasingly diminished and focused treatment methods.

6.3. Interaction with Environmental Factors and Other Gene Variants

The role of CTLA-4 polymorphisms in allergic disorders is greatly influenced by the interaction with environmental components and other gene variants, as seen with the complexity of immune regulation. In Iran, for instance, risk of asthma associated with the +49 A/G polymorphism was shown to greatly vary by smoking status, gender, and age. These findings illustrate the importance of gene–environment interactions in establishing disease susceptibility (Roshanizadeh *et al.,* 2021; Amininia *et al.,* 2021). In addition, gene–gene interactions also play a role. In Chinese children analysis, −1147CT variant was the best single predictor of soluble CTLA-4 concentration and is suggested to regulate immune function more subtly than single SNP effect (Chan *et al.,* 2010).

Apart from this, newer evidence from Asia and Europe indicates that CTLA-4 polymorphisms are integral to extended immunologic gene networks. Most significantly, the polymorphisms also appear to interact with IL-33 and PTPN22 variations, key modulators of IgE secretion, as well as with exposures to influence TH2-dominant immune responses. Integration of these exposures and genes into comprehension provides additional insight into allergic and asthmatic phenotypes' development and heterogeneity in populations (Li *et al.,* 2017).

6.4. Integrative Insights into Immune Equilibrium

CTLA-4 gene polymorphisms control inhibitory T-cell signaling, affecting TH1/TH2 equilibrium. +49 A/G and −318C/T alleles are able to abolish CTLA-4 regulatory activity and thus augment TH2-dominant immunity: enhancing IgE, airway hyperreactivity, and asthma severity. Conversely, SNPs beneficial to TH1-autoimmunity tend to be protective against atopic phenotypes. Furthermore, CTLA-4 Ig fusion proteins in mice have been shown to inhibit airway inflammation and reduce TH2 cytokine secretion and IgE, which suggests the therapeutic potential of CTLA-4 (Ni *et al.,* 2015).

7. Clinical Implications and Future Directions

7.1. CTLA-4 Polymorphisms as Potential Biomarkers for Allergy/Asthma Risk

Accumulating data indicate that CTLA-4 SNPs such as +49 A/G, −318 C/T, CT60 (rs3087243), and −1147CT can serve as genetic biomarkers for asthma and allergy risk stratification. In Chinese children, the CT60 A/A genotype was significantly more common in patients with allergic rhinitis and asthma compared with controls (Song *et al.,* 2016; Zheng e tal., 2018; Alska *et al.,* 2025). In southwest Iranian, the −318 T allele carriers were at higher risk for asthma (OR ≈ 1.8), with the effect modified by age, sex, and smoking status (Roshanizadeh *et al.,* 2021). Chinese pediatric data also showed that −1147CT genotype predicted lower plasma soluble CTLA-4 and was also linked to poorer lung function (FEV_1/FVC), once more in favor of its role in identifying at-risk individuals.

7.2. Predictive Value for Therapeutic Response (e.g., Corticosteroids, Biologics)

Genotype-based treatment selection is on the horizon. Slovenian children's data showed that CT60 A/A homozygotes responded with a considerable 21.7% increase in FEV_1 after 4 weeks of inhaled corticosteroid treatment, far more than in other genotypes, highlighting the value of CTLA-4 genotyping for predicting corticosteroid response (Berce *et al.,* 2010). With biologics, such as antidepressants targeting IL 4Rα (dupilumab) and TSLP (tezepelumab) gaining traction, association of CTLA-4 variants with biologic response might enhance personalized therapeutic paradigms, particularly in non–Th2-endotype asthma (Alska *et al.,* 2025).

7.3. Potential for CTLA-4 Pathway Targeting for Immunomodulation

CTLA-4–Ig fusion proteins (such as abatacept) and checkpoint inhibitors are therapeutic modalities employing the same mechanism of action in both

autoimmunity and oncology. Asthma models at the preclinical stage indicate that CTLA-4 activation reduces the inflammation of the airways, the production of IL 4/IL 5 and that of IgE. Conversely, CTLA-4 blockade enhances TH2 responses (Lenschow *et al.,* 1997; Hellings *et al.,* 2002; Ortega *et al.,* 2007; Chan *et al.,* 2010). These observations suggest that selective targeting of CTLA-4 with agonists will restore TH1/TH2 balance in asthma and allergy. Clinical exploration of CTLA-4 agonists (or CTLA-4–Ig analogs) in allergic disease is an untapped but exciting avenue.

