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The Role of Hla Genes in Immune Response, Disease Susceptibility, and Social Behaviours: A Comprehensive Review

Simi N[1,5], Arumugam Suresh*[1], Dinesh Roy D[2], Natarajan Muninathan[1], Velam Chokkalingam Punitha[3] Kuppusamy Baskaran[1,] Venugopal Gopikrishnan[4], Poornima R Varma[5]

[1]*Central research laboratory,* [1]*Meenakshi Medical college Hospital and Research Institute, Meenakshi Academy of Higher Education and Research, Kanchipuram India.*
[2]*Genetika, Centre for Advanced Genetic Studies, Thiruvananthapuram, Kerala, India.*
[3]*Department of Community Medicine, Meenakshi Medical College Hospital and Research Institute, Meenakshi Academy of Higher Education and Research Institute, Enathur, Kanchipuram, Tamil Nadu.*
[4]*Centre for Drug Discovery and Development, Sathyabhama Institute of Science and Technology, Chennai, Tamil Nadu, India.*
[5] *Research Scholar, Meenakshi Academy of Higher Education and Research, Kanchipuram India.*
Email: kpm_suresh@yahoo.com

*Corresponding author's E-mail: kpm_suresh@yahoo.com

Article History	*Abstract*
	Major Histocompatibility Complexes (MHC), which assist to code for proteins that distinguish between self and non-self, are significantly influenced by the Human Leukocyte Antigen (HLA) genes. Particularly important in the suppression of immune response are the HLA genes. The bulk of the genes in the MHC region shows considerable variation. The two most important functions of HLA molecules are selection of T cell accumulation and the formation and control of immunological responses. The causes of HLA-G gene-associated illnesses and the underlying mechanisms are still up for dispute. The HLA-G gene has an impact on social behaviour as well. Numerous polymorphisms have been connected to heightened susceptibility to the beginning of autoimmune illnesses as well as heightened disease severity. The lifetime of some HLA genes is shorter.Genetic background, environmental circumstances, and certain polymorphisms have been linked to increased illness severity. certain HLA genes have shorter life spans than others, and vice versa. The major functional elements of HLA-G in both normal and autoimmune disorders are summarized in this study.

1. Introduction

HLA-G is one of the non-classical class I molecules that make up the Human Major Histocompatibility Complex, according to the first theory put out by Geraghty et al. in 1987. This subclass is distinguished by its restricted pattern of tissue expression and function in encoding immune-modulatory chemicals. The HLA region's class I genes were divided into three categories by Sommers (2003). These groups included the non-classical HLA-E, -L, -J, -K, -H, and -G genes as well as the classical HLA-A, -B, and -C genes. Moreau et al. (2009) noted that HLA-G has a distinct tissue-specific expression, especially in non-pathological situations, although sharing considerable similarities with classical HLA-class I genes. The crucial function of HLA-G in preserving fetal-maternal tolerance was clarified by Kovats et al. in 1990. Castelli (2014) separated HLA-G molecules (class Ib) from traditional HLA-A, HLA-B, and HLA-C molecules (class Ia) by highlighting restricted protein variability and the existence of numerous isoforms owing to alternative splicing of mRNA. HLA-G, which was originally discovered on extravillous cytotrophoblasts, is a key factor in the mother immunological tolerance for the semi-allograft fetus throughout pregnancy, according to Xu et al. (2020).

Polymorphic variations in the HLA-G gene may have an effect on the transcription level of the gene, according to Donadi et al. (2011). HLA-G genes have less polymorphism than traditional HLA

molecules. Between exon 1 and intron 6, there are 72 single nucleotide polymorphisms (SNPs) that distinguish it, and there are 44 alleles that code for HLA-G. Fan et al. (2014) pointed out that attempts to link the expression of the HLA-G protein and these polymorphism sites to illness susceptibility, treatment response, and HLA-G protein have not been successful. Coniti et al. (2020) highlighted HLA-G's changing levels of expression in various organs and its role in immunological responses and tolerance development throughout pregnancy. HLA-G was identified as the ligand with the greatest affinity for ILT2 and ILT4 receptors by Kovats et al. in 1990. But there is still disagreement over how the KIR2DL4 receptor interacts with HLA-G and how its inhibitory effects work.

The unique and tissue-specific control of HLA-G expression was underlined by Yaghi et al. (2016), who also noted that stress may be able to induce it. In addition to being ectopically expressed on monocytes, malignancies, viral infections, and autoimmune disorders, Carosella et al. (2008) noted that HLA-G is also expressed ectopically in transplantation. Due to their function in promoting graft acceptance, immunological tolerance during pregnancy, and reducing inflammatory responses, these antigens are classified as immune-modulatory. The restricted polymorphisms in the HLA-G gene's coding region, which give rise to just a few different molecules, were emphasized by Paul et al. in 2000. Seven different HLA-G isoforms, however, have been discovered, including four membrane-bound (HLA-G1 to -G4) and three soluble (HLA-G5 to -G7) varieties. The 5′ upstream regulatory region (5′ URR) and the 3′ untranslated region (3′UTR) polymorphisms control the expression of the HLA-G gene and protein. Although several research have sought to link these polymorphic locations to disease propensity, therapeutic response, and HLA-G protein expression, the results have frequently been conflicting, as evidenced in studies by Kim et al. (2015) and Zangh et al. (2014). In light of this, the goal of this review is to investigate the role of the HLA-G gene in autoimmune illnesses, with an emphasis on studying the polymorphism characteristics of the HLA-G gene across many dimensions in this article.

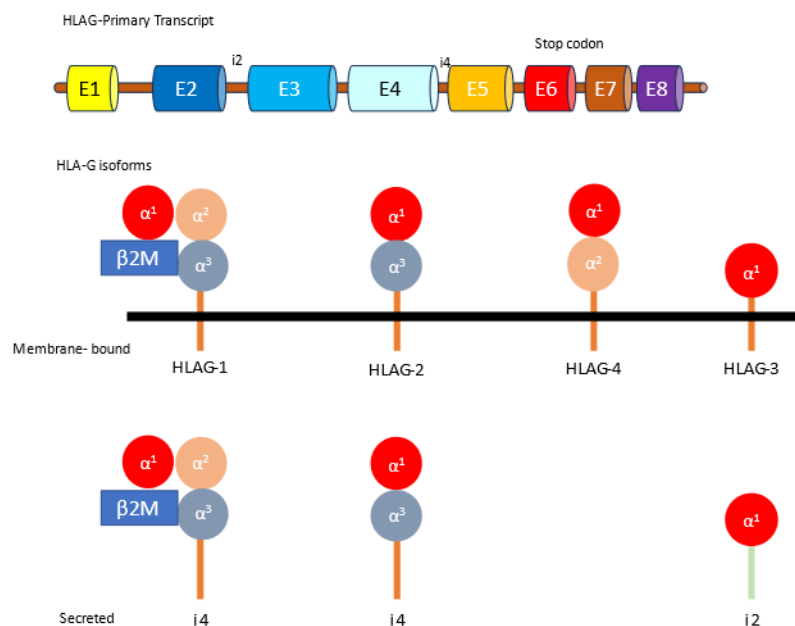**Molecular Characterization of the HLA-G Antigen**

Figure 1: HLA-G structure and its Isoforms

The genetic structure of the HLA-G gene bears resemblance to other conventional HLA class I genes, although its sequence exhibits notable conservation (Heinrichs et al.). Positioned within the major histocompatibility complex on chromosome 6's p21.31 region, the HLA-G gene constitutes the heavy chain encoded on chromosome 6, which is non-covalently linked to -2 microglobulin encoded on chromosome 15. Comprising 8 exons and 7 introns, the HLA-G gene, similar to other HLA genes, follows a consistent pattern. Exon 1 encodes the signal peptide, while exons 2, 3, and 4 give rise to extracellular domains 1, 2, and 3, respectively. Exons 5 and 6 respectively encode the transmembrane and cytoplasmic domains. An early stop codon in exon 6 results in a shorter cytoplasmic domain than in more typical class I molecules, which is noteworthy. Exon 8 does not occur in the finished protein

if exon 7 never does in mature mRNA. Exon 8 nonetheless produces the crucial 3'UTR that controls the expression of the HLA-G gene (Castelli et al., Donadi et al.).

According to Paul et al., alternative splicing produces seven different HLA-G mRNA isoforms, including four membrane-bound (HLA-G1, -G2, -G3, and -G4) and three soluble isoforms (HLA-G5, -G6, and -G7) isoforms. Notably, the important functional isoforms under investigation include membrane-bound HLA-G1 and soluble HLA-G5 (HLA-G5) (LeMaoult et al. 2003). HLA-G1 and HLA-G5 have a heavy chain with three globular domains that are non-covalently linked to -2-microglobulin (B2M) and a peptide. Other isoforms, on the other hand, are shorter, missing one or two heavy chain domains, and are unable to bind B2M. Importantly, the 1 domain is present in all HLA-G isoforms (HoWang et al. 2012). The HLA-G gene has 74 alleles that collectively encode 24 unique full-length proteins, as well as four null alleles that result in a protein variation with a shortened amino acid (Simon et al., IPD78/IMGT/HLA; March 2020).

