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Hyper IgE Syndromes: Understanding, Management, and Future Perspectives: A Narrative Review

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ABSTRACT

Background and Aim: Hyper IgE syndromes (HIES) are rare primary immunodeficiency characterized by susceptibility to specific infections, eczema, and elevated IgE levels. Pathogenic mutations in *STAT3*, *IL6R*, *IL6ST*, *ERBB2IP*, *PGM3*, *ZNF431, SPINK5, TGFBR1/2*, and *CARD11* have been identified as genetic factors contributing to phenotypes of HIES lead to hindered differentiation and activity, aberrant signaling cascades and disrupting immune regulation. HIES present a diverse clinical symptoms, challenging diagnosis and management; understanding its pathophysiology, genetics, and immunological abnormalities offer hope for improved outcomes. In this review we aim to provide a comprehensive understanding of the condition and also discuss latest updates on pathological features, clinical spectrum and its variability, immunological abnormalities, inheritance patterns, new candidate genes, challenges, management strategies, epidemiology and future directions of HIES.

Methods: This review conducted an extensive search of information from multiple databases, including PubMed, Scopus, WHO, and ClinVar to ensure comprehensive coverage. Preference was given to articles published recently to capture the latest research and developments. Endnote was employed as a reference manager. The relevant literature was meticulously reviewed to address the objectives of the study.

Results: Missense, nonsense, and frameshift variants are commonly observed in HIES. Understanding these genetic mutations is key to diagnosing and managing conditions such as Hyper-IgE recurrent infection syndromes (linked to IL6R, STAT3, and ZNF341 mutations), Atopy associated with ERBIN mutations which links STAT3 and TGF-β pathway, Immunodeficiency 23 (caused by PGM3 mutations), Netherton syndrome (resulting from SPINK5 mutations), and Loeys-Dietz syndrome (related to TGFBR mutations). Each year, new genes and variants responsible for this type of immune deficiency are added to the list.

Conclusion: Although rare, HIES significantly impacts patients due to its complex medical manifestations and need for lifelong management. Identifying casual variants is essential for effective clinical management of these complex conditions.

Summary

- Hyper IgE syndromes (HIES) is characterized with diverse clinical manifestations, caused by mutations in genes like STAT3, IL6R, PGM3, and others.
- Diagnosis is complex due to clinical variability and overlap with other disorders, requiring genetic analysis and standardized diagnostic criteria.
- Management includes antimicrobial prophylaxis, immunomodulators, biologics like dupilumab, and, in severe cases, hematopoietic stem cell transplantation (HSCT).
- Despite therapeutic advances, challenges remain in early diagnosis and personalized treatment. Emerging therapies like gene editing and targeted immunomodulation offer hope.
- Although rare, underdiagnosis and misdiagnosis contribute to challenges in understanding its true prevalence.
- Research priorities include identifying novel genetic causes, improving diagnostic tools, and developing advanced treatments like CRISPR-based gene therapy.

1 | Background

In the past, the term "Hyper-IgE syndrome" (HIES) was used interchangeably with "Job syndrome." However, currently, Job syndrome specifically refers to one of the autosomal dominant forms of Hyper-IgE syndromes. HIES are uncommon primary immunodeficiency conditions marked by severe vulnerability to a limited range of infections, eczema, and increased levels of serum immunoglobulin E (IgE). Other features include sinopulmonary infections, pulmonary pneumatoceles, severe pruritic eosinophilic dermatitis, coarse facial features, delayed shedding of baby teeth, osteopenia, and recurrent fractures. First reported by Davis et al. in 1966, this syndrome exhibits a diverse range of clinical symptoms that can differ significantly from person to person [1].

Although uncommon, diagnosing and managing HIES can be quite challenging because of its varied presentation or heterogeneous nature among individuals and the risk of severe complications [2]. In recent years, progress in comprehending the pathophysiology, genetics, and immunological abnormalities linked to HIES has revealed possible treatment targets and management approaches, providing optimism for enhanced outcomes and quality of life among those affected [3, 4].

By synthesizing current research findings and clinical insights, this review article seeks to provide healthcare professionals with a comprehensive understanding of HIES, including its variability in presentation, underlying immunological and genetic mechanisms, diagnostic considerations, available management options, prognosis, and the importance of multidisciplinary care and patient support. Furthermore, the article aims to highlight future perspectives in HIES research and therapeutic developments, aiming to improve outcomes and quality of life for individuals affected by this rare immunodeficiency disorder.