7.4. Interaction with Other Genetic and Epigenetic Factors

The CTLA-4 variants must be viewed within the perspective of other genetic and epigenetic interactions that orchestrate immune function and disease susceptibility. There are data that gene–gene synergy plays a central role in allergic disease. For example, combined analysis of PTPN22 and CTLA-4 polymorphisms was found to increase predictive value for allergic rhinitis with concurrent asthma in Han children (Munthe-Kaas *et al.,* 2004). This would indicate a necessity to investigate CTLA-4 variants not in isolation but as part of a larger genetic network. Epigenetic effects introduce an additional layer of complexity and function. Alterations in DNA methylation, like in the regulatory elements of the FoxP3 gene, could alter the behavior of regulatory T cells (Tregs) here in the case of allergen immunotherapy. The CTLA-4 gene polymorphisms are likely working together with these epigenetic mechanisms (Sharma *et al.,* 2022; Floess *et al.,* 2007). They might be influencing the methylation process or the changes in histones and thus affecting the immune cells' function and response to allergens. Also, polygenic risk scores are a potentially bright path to effectively combining CTLA-4 SNPs with other markers, for instance, IL33, IL4Rα, and HLA loci, for example.

Given the epigenetic signatures and the data regarding environmental exposures, the potential of such models to allow for differentiated risk stratification and focused prevention of allergy and asthma is huge. In combination, the results emphasize the power of viewing CTLA-4 genetic variation as part of a combined systems-level model that factors not only genetic but also epigenetic aspects of immune regulation.

8. Challenges and Limitations in Current Research

8.1. Limitations of Earlier Research: Ethnic Heterogeneity & Sample Size

Most earlier investigations into CTLA-4 polymorphisms and allergy/asthma have drawn on reasonably small, single-center cohorts. For instance, the groundbreaking European family study with ~360 families were the largest so far for CTLA-4 SNPs, yet still reasonably restricted in ethnic diversity and statistical power for less frequent variants (Munthe-Kaas *et al.,* 2004; Torgerson *et al.,* 2011). Case-control meta-analyses (up to ~4,800 cases) confirmed +49A/G associations in Asians but not consistently in Europeans or adults (Wan *et al.,* 2012; Zheng *et al.,* 2018). As an exception, a study of 200 patients in Southwest Iran found significance for the −318 T allele but not for +49A/G, with population-specific effects and highlighting the urgent need for multi-ethnic replication (Roshanizadeh *et al.,* 2021).

8.2. Small Sample Sizes and Lack of Replication

Many individual studies are underpowered, with minute case (often <300) and control populations, which diminish statistical power. Meta-analyses that pool up to ~6,000 cases may still suffer heterogeneity and publication bias. The field also exhibits limited replication efforts, particularly for less-studied SNPs like CT60, −1147 CT, and JO-series variants (Nie *et al.,* 2012; von Hippel, 2014).

8.3. Conflicting Results Across Populations

Polymorphism CTLA-4 association studies for asthma/allergy generate inconsistent findings. First of all, while a number of European and Asian meta-analyses agree that the +49 A/G variant is a risk factor, mostly for Asians and kids, one is absent or insignificant in Europeans and adults (Nie *et al.,* 2012; Zheng *et al.,* 2018;). Some researches do not show any correlation (Polish cohorts) with +49 A/G, −318 C/T, and −1147 C/T that are no significantly related with allergic asthma (Jasek *et al.,* 2006). The differences that have been depicted in the current study are indicating that the populations are different in terms of allele frequencies, they are exposed to different environments and they have different age or phenotype definitions.

8.4. Need for Longitudinal, Mechanistic, and Functional Studies

Thus far, all evidence is based on cross-sectional association or case-control studies implicating correlation and not causality. Few have a follow-through of the effects of CTLA-4 variants on disease course, response to therapy, or immune development longitudinally. Longitudinal omics-based cohorts, such as the CAMP study integrating genetics with time-series phenotyping, provide a template for future asthma-genetics work (Reimherr *et al.,* 2014). Moreover, while functional SNPs like CT60 and −1147CT have been linked to soluble CTLA-4 and lung function, only limited *in vitro* work has connected these variants to immune cell outputs (Munthe-Kaas *et al.,* 2004). Mechanistic assays, such as promoter reporter assays, Treg functional studies, are essential to validate the biological significance of CTLA-4 polymorphisms.

8.5. Integrative Genomics and Systems Biology Approaches

Single-gene studies are giving way to multi-omic research. Present asthma research incorporates GWAS, eQTL, transcriptomics, methylation, and proteomics data to define regulatory architecture.

However, CTLA-4 has not yet been systematically examined within these frameworks. Emerging approaches, such as single-cell RNA-seq and multi-modal data integration, are uncovering cell-specific expression modules and molecular networks underlying TH2-driven allergy (Tang *et al.,* 2020). Applying these tools to CTLA-4 could identify the cell types and circuits most affected by variants. Ultimately, systems biology models of the CTLA-4 genotype will establish connections with cell functions, immunophenotype, and clinical endpoints for decision-making through the inference of causal relationships and therapeutic prediction.