The inhibitory receptors ILT2/CD85j/LILRB1, ILT4/CD85d/LILRB2, and KIR2DL4/CD158d are where HLA-G's immunomodulatory action is accomplished. LILRB1 is expressed by all monocytes/dendritic cells, B cells, some T cells, some NK cells, and some myeloid cells, but LILRB2 is myeloid-specific and only by monocytes/dendritic cells. The CD56bright subset of NK cells is the only cell type that expresses the HLA-G-specific KIR2DL4 receptor. HLA-G1 efficiently reduces the proliferation of T cells, peripheral blood NK cells, dendritic cells, antigen-specific cytolytic T lymphocytes, cytolytic uterine and peripheral blood NK cells, and alloproliferative response of CD4+ T cells. Additionally, according to Moreau et al., HLA-G might encourage the growth of suppressive cells.
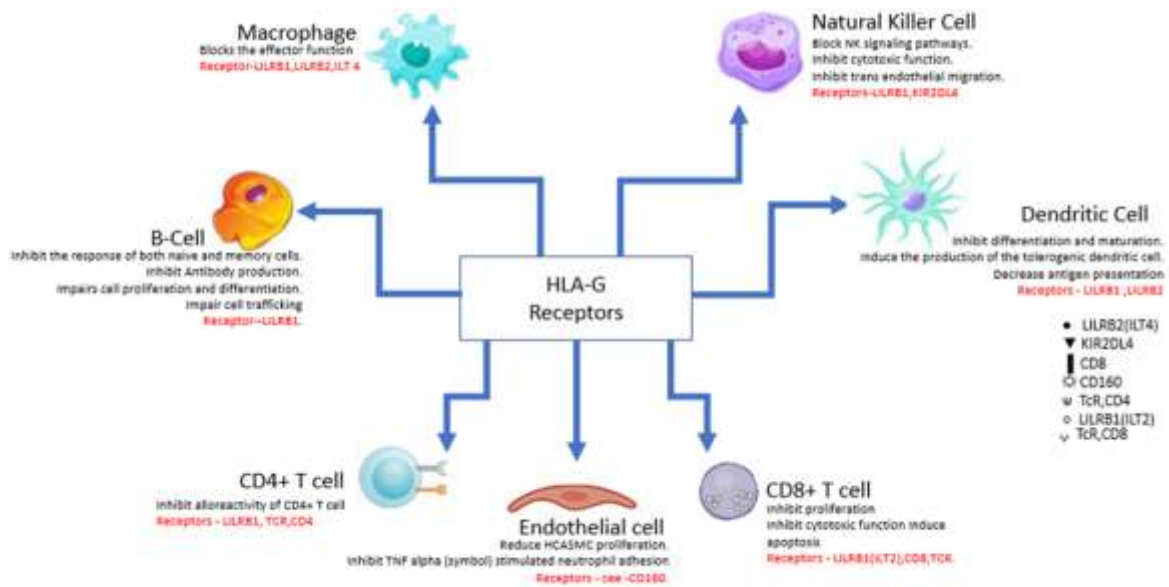
HLA- G Receptors

Figure 2: HLA-G Receptors

The CD8 co-receptor can interact with HLA-G and form linkages with it. The CD8+ T cell ILT2 receptor in this situation competes with the co-receptor for binding to HLA class I molecules. Shiroishi et al. in 2003 described how HLA-G inhibits CD8 binding and as a result has a regulatory influence on the activation of cytotoxic T lymphocytes.

➤Regulation of HLA-G Gene Expression and HLA-G Gene Polymorphisms.

The promoter, which has distinctive structural components like enhancer A, interferon-stimulated regulatory element (ISRE), and SXY modulator containing regulatory sequences common to class I and II HLA genes, is the main regulator of the constitutive expression of HLA-G, according to Solier et al. (2001). "HLA-G expression may be influenced, similar to other genes, by regulatory regions located in both the 5' URR and 3' UTR regions of the gene," claim Dias et al. (2018). The function of the 5' URR region in the generation of HLA-G molecules and its significance in illness are still comparably little known, despite the 3' UTR region having received greater attention.

Lin (2018) noted that control of HLA-G gene expression occurs during both transcription and translational processing. Progesterone, interleukin 10 (IL-10), GM-CSF, interferons (IFNs), TNF- and

TGF-, as well as stress, deprivation, hypoxia, and other external stimuli can all increase HLA-G expression. HLA-G expression varies across people depending on genetic variables as well. The 3' UTR of the HLA-G has a key role in controlling expression, according to Amodio (2020). A "stop" codon at exon 6 in the mature HLA-G mRNA prevents exon 7 from being included in the protein. Exon 8, which contains crucial elements for the control of transcription and translation, is therefore left untranslated. An important part of these processes is played by adenine- and uracil-rich motifs (AU-rich motifs) or adenine-rich regions (Poly-A).

Due to the presence of HLA-G on placental trophoblast cells, Martinez-Laso (2013) underlined the expectation of functional conservation, supporting fetal growth despite the maternal immunological response. Additionally, in gene regulatory regions, some polymorphism sites are close to nucleotide sequences that act as gene regulatory elements. According to Copeman (2000), post-translational processes, particularly during cytotrophoblast invasiveness, have a major impact on HLA-G expression. These mechanisms include mRNA stability and protein translation. In cells expressing HLA-G on the surface, exposure to low oxygen concentrations has also been linked to down-regulated HLA-G expression (Kilburn, 2000). According to Carosella (2008), the presence of progesterone, hypoxia, cell stress, malnutrition, and the participation of cytokines (GM-CSF, IL-10, TNF-, TGF-, and interferons) can all increase HLA-G expression.

Fan et al. (2014) outlined the mechanisms by which polymorphisms in the promoter (5' URR) and the 3' untranslated region (3' UTR) control the amounts of HLA-G gene and protein production. The HLA-G gene's earliest and most well researched polymorphism was a crucial 14-base-pair insertion/deletion (14-bp INS/DEL) polymorphism in the 3' UTR, according to Pascale et al. (2000). A more thorough genetic analysis revealed 16 additional SNPs in the HLA-3'UTR, nine of which have been verified as real polymorphisms, including the 14-bp INS/DEL polymorphism, +3003 C/G, +3010 G/C, +3027 C/A, +3035 C/T, +3142 C/G, +3187 A/G, +3196 C/G, and +3227 G/A. According to Sabbagh et al. (2014), only nine UTRs make up more than 95% of all haplotypes worldwide. But their research on a significant linkage disequilibrium resulted in the discovery of the 41 3' UTR.
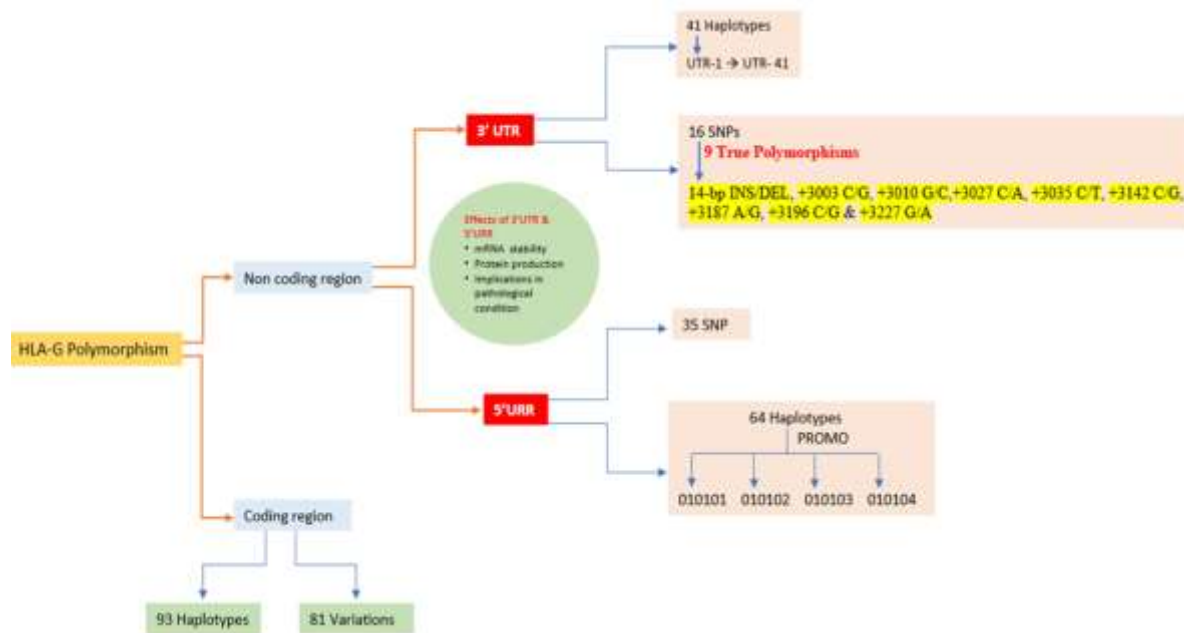

Figure 3: Major HAL-G gene polymorphisms

The significant heterogeneity seen in both the HLA-G locus's coding region and 5' untranslated region (5' URR) was noted by Castelli et al. Single nucleotide polymorphisms (SNPs) in these areas cause linkage disequilibrium, in which a small number of haplotypes are grouped into families. These haplotypes, notably PROMO 010101, 010102, 0103, and 010104, have been studied separately or in combination with 3' UTR alleles to provide in-depth explanations of this phenomena. Surprisingly, out of the 64 different haplotypes revealed by analyzing 35 SNPs in the 5' URR, just nine of them— collectively referred to as PROMO—account for over 95% of the alleles that have been detected worldwide. It is important to keep in mind that some pathological circumstances may result in the emergence of new isoforms. In particular, as reported by Tronik et al. in 2017, distinct HLA-G isoforms have been found in people with clear cell renal cell carcinoma. 29 SNPs were discovered by Solier et al. (2001) when analyzing the HLA-G promoter area, with the hypothesis being that these SNPs "might play a role in HLA-G expression regulation due to their proximity to known or putative

regulatory elements." The 5' URR of the HLA-G gene stands out among the assortment of HLA genes thanks to its unique qualities.