1.1 | Pathological Features of Hyper IgE Syndrome

Since 1970, World Health Organization (WHO) convened a group of investigators to propose a classification of the primary immunodeficiencies. Figure 1 highlights the evolving understanding of the genetic basis of HIES, reflecting significant progress in identifying the genes involved in this group of primary immunodeficiencies over the past three decades. The defect associated with HIES was initially not well understood, but with advancements in genetic research, several responsible genes have been identified over time (Figure 1). Moreover, the most recently variants of these genes that contribute in resembling HIES phenotypes are mentioned in Table 1.

1.2 | Defects in STAT3 Signaling Pathway

One of the autosomal dominant form of HIES is associated with mutations in the signal transducer and activator of transcription 3 (*STAT3*) gene that has 24 exons, leading to aberrant signaling cascades. *STAT3* deficiency was identified as the genetic origin of AD-HIES in 2007 [6].

This protein serves as a crucial mediator in incorporating external signals from cytokines and hormones, thereby adjusting cellular processes to suit their environment [7]. Alternatively-spliced *STAT3* isoforms are composed of the full-length *STAT3α* isoform and the truncated *STAT3β* isoform [6]. The predominant isoform (*STAT3α*) yields a complete protein of 770 amino acids, weighing 92 kDa, and consists of six functional domains [8].

STAT3 plays a crucial role in mediating responses to various cytokines and growth factors including interleukins (IL)-5, IL-6, IL-17, leukemia inhibitory factor (LIF), interferons (IFN α/β and γ), epidermal growth factor (EGF), hepatocyte growth factor (HGF) and bone morphogenetic protein 2 (BMP2) which are vital for immune regulation and inflammatory responses [9–11].

STAT3 gene responds by being phosphorylated by receptor-associated kinases. It then forms homo- or heterodimers, which translocate to the cell nucleus and act as transcription activators. Pathogenic mutations in *STAT3*, particularly those affecting the linker domain, interfere with its phosphorylation and consequent activation. This impairment disrupts downstream signaling pathways, thus contributing to the immune response dysregulation seen in HIES [12].

In very recent literature, cases with systemic *Talaromyces marneffei* infections due to *STAT3*-HIES were identified which indicate that we still need to know about the clinical characteristics of *STAT3*-HIES [13]. The impact of 105 *STAT3* mutations in different domains and the severity of the clinical manifestations also recently were analyzed. The results indicated that 73% of the mutations studied affect the protein's physicochemical properties, modifying its stability, flexibility, and function to different extents. Specifically, mutations in the DNA binding domain (DBD) and the Src Homology 2 (SH2) domain (A part of a protein that helps it