8.6. Gene–Environment and Gene–Gene Interactions

Single-SNP modeling obscures complex interactions. CTLA-4 effects fluctuate by smoking status, age, gender, and exposure to allergens (Munthe-Kaas *et al.,* 2004). Moreover, the clinical variable "asthma" aggregates mechanistically distinct phenotypes, reducing ability to detect SNP effects (atopic vs. non-atopic asthma). Gene–gene interactions (e.g., CTLA-4 × IL-4, IL-13, PTPN22) remain under-explored in most studies, further weakening insight into the functional network.

9. Future Research Suggestions

Subsequent research should focus on the formation of large, multi-ethnic, age-stratified cohorts to replicate proven single nucleotide polymorphisms (SNPs), including +49A/G, CT60, −318C/T, and −1147CT, within and between different populations and environments. Such validation to a larger extent will enhance the external validity of genetic associations for CTLA-4. In addition, genetic studies should incorporate functional assays and follow-up in longitudinal fashion to examine how CTLA-4 variants modulate biological endpoints over time. Specifically, future research will need to examine how such variants influence soluble protein levels, regulatory T cell (Treg) activity, cytokine profiles, and lung function dynamics. More insight into CTLA-4's mechanism of action in immune regulation can be achieved by situating it within multi-omics networks through superimposing genomic, epigenomic, transcriptomic, and proteomic data, ideally at single-cell resolution, to follow its impact on states of immune cells and the allergic inflammatory process.

Furthermore, using systems biology methods, such as expression quantitative trait loci (eQTL) analysis, Mendelian randomization, network modeling, and pseudo-temporal single-cell analysis will elucidate causal mechanisms and identify therapeutic targets for CTLA-4. With these methods, future research will avoid current limitations and have a better understanding of the role of CTLA-4 in TH1/TH2 immune balance. This will eventually be the gateway to the development of predictive biomarkers and new therapies for allergy and asthma.

9.1 Prognosis and Recommendations

The future promises promising potential for the advancement of personalized medicine in allergy and asthma therapy based on research into CTLA-4 polymorphisms. An interesting area is biomarker development. CTLA-4 genotyping will be capable of designing personalized diagnostic panels that more accurately assess susceptibility to asthma and allergic disease in a range of groups including children, smokers, and various ethnic populations. In therapeutic decision-making, CTLA-4 genetic status can potentially direct the treatment decision, including corticosteroid dose optimization and selection of effective biologics, such as dupilumab or tezepelumab. This could potentially enable true personalized; precision therapy on the basis of the patient's immunogenetic signature.

Furthermore, identification of novel therapeutics that modulate CTLA-4 is an area of development on the horizon. CTLA-4 agonists, possibly in the form of fusion proteins or other biologic therapies, are worthy of translational research as therapies for the prevention of TH2-dependent inflammatory reactions in allergic disease. To more effectively harness the potential of CTLA-4 in asthma and allergy, future studies will need to shift to an approach of systems biology. This would involve integrating CTLA-4 SNP profiling with other orders of biological information, including epigenomic, transcriptomic, and exposomic information, to crack the intricate regulative networks that govern immune tolerance, allergic sensitization, and response to therapy. By pursuing these options, research on CTLA-4 polymorphisms may usher in an age of predictive, preventive, and personalized medicine for patients with allergy and asthma.

10. CONCLUSION

The CTLA-4 polymorphisms exert significant effects on the asthmatic and allergic immune context by regulation of the delicate TH1/TH2 balance. Polymorphisms +49 A/G, −318 C/T, and CT60 alter CTLA-4 expression or function, typically predisposing immune responses to the TH2-predominant type of susceptibility to allergic inflammation. Polymorphisms are factors in the disease susceptibility, severity, and treatment response that are most evident among the atopic and children. Allele frequencies differences in various ethnic groups and gene–environment interactions exacerbate the complexity of the genetic architecture of such disorder. Even though data up to this point clearly indicate CTLA-4 SNPs as biomarkers and therapeutic targets, the majority of research suffers from small sample sizes, homogeneity and inability to include various populations. Future studies must give highest priority to multi-ethnic, large-scale, mechanistic studies to disentangle causality and achieve maximum translational impact. The incorporation of CTLA-4 genotyping into the personalized medicine approach will hopefully improve diagnostic sensitivity, risk stratification, and drug efficacy in allergic and asthmatic

patients. CTLA-4 is thus at the center of immune-genetic research.

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