Using these findings as a foundation, there has been significant clinical interest in investigating the prospect of using HLA-G as a molecular target to treat autoimmune and inflammatory illnesses (Bortolotti et al., 2014). Several allelic polymorphisms may affect a person's susceptibility to infectious illnesses, according to Lai et al.'s (2018) analysis, which emphasized the crucial function of HLA in antigen presentation. Numerous infectious diseases have been linked to specific genetic variations within the HLA gene, including hepatitis B virus (HBV) and hepatitis C virus (HCV), as well as Chikungunya, Chagas, dengue, influenza A(H1N1), and TB (Lai et al., 2018). This interaction emphasizes how important HLA polymorphisms may be in determining a person's susceptibility to and response to different illnesses.

Contribution of the HLA-G Antigens to the Immune Response

Le Bouteiller et al. (1996) noted that HLA-G, which is included in the "non-classical" HLA-class Ib molecules with HLA-E, -F, and -H, has important immunomodulatory features. HLA-G is a key player in triggering tolerance and, thus, reducing immunological responses, according to Attia et al. (2020). In particular, Liu et al. (2021) stressed the expanding relevance of HLA as a research topic that connects the fields of immunology and clinical disorders. It is anticipated that this subject would continue to grow in terms of discoveries and technology, opening up more opportunities. Additionally, according to Miles et al. (2015), deciphering the structural details of disease-relevant peptide HLA and HLA peptide-TCR complexes is crucial for understanding the molecular mechanisms underlying the development of specific protective immunity against pathogens and the adverse T cell reactivity that drives diseases.

This knowledge lays the groundwork for comprehending the beneficial and harmful features of immune responses in varied situations.ITIMs, or tyrosine-based immunoreceptor inhibition motifs, are specific signaling motifs that are present in ILT2 and ILT4 receptors, as described by Lin et al. (2019). The consensus sequence for these motifs is S/I/V/LXYXXI/V/L. On the other hand, the KIR2DL4 receptor consists of the ITIM domain as well as a second domain called ITAMs, or tyrosine-based immunoreceptor activation motif. Surprisingly, YXXI/LX6-12YXXI/L is the common consensus sequence shared by both of these domains. Their intracellular behavior is affected by the difference in receptor structure. Notably, research has shown that receptors with an ITIM domain result in the opposite kinds of signaling results from those produced by receptors with an ITAM domain.

Contrary to receptors with ITIM domains, which often elicit inhibitory signaling, ITAM-containing receptors typically result in cellular activation. The work carried out in 2019 by Würfel et al. highlights the function of HLA-G in orchestrating immune suppression across a varied spectrum of both healthy and disease-related situations, building on past studies into fetal-maternal immunological tolerance. Notably, HLA-G expression not only encourages the successful acceptance of allograft organ transplants but also gives cancer cells a different route to evade immune monitoring and eradication. The main site of HLA Class II gene expression in the context of antigen presentation is found in antigen-presenting cells.

According to de Araujo Souza et al. in 2019, these genes, which are encoded by the DR, DQ, and DP genes, are crucial for exposing the immune system to viral peptides, particularly those linked to HPV. When considering immunological tolerance, Conteduca et al. (2018) pointed out that this complex process centres around a complicated series of mechanisms meant to both get rid of foreign antigens and protect host tissues from unintentional injury. This more general idea is divided into central and peripheral tolerance mechanisms, all of which play a part in the delicate coordination of immune responses.
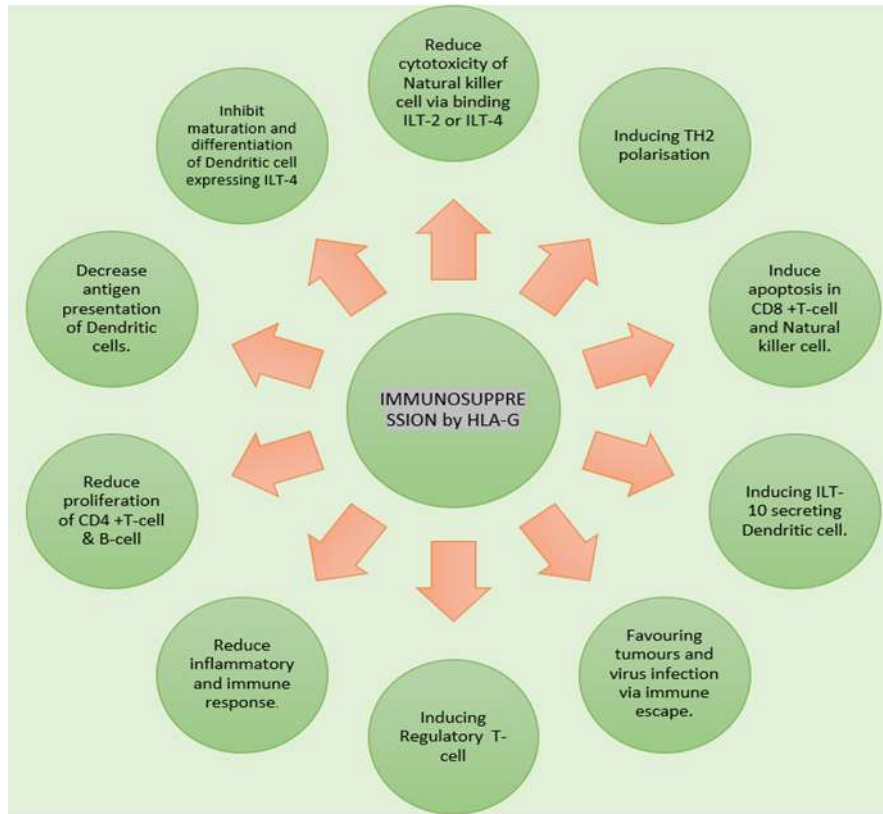
Figure 4: Immune Suppression mechanism by HLA-G

The Role of the HLA-G Molecule in the Pathogenesis of Autoimmune Diseases

Autoimmune disorders develop when self-antigens are erroneously attacked by the body's immune cells or antibodies, potentially causing structural or functional damage. There is increasing worry since these disorders are becoming more common. Our understanding of the fundamental processes behind the development of autoimmune illnesses, however, is still restricted despite increasing scientific investigation. Because of this information gap, we must investigate new molecules, markers, and pathways that may be involved in the onset of autoimmunity.

HLA-G (Human Leukocyte Antigen-G) is one such molecule of interest, well known for its immunomodulatory qualities and its potential to interact with different immune cells, therefore altering immune system processes. HLA-G is at the cutting edge of immunology and transplantation therapy due to its fascinating immunomodulatory properties. To fully understand its precise effects on immune system dynamics and its possible therapeutic uses, researchers are actively probing its activities across a variety of physiological and pathological circumstances.

Variations in the HLA-G genes of the MHC have a big impact on how susceptible a person is to certain illnesses, such autoimmune disorders. In particular, Matern et al. (2020) noted that "given its pivotal involvement in immune responses, HLA-G exhibits associations with a wide array of human diseases," such as but not limited to multiple sclerosis, Alzheimer's disease, penicillin allergy, ulcerative colitis, and dry eye disease. It is necessary to thoroughly explore the polymorphisms within HLA-G to understand the complex patterns of disease inheritance within this genomic area since the underlying biological mechanisms causing these diseases can display a wide range of characteristics.

According to Carosella et al. (2015), it is noteworthy that the influence of HLA-G is felt by both innate and adaptive immune responses. Their findings highlight the important function HLA-G plays in promoting immunological tolerance in a range of clinical settings. This includes its helpful role in avoiding rejection in pregnancies, post-transplantation situations, and autoimmune diseases. These newer understandings help us better comprehend the complex roles that HLA-G plays in preserving immunological homeostasis in many medical contexts.

Celiac Disease

Consumption of the protein gluten, which is found in wheat, barley, and rye, causes celiac disease, an autoimmune condition. People who have this disorder experience an unusual immunological response when they consume gluten-containing meals, which leads to damage to the small intestine's lining. The most prevalent genetic risk factors for celiac disease are HLA-DQ2 and HLA-DQ8. These genetic markers increase the risk of celiac disease in those who inherit them. Two distinct alleles,

DQA105 and DQB102, encode the HLA-DQ2 haplotype. The likelihood of getting celiac disease rises noticeably if you have two copies of these alleles—one from each parent. Despite being less frequent, the HLA-DQ8 haplotype is nonetheless linked to celiac disease. DQA103 and DQB103:02 alleles are responsible for encoding it. The chance of developing celiac disease is increased by having two copies of the HLA-DQ8 allele, like HLA-DQ2. Not every component of gluten is immunogenic in people with celiac disease, at least not in terms of molecules. Instead, it's a unique peptide sequence inside gluten called the "gluten epitope" or "toxic peptide." Alpha-gliadin, a component of gluten, contains a dangerous peptide that causes celiac disease. The N-terminal region of the alpha-gliadin protein, namely amino acids 57 to 89, is home to this poisonous peptide. The amount of proline and glutamine residues in this sequence, which is notable, makes it particularly resistant to the stomach and small intestine's digestive enzymes.

The HLA-G gene has many polymorphisms, including 477 C > G, 369 C > A, 14 bp del/ins, 3187 A > G, and 3196 C > G. Loftus et al. (2016) proposed the notion that these polymorphisms may be linked to an increased vulnerability to celiac disease. Additionally, their study discovered a unique HLA-G haplotype known as (TCGGTACGAAITCCCGAG), which showed a greater prevalence in those with celiac disease in comparison to those without the ailment. HLA-G was found in the biopsies of patients with celiac disease, and Torres et al. found that the quantities were significantly greater than in the control group. There was shown to be a higher frequency of the 14bp INS/INS genotype among celiac patients than there was among control subjects among those who were classified according to the presence of the HLA-DQ2 molecule, which is encoded by the DQA1*05/DQB1*02 genes. These results imply that the 14bp INS allele may possibly increase the risk of persistent gut inflammation.
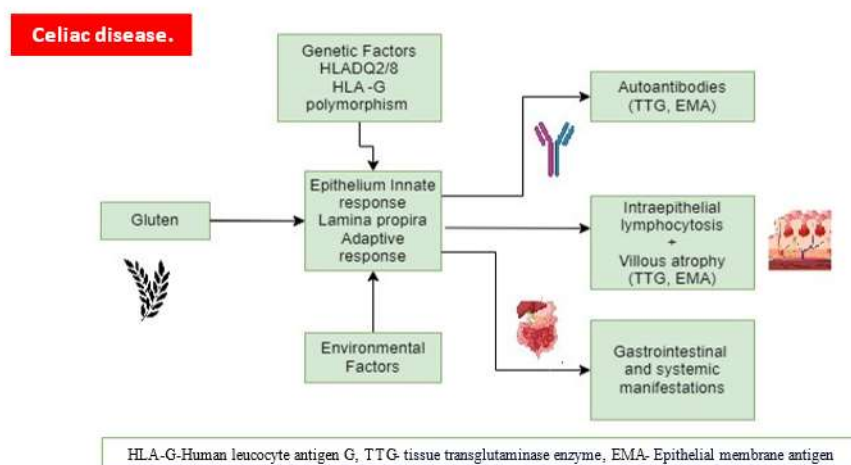

Fig 5: Pathophysiology of Celiac disease

Crohn's disease
The inflammatory bowel disease (IBD) known as Crohn's disease. The digestive tract's lining being inflamed is one of its hallmarks. Anywhere along the digestive tract, from the mouth to the anus, may become inflamed. The colon (large intestine) and the small intestine, particularly the terminal ileum, are the two organs it most frequently affects. A growing body of research points to a possible connection between the HLA-G gene and the start of Crohn's disease. There are three primary theories about how HLA-G may contribute to Crohn's disease:

Endogenous antigens, which frequently come from viruses or bacteria found in the colon, can be shown to the immune system by HLA-G. The immune system may launch an immunological attack against certain antigens when it identifies them. This may result in gastrointestinal tract autoimmune disease and inflammation. The pathophysiology of Crohn's disease may be influenced by variations in the expression levels of HLA class I and II molecules. CD8+ T cells are exposed to antigens through HLA class I molecules, whereas CD4+ T cells are exposed to antigens through HLA class II molecules. These T cell subsets may get different antigen presentations depending on the degree of HLA class I and II expression variation. Antigen presentation to CD8+ and CD4+ T lymphocytes may

be enhanced by certain HLA alleles associated with disease risk. When viewed in the context of Crohn's disease, this could have an impact on the immune system's reaction and inflammation. Natural killer (NK) cell activity may be inhibited by HLA class I molecules. An immune cell known as an NK cell aids in the body's defense against infection. NK cells cannot assault healthy cells because of an interaction between HLA class I molecules on the surface of normal cells and inhibitory receptors on NK cells. Alterations in NK cell activity and the immune response in the gastrointestinal tract may be caused by changes in the ratio of activating to inhibitory receptors on NK cells, which may be impacted by HLA class I polymorphisms and contribute to Crohn's disease.

Studies on HLA-G & Chron's disease

sHLA-G (soluble Human Leukocyte Antigen-G) and IL-10 are secreted in Crohn's disease and ulcerative colitis (UC), two IBDs, according to a research by Rizzo et al. This is an intriguing result. The findings raise the possibility that sHLA-G and IL-10 may play a role in the etiology of various illnesses, as well as disparities in immunological responses. Peripheral blood mononuclear cells (PBMCs) were shown to spontaneously produce sHLA-G in Crohn's disease patients. Patients with ulcerative colitis or the control group, however, did not experience this phenomenon. Zelante et al. emphasized the differential behavior displayed by these two diseases and suggested assessing sHLA-G levels as a viable tool for differentiating between patients with ulcerative colitis and Crohn's disease as well as for tracking the efficacy of therapy interventions.
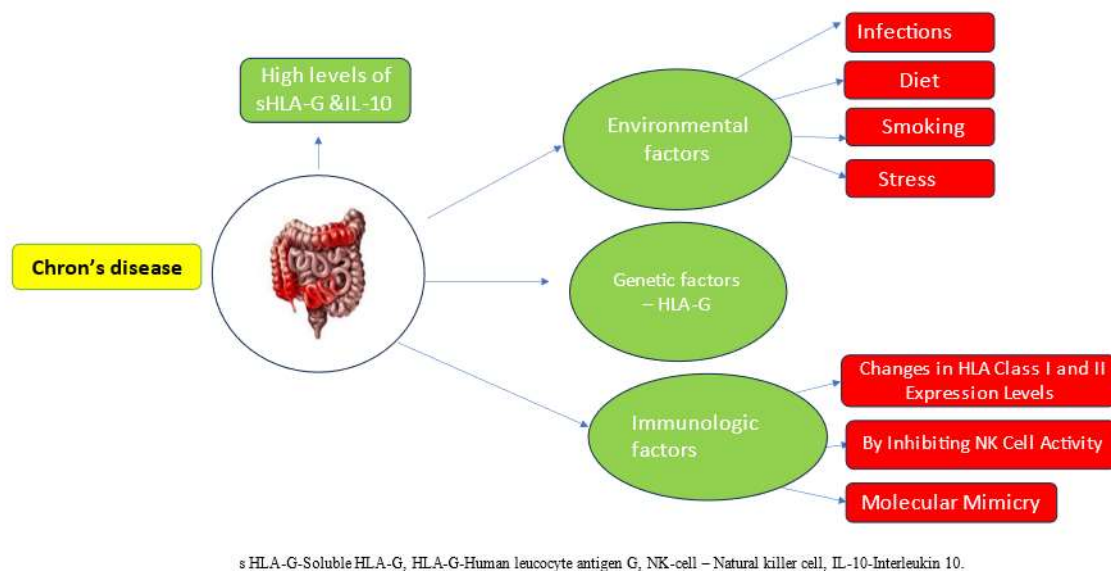

s HLA-G-Soluble HLA-G, HLA-G-Human leucocyte antigen G, NK-cell – Natural killer cell, IL-10-Interleukin 10.

Fig 6: Pathophysiology of Chron's disease

Rheumatoid Arthritis

An inflammatory illness that damages the joints over time is rheumatoid arthritis (RA). Other bodily tissues and organs may also be affected. One of the most prevalent types of inflammatory arthritis is RA. There may be a link between the HLA-G gene and the onset of rheumatoid arthritis (RA), according to recent research. A protein called HLA-G, which is expressed on cell surfaces, is thought to have a part in controlling the immune system.

Studies on HLA-G and RA

Mononuclear cells taken from the bone marrow of people with rheumatoid arthritis (RA) were shown to have the HLA-G gene in research by Veit et al. This finding suggests that HLA-G may play a role in the immunological pathways underlying the development of RA. A noteworthy association between polymorphisms in the HLA-G gene's 3′ untranslated region (3′ UTR) and rheumatoid arthritis (RA) was discovered in a separate study conducted by Catamo et al. This research suggests that those who have certain HLA-G gene variants are more likely to acquire RA. The HLA-G+ 3142G > C polymorphism and RA are linked, according to research by Hashemi et al. and Gautam et al. People with RA are more likely to have this polymorphism, which is a variation in the HLA-G gene's DNA sequence. HLA-G molecules are increased in synovial fibroblasts from inflamed joints, according to Prigione et al. Therefore, individuals with RA have higher levels of HLA-G production in their joints. In rheumatoid arthritis (RA), elevated quantities of soluble HLA-G (sHLA-G), a soluble version of

HLA-G, have been seen to correlate with the degree of disease activity. The HLA-G 14bp INS/DEL polymorphism may be used as a pharmacogenetic marker, according to research by Rudwaleit et al. and Rizzo et al.
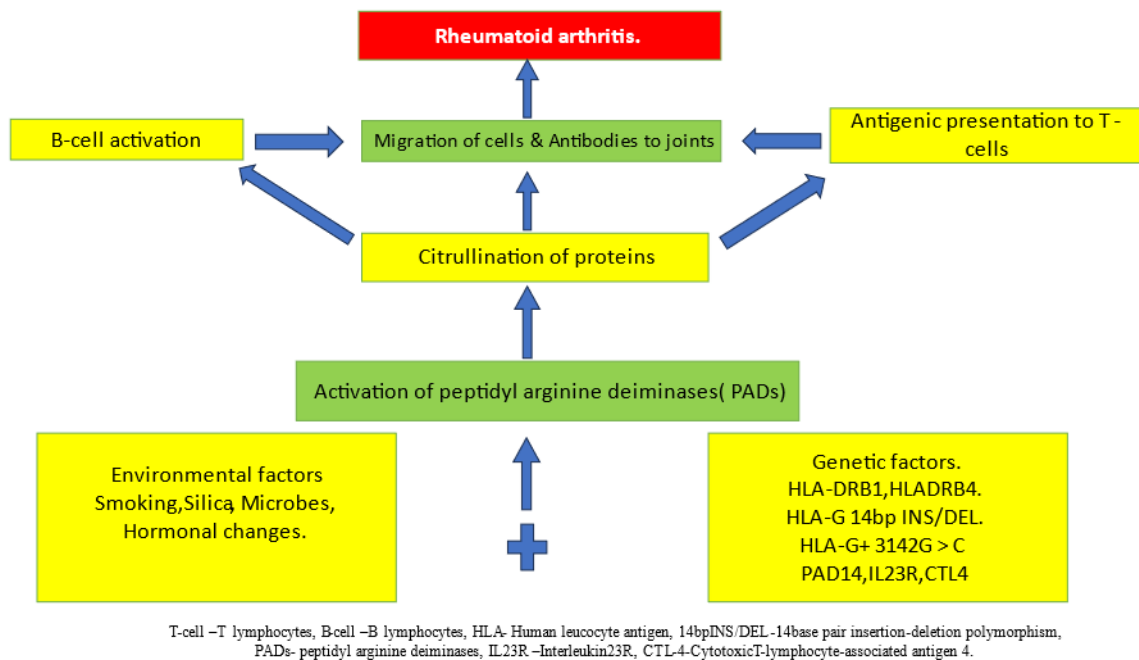

T-cell –T lymphocytes, B-cell –B lymphocytes, HLA- Human leucocyte antigen, 14bpINS/DEL-14base pair insertion-deletion polymorphism, PADs- peptidyl arginine deiminases, IL23R –Interleukin23R, CTL-4-CytotoxicT-lymphocyte-associated antigen 4.

Fig 7: Pathophysiology of Rheumatoid Arthritis

Systemic scleroderma (SSc)
Skin and internal organs are both impacted by systemic scleroderma (SSc), a complicated autoimmune rheumatic disease. The skin and other organs exhibit fibrosis, or an abnormal accumulation of scar tissue. Recent research raises the possibility that the HLA-G gene and the onset of systemic sclerosis (SSc) are related. The immune system is thought to be regulated by the protein HLA-G, which is expressed on cell surfaces.

Studies on HLA-G and SSc
In skin biopsies taken from individuals with systemic sclerosis (SSc), Wastowski et al.'s research revealed elevated expression of HLA-G molecules. This data suggests that HLA-G may be involved in the immunological response in the setting of SSc. The fraction of HLA-G-positive monocytes is increased in people with SSc, according to a different research by Negrini et al. This discovery further suggests that the immunological response in SSc may be influenced by monocytes that express the HLA-G gene. Additionally, research has demonstrated that SSc patients have much more CD4+ and CD8+ cells that express the HLA-G molecule compared to healthy controls. This shows that HLA-G might have a role in the development of SSc.
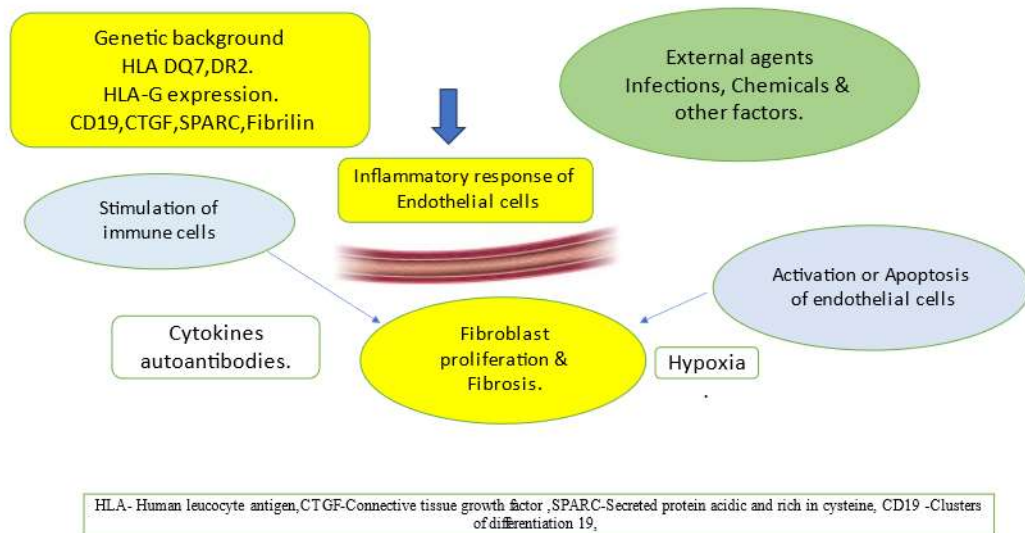
Fig 8: Pathophysiology of Systemic Sclerosis

Systemic lupus erythematosus (SLE)
A complicated autoimmune condition that affects several body organs is known as systemic lupus erythematosus (SLE). Autoantibodies and immune complexes, which can build up in many tissues and organs, are produced as a result of this condition's aberrant immunological response.Chronic tissue damage and inflammation are results of this aberrant immune response.

Studies on HLA-G and SLE
Systemic lupus erythematosus (SLE) development and the HLA-G gene may be related, according to research. According to certain studies, people with systemic lupus erythematosus (SLE) may have higher levels of soluble HLA-G (sHLA-G), a form of HLA-G that is soluble when compared to healthy people. The immunological response in SLE may be influenced by HLA-G, according to this observation. As an alternative, many investigations have demonstrated that sHLA-G levels in SLE patients may be lower. As a result, it is possible that decreased HLA-G expression may help to cause SLE.

Genetic variations
Moreover, many studies have discovered certain genetic variants within the HLA-G gene that seem to be connected to systemic lupus erythematosus (SLE). For instance, research found that those with the 14bp INS/INS genotype of the 14bp INS/DEL polymorphism have a higher risk of developing SLE. The +3142G allele and the +3142G/G genotype of the +3142C>G polymorphism are likewise associated with an increased risk of getting SLE, according to different research.
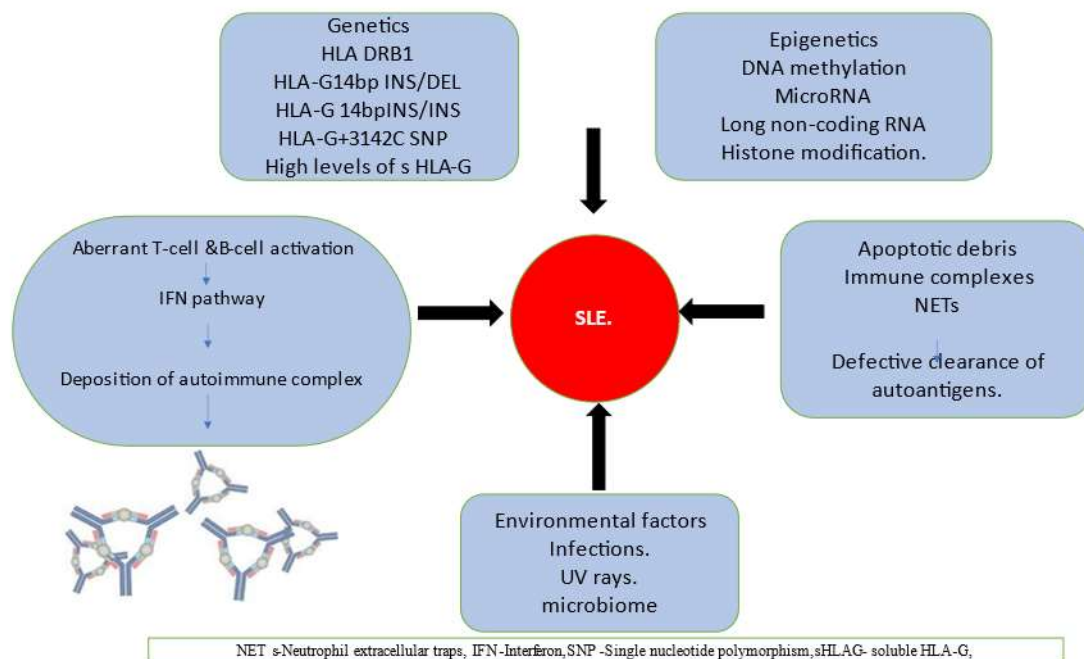
Fig 9: Pathophysiology of Systemic Lupus Erythematosus

Multiple sclerosis
The most frequent neurological condition that disables young adults is multiple sclerosis (MS).

Studies on HLA-G and Multiple sclerosis
According to research by Mohammadi et al., people with MS are noticeably more likely than healthy controls to possess the 14bp INS allele of the 14bp INS/DEL polymorphism. Furthermore, it has been discovered that MS patients with the 14bp INS/INS genotype had decreased plasma sHLA-G levels (91). Ben Fredj et al. conducted another study that reveals MS patients are more likely to have the +3142G allele of the +3142C>G polymorphism than healthy controls are. It is interesting to note that the +3142C/C genotype is more commonly found in the healthy control group, suggesting that it may have a protective impact against the onset of MS.

The etiology of MS may be influenced by HLA-G molecules, according to certain research, Wiendl said. The HLA-G protein was demonstrated to be highly expressed in brain tissue from MS patients in contrast to nonpathological control specimens. Recent studies, according to Airas, "have revealed a relationship between postpartum MS activation and HLA-G down-regulation."

Type 1 diabetes mellitus (T1DM)
A long-lasting autoimmune condition that damages the pancreas is type 1 diabetes mellitus (T1DM). Insulin, a hormone that aids the body in using sugar as fuel, is produced by the pancreas, an organ. The beta cells of the pancreas, which are the cells that create insulin, are wrongly attacked and destroyed in T1DM by the immune system. Lack of insulin results from this, which can raise blood sugar levels. A higher risk of type 1 diabetes (T1DM) has been associated with certain HLA genes.

The endocrine portion of the human pancreas is where HLA-G is expressed, according to a research by Cirulli et al. This indicates that the cells that make insulin express the HLA-G gene. According to the study, insulin secretion stimulation may cause HLA-G expression on the surfaces of pancreatic islet cells to increase. According to this research, HLA-G may be able to influence how the immune system reacts to cells that make insulin.

Association with T1DM
The 14bp INS/DEL polymorphisms in the HLA-G gene have been linked to T1DM susceptibility, according to research. The homozygous deletion genotype, which occurs when both copies of the HLA-G gene carry the DEL allele, is linked in particular to an earlier onset of T1DM. This suggests that persons with two copies of the deletion allele would get T1DM earlier than those with other genotypes at this particular location.

Implications for T1DM susceptibility

According to the research, a substantial genetic risk factor for T1DM that contributes to an earlier start is the 14bp INS/DEL genotype of the HLA-G gene. In contrast to those with other genotypes, this suggests that people with this particular genotype may be more likely to develop T1DM at a younger age. The HLA-G molecule, which serves as a defense mechanism against cytotoxic cells, is naturally generated in the pancreas, according to Albuquerque et al. (2016). A decline in HLA-G expression might be harmful for those who are genetically predisposed to producing less of it. Shareef et al.'s (2019) further findings showed that patients had a considerably greater prevalence of the 14bp INS allele than healthy controls do. In addition, SNPs like rs4122198, rs2394186, rs1619379, and rs1611133 that are close to the HLA-G gene have been linked to type 1 diabetes, according to Eike et al. (2009).
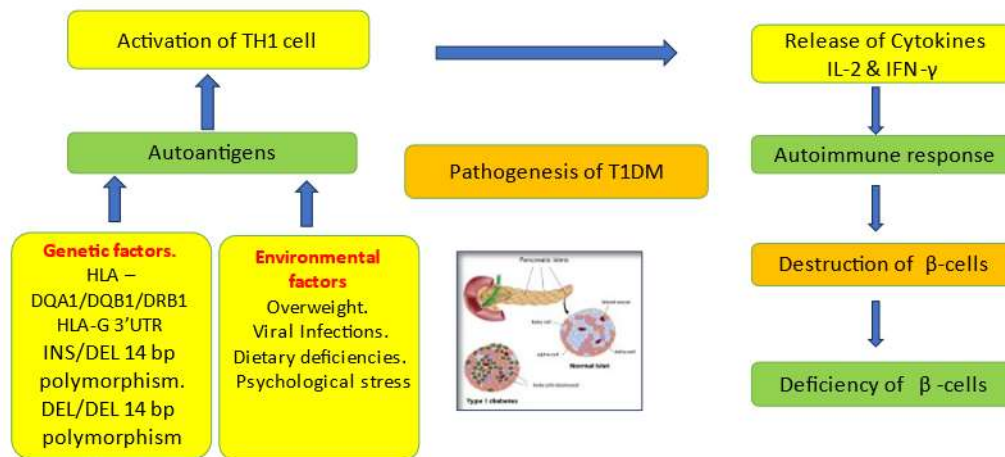
T1DM- Type 1 Diabetes mellitus, TH1-T-hepler 1 cell HLA- Human leucocyte antigen, 3'UTR – 3'Untranslated region, 14bpINS/DEL-14base pair insertion-deletion polymorphism, DEL/DEL 14 bp polymorphism14 base pair deletion polymorphism, IL-2-Interleukin-2, IFN-γ-Interferon γ.

Fig 10: Pathophysiology of Type 1 Diabetes mellitus

Behçet's disease (BD)

Behçet's disease (BD) is a complicated inflammatory ailment that belongs to the category of diseases known as systemic vasculitis. Skin rashes, ocular irritation, and repeated oral and vaginal ulcers are its hallmarks. While the specific etiology and processes of BD are still unknown, it is believed to result from a confluence of genetic, environmental, and autoimmune factors. Research has shown a connection between particular changes in the HLA-E, HLA-F, and HLA-G genes with the prevalence of BD in Korean and Japanese patients with regard to the correlation between HLA-G and BD. A probable link between BD and the HLA-G 14 bp ins/del polymorphism has been proposed, according to Sakly et al. In addition, during BD's active periods, elevated plasma concentrations of sHLA-G have been seen. A research by Park et al. on the risk of getting BD found a relationship between the HLA-G* allele 01:01:01 and a lower probability of doing so. On the other hand, alleles G*01:05N and 01:01:02 are linked to a higher chance of contracting the illness.
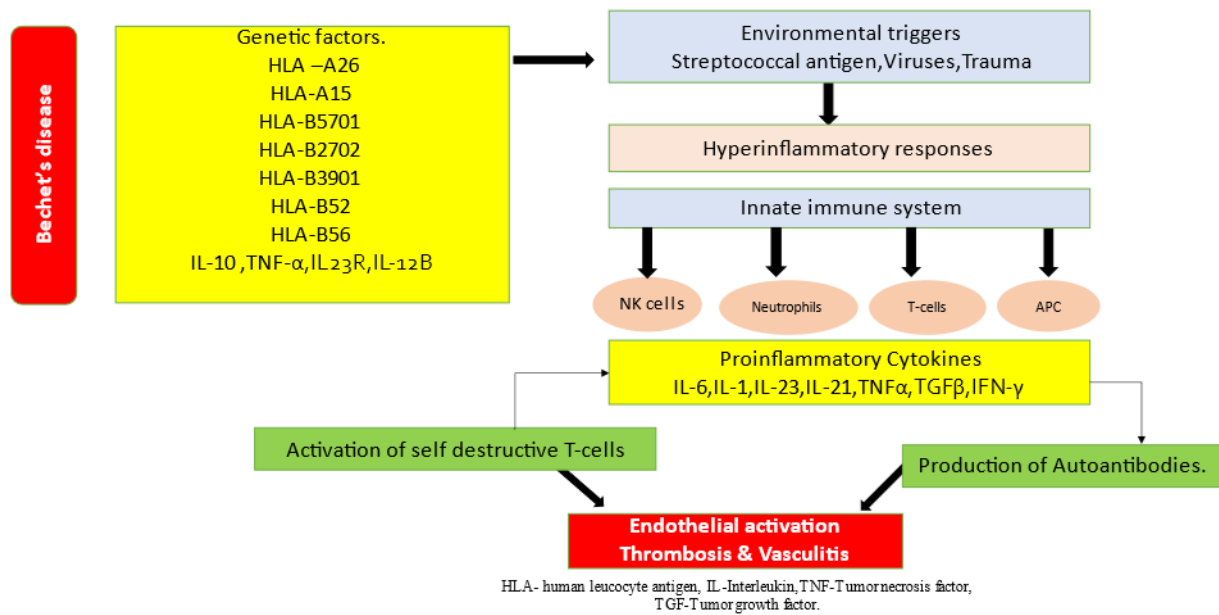
Fig 11: Pathophysiology of Bechet's disease

Kawasaki disease (KD)

An acute inflammatory disorder called Kawasaki disease (KD) is most frequently found in children. Inflamed blood vessels, particularly the medium-sized arteries, are its defining feature. KD is a significant contributor to acquired cardiac problems among children in affluent countries because it can lead to consequences such the development of aneurysms and myocardial ischemia. Uncertainty exists about the specific mechanism by which the non-synonymous SNP +755A/C of the HLA-G gene affects the susceptibility to KD. But it's believed that the C allele may result in more HLA-G expression, which would inhibit the immune response and make it harder for the body to fight off the infection that's suspected to cause KD. According to research by Jae-Jung Kim et.al,the non-synonymous SNP +755A/C of the HLA-G gene (rs12722477),G*01:04) could be connected to the prevalence of Kawasaki illness.As a result , those who have the SNP's C allele are more likely to get KD than those who carry the A allele.
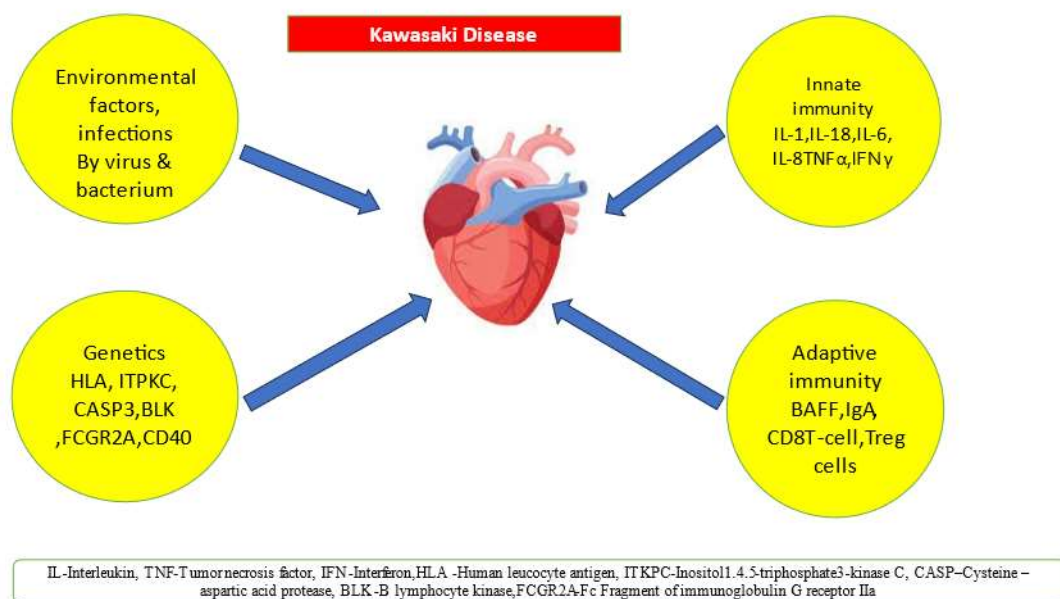

Fig 12: Pathophysiology of Kawasaki Disease

Asthma

A respiratory illness that affects the airways, asthma is a chronic inflammatory condition. The symptoms of asthma include coughing, dyspnea (shortness of breath), reversible airway blockage, and bronchospasm.

HLA-G and asthma

HLA-G gene involvement in asthma susceptibility may be supported by some studies. A protein termed HLA-G, which is expressed on the surface of cells, is created by the HLA-G gene. HLA-G has been demonstrated to have immunosuppressive properties, which means that it has the ability to weaken the immune system. Considering this, it is possible that HLA-G controls the immune response in the airways.

Studies on HLA-G and asthma

The HLA-G gene may be linked to an increased risk of getting asthma, according to a research by Nicolae et al. The study also discovered that persons with asthma are more likely than non-asthmatics to have the gene variation HLA-G5, which is a particular form of the HLA-G gene.

It was discovered in a different study by Tahan et al. that HLA-G may be found in the bronchoalveolar lavage fluid and respiratory epithelial cells of people with asthma. This discovery suggests that HLA-G may contribute to the development of asthma.

Type of asthma and HLA-G

Additionally, studies have indicated that HLA-G may have an impact on the kind of asthma. For instance, a research by Zheng et al. discovered that children with atopic asthma, an allergy-related form of asthma, have greater plasma levels of soluble HLA-G (sHLA-G) than children without atopic symptoms or asthma. The pathophysiology of atopic asthma may be influenced by sHLA-G, according to this. Furthermore, compared to those with conventional asthma, those who suffer from isocyanate-induced asthma—a particular type of asthma brought on by exposure to isocyanates—display elevated levels of soluble HLA-G (sHLA-G) expression. This finding suggests that sHLA-G may have a role in the underlying processes of the onset of asthma produced by isocyanates.
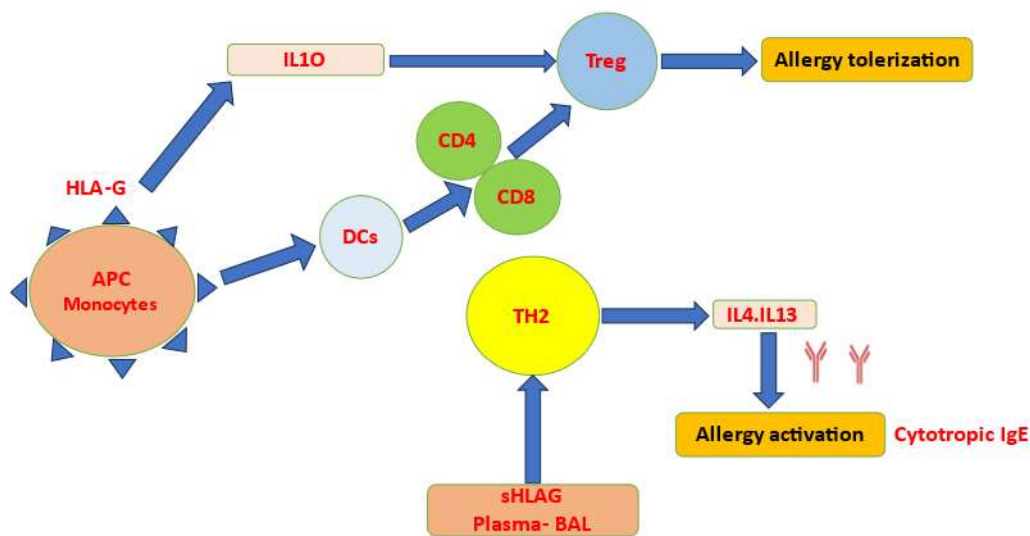
Asthma ,APC-Antigen processing cells, HLA-G-Human leucocyte antigen G, DC-Dendritic cells,Treg- T regulatory cells,IL-Interleukin, s HLA-G-Serum HLA-G,BAL –BAL-Bronchoalveolar lavage,TH2 -T-hepler 2 cell,CD4-Clusters of differentiation 4, CD8 -Clusters of diffe rentiation 8,

Fig 13: Pathophysiology of Asthma

Allergic rhinitis (AR)

An inflammatory condition of the nasal mucosa is known as allergic rhinitis (AR). It is brought on by an erroneous immune reaction to chemicals (allergens) that are typically innocuous. As a result, allergy symptoms including runny nose, congestion, and sneezing start to appear.

Studies on sHLA-G in AR

The sHLA-G levels in the sera of AR patients have been found to be increased, according to studies. Given this, it's plausible that sHLA-G influences how the immune system responds to allergens during AR. It was discovered in a study by Ciprandi et al. that those who are susceptible to pollen may have a decrease in blood soluble HLA-G (sHLA-G) levels after receiving sublingual

immunotherapy (SLIT), a treatment for allergic rhinitis. This exciting discovery may have clinical ramifications.

Psoriasis

Skin lesions that are clearly defined, red, inflammatory, and coated in thick, silvery-white scales are the hallmark of the chronic and complicated skin condition psoriasis. According to theory, the illness is brought on by an aberrant immunological response that speeds up skin cell renewal. Thus, the skin's surface experiences a fast buildup of skin cells, resulting in the distinctive plaques.

Studies on HLA-G in Psoriasis

Cardili et al. claim that membrane-bound and soluble HLA-G proteins are present in the major part of psoriatic skin lesions, which are characterized by macrophage lining at the dermo-epidermal junctions. A difference in systemic HLA-G expression that may be connected to the IL-10 deficiency that is typical of psoriasis was brought to light by Borghi et al. by pointing out that plasma sHLA-G levels in psoriatic patients were significantly lower than those of controls. As people with psoriasis who carry the 14bp DEL allele and the DEL/DEL genotype of the 14bp INS/DEL polymorphism tend to respond more positively to acitretin therapy, examining this polymorphism may help in the development of customized therapies for these people.

Major HLA -G gene polymorphism and its disease associations

polymorphism	Disease / functions
14bps INS/DEL	Provides mRNA stability.
	Risk of pre-eclmapsia.
	Marker for Rheumatoid Arthritis therapy.
	Increases frequency of thyroid tumors.
	Increases gastric carcinoma risk.
	Role in Multiple sclerosis.
	Significant rise in T1DM.
	Role in colorectal carcinoma.
	Protective role against allograft rejection.
14bp INS -allele	Provides mRNA instability.
	Increase the risk of gut inflammation.
+3142bp	Target for mi RNA.
	Immunoprotection of semi allogenic embryo.
	Role in human placental development.
+3142G	Reduce soluble protein production.
	Role in SLE.
	Role in Multiple sclerosis.
+3187	Sepsis susceptibility
14bpDEL/DEL	High level in breast cancer patients.
	Cause IL-6 mediated inflammation in Schizophrenic patients.
SNP-964 G/A	Seen in children with Asthma.
+3142C/C	Increase risk and severity of Rheumatic heart disease.
+3142C/G	Role in gastric carcinoma & colorectal carcinoma.
+3035 C/T	Role in colorectal carcinoma.
14bp allele	Increased frequency in SLE patients.
	Higher risk for developing juvenile idiopathic arthritis.
-477C>G,-369C>A,14bpDEL/INS,3187A>G,3195C>G	Role in celiac disese.
14bpDEL/+3142G	Role in Multiple sclerosis.
-725C>G>T	Role in Multiple sclerosis.
-716T>G	
SNP +755A/C	Increases the risk of Kawasaki disease.
HLA-G*01:01:02	Increase the risk of developing Behcet's disease.
HLA-G*01:01:05	

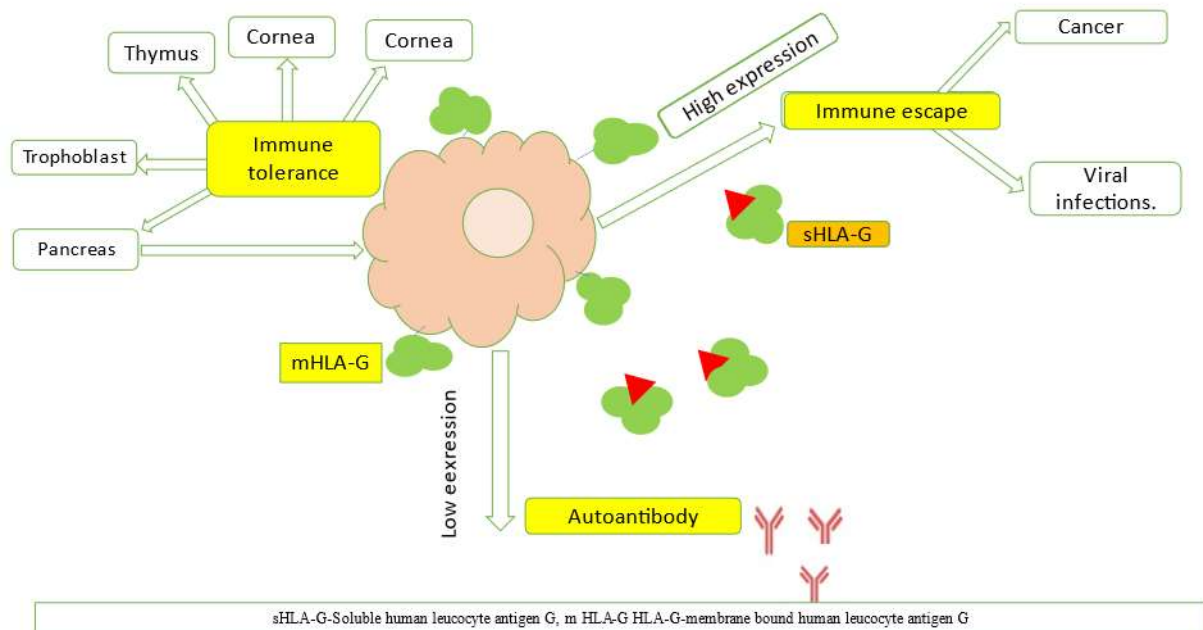| HLA-G*01:01:03:01 | Risk factor for gastric adeno carcinoma. |
| HLA-G*01:01:08 | |

Fig 14: HLA-G expression & various immune mechanisms

HLA -G Relevance in Tumour
Immune system and tumor cells
MHC class I molecules, which are found on the surface of all cells, including tumor cells, help the immune system recognize tumor cells. The immune system launches a reaction to get rid of tumor cells when it discovers them.

Evasion of immune detection
Tumor cells, however, have a variety of strategies for avoiding immune identification. They may, for instance, exhibit mutant MHC class I molecules that the immune system cannot identify or low quantities of MHC class I molecules.

Role of HLA-G
Immunoregulatory molecules, such as HLA-G, can significantly affect the course of the disease in the setting of cancer. A protein called HLA-G, which is present on the surface of certain tumor cells, has been discovered as a significant factor in thwarting the immune response meant to eliminate malignant cells. Tumor cells are helped by this interference to avoid immune detection and to thrive.

Notably, Frumento et al. (2000) pointed out that melanoma was where HLA-G expression in the setting of malignancy was first identified in 1998. According to De Figueiredo-Feitosa et al. (2017), further knowledge on the role of HLA-G polymorphisms in cancer has come to light. Research by Lin et al. (2018) revealed that tumor tissues do in fact express HLA-G, and in vitro tests verified that tumor cell lines expressing HLA-G were less vulnerable to immune-mediated cytotoxicity. The idea that this molecule plays a role in the development of cancer is further supported by the vast amount of research that consistently links HLA-G expression to a variety of cancers.

According to Erikci et al., "both hematological and solid malignancies have been discovered with elevated HLA-G serum levels and a high frequency of HLA-G surface expression. B and T acute lymphoid leukemia, chronic B lymphocyte leukemia, and acute myeloid leukemia patients had greater rates of HLA-G expression. A function in the immune escape mechanism of malignancies is suggested by the correlation between HLA-G and HLA-G expression and poor clinical outcomes in tumor patients.

Gastric carcinoma
Gastric adenocarcinoma has a considerable global frequency, particularly in places like Japan, as noted by Correa (1991). This finding is consistent with the fact that gastric cancer (GC), which is the second greatest cause of cancer-related death worldwide (Parkin et al., 2005), presents a significant public health concern.

The 14bp INS/DEL and +3142C/G polymorphisms were shown to be more common in patients with gastric cancer than in control groups in a more recent research by Vaquero-Yuste et al. (2021). According to Vaquero-Yuste's results, which emphasize their significant participation as key risk factors influencing gastric cancer susceptibility, this research underlines the notable influence of these unique HLA-G gene variants.

Lung carcinoma

Urosevic et al. (2001) provided an excellent explanation of how structural and functional changes to HLA class I molecules occur in lung cancer together with the local production of immunosuppressive cytokines to cause immune evasion mechanisms. Paul et al. (1999) made an exciting discovery when they discovered that samples from all types of tumors they looked at had both full-length membrane-bound and soluble HLA-G transcripts, despite the fact that HLA-G1 transcriptional levels usually exceeded those of HLA-G5.

In the area of genetic susceptibility, Lee et al. (1996) revealed an expanding body of data linking genetic variables to the development of cancer, particularly lung cancer. The ability of HLA-encoded cell-surface MHC molecules to operate affects how well the cellular immune system recognizes antigens. Across a range of sources, primary tumors frequently show altered expression levels of HLA molecules, whether diminished, increased, or deleted.

Intriguingly, Urosevic et al. (2001) also noted that HLA-G expression is a distinguishing characteristic in lung carcinoma and may play a key role in the tumor's manipulation of the host immune response, ultimately resulting in immune evasion.

Colorectal carcinoma

Garziera et al. (2015) found important polymorphisms in their study, including 14bp INS/DEL, +3142C/G, +3187A/G, and +3035 C/T, which may be used as useful prognostic indicators for assessing the prognosis of colorectal cancer (CRC) patients. A convincing link between HLA-G expression and the risk of getting CRC was demonstrated by Ye et al. (2010) on the basis of this. Their analysis showed that 64.6% of CRC patients had HLA-G gene expression that was active.

Lázaro-Sánchez et al. (2020), expanding the field of study, discovered that those with CRC had significantly higher levels of salivary sHLA-G (18.8 U/ml vs. 6.3 U/ml, p = 0.036) than people in the general population. Additionally, an unexpected pattern showed that people with more advanced stages of CRC had greater salivary sHLA-G concentrations than those with early stages (24.2 U/ml vs. 8.1 U/ml, p = 0.019). This finding highlights the potential use of sHLA-G as a new biomarker for identifying and monitoring the development of this specific kind of cancer.

Ovarian carcinoma

In their grim 2009 study, Jemal et al. noted that "ovarian cancer stands as the foremost cause of mortality among gynecologic cancers in developed nations." Notably, Singer et al. (2003) made an important discovery: in their immunohistochemical analysis, they found HLA-G immunoregulation in 61% of 74 high-grade serous (Type II) carcinomas, whereas it was seldom ever seen in Type I carcinomas. This finding emphasizes the relevance of HLA-G's role in ovarian cancer and the possible therapeutic implications it carries, an issue underlined by Sheu et al. (2007).

Another significant finding was reported by Rebmann et al. (2003). They discovered that HLA-G expression may give tumor cells the ability to evade immune monitoring in the tumor microenvironment, rather of just being connected to Type II ovarian cancer. It is important to point out that different ovarian cancer specimens have different percentages of tumor cells that express the HLA-G gene. Additionally, ovarian cancer patients' malignant effusion supernatants have been shown to include the secreted form of HLA-G (sHLA-G). The complexity and wide-ranging functions of HLA-G in the context of ovarian cancer are highlighted by this multidimensional environment.

Breast carcinoma

A crucial realization was provided by Kleinberg et al. (2006), who reported that "based on immunohistochemical analysis, aberrant HLA-G expression was found in 25-41% of breast cancer patients." The clinical use of HLA-G immunohistochemistry detection in breast cancer hasn't been studied, despite the fact that it is notable.

In contrast, a thorough analysis was carried out by He et al. (2010). They discovered a striking pattern: HLA-G is overwhelmingly expressed in breast cancer specimens, in contrast to its notably missing expression in healthy tissues or benign illnesses. The size of the tumor, the presence of nodes, and the stage of the illness were all significantly correlated with this HLA-G expression. In-depth

examination of outcomes by Eskandari-Nasab et al. (2013) led them to hypothesize a correlation between patients' greater HLA-G expression and poorer prognosis.

The surprising discovery that the HLA-G 14bp DEL/DEL genotype was more common in breast cancer patients than in the control group (33.9% vs. 24.1%) was given by Eskandari-Nasab et al. (2013), adding to the discussion. According to this finding, the 14bp INS/DEL polymorphism may behave as a genetic risk factor, perhaps predisposing individuals to developing breast cancer.

4. Conclusion

Extensive polymorphism of immune system genes is a trait that is assumed to indicate an organism's adaptive response to a constantly changing environment. Particularly, the polymorphism in the HLA-G gene has been connected to a number of autoimmune illnesses, including gastrointestinal disorders, systemic sclerosis, multiple sclerosis, Type I diabetes mellitus, and different carcinomas. Additionally, a variety of autoimmune illnesses are greatly influenced by variations in antigen presentation systems. The HLA-G gene's polymorphism character has been comprehensively investigated across a number of studies, shedding light on its correlations with a variety of disorders. The role of the HLA gene in the development of autoimmune illnesses is a critical factor to take into account, it is clear after reading this extensive review. As a result, the knowledge gained from this research provides a crucial basis for comprehending the complex polymorphism aspects of the HLA-G gene and revealing its possible genetic vulnerability in the context of various cancer types and autoimmune illnesses.

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