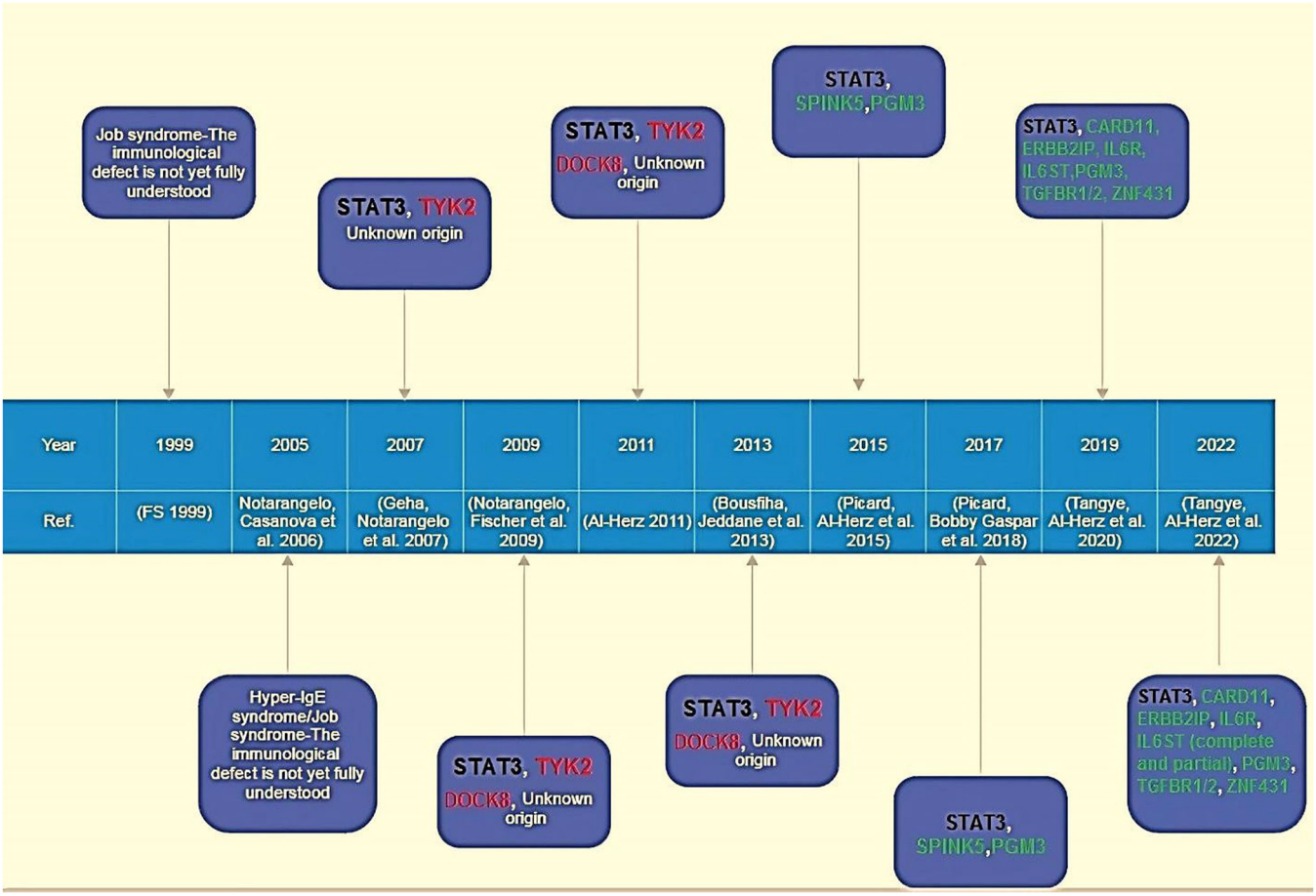

FIGURE 1 | The evolving understanding of the genetic basis of HIES. Pathogenic mutations in other genes contributing to phenotypes resembling HIES have been gradually reported. While some genes with possible pathogenic mutations have been excluded from the list (indicated in red, refer to subheadings of 2.9 and 2.10). STAT3 was the first discovered gene and remained to date (black), other added genes indicated in green.

interact with other proteins in cell signaling) significantly impact the protein structure, disrupting its interaction with DNA or other *STAT3* proteins to form a heterodomain complex. This disruption leads to severe clinical phenotypes [14].

Lately, besides *STAT3* mutations, pathogenic mutations in *CARD11*, *ERBB2IP*, *IL6R*, *IL6ST*, *PGM3*, *TGFBR1/2*, *SPINK5* and *ZNF431* have also been identified as additional genetic factors contributing to phenotypes resembling HIES which will be followed in detail.

1.3 | Inborn Errors of IL-6 Receptor in HIES

IL-6 receptor deficiency with recurrent infections is an autosomal recessive immune disorder and caused by homozygous mutation in the *IL6R* gene on chromosome 1q21.3. It typically begins in early childhood and is marked by abnormal acute-phase responses, notable lack of inflammatory response associated with infection, poor neutrophil response, frequent sinopulmonary and deep skin infections, primarily due to bacteria like *Haemophilus influenza* and *Staphylococcus. aureus*. Other symptoms include atopic dermatitis, weakened inflammatory responses during infections, elevated serum IgE, and increased IL-6 levels [15].

1.4 | Mutations in Glycoprotein 130 (gp130) Exhibit Different Patterns of Inheritance

IL-6 signaling pathway has different component encoding by *IL6ST, STAT3*, and *ZNF341*, genes. GP130 is a transmembrane protein which forms one subunit of the type I cytokine receptor within the IL-6 receptor family. Complete cytokine-selective loss of function (LOF) in GP130 or incomplete LOF variants in the common receptor chain GP130 as well as genes that affect GP130 glycosylation lead to complex phenotypes including features of hyper-IgE syndrome [16]. The loss of function ranging from partial to complete loss in GP130 with different inheritance pattern explains the variability of clinical manifestations, differences in symptoms and severity of a disease from person to person.

1.5 | Inherited Human ZNF341 Deficiency and STAT3 Expression Control

ZNF341-deficient cells exhibit *STAT3* levels at 50% of the normal amount when in a resting state. However, since there is no definitive proof that having only one functional copy of *STAT3* (haploinsufficiency) leads to HIES, this reduction alone likely does not account for the HIES phenotype seen in *ZNF341*-deficient patients. Instead, the more plausible pathophysiological mechanism is thought to be the combination of reduced basal

TABLE 1 | The most recently reported variants contributing in HIES (https://www.ncbi.nlm.nih.gov/clinvar/).

Name	Gene (s)	Condition(s)	GRCh38 Chromosome	GRCh38Location	dbSNP ID	Canonical SPDI	Variant type	Molecular consequence	Germline classification
NM_000565.4(IL6R):c.836 T > A (p. Ile279Asn)	IL6R	Hyper-IgE recurrent infection syndrome 5	1	154435997	rs1689606931	NC_000001.11:154435996:T:A	SNV	missense variant	p
NM_139276.3(STAT3):c.1909G>-A (p. Val637Met)	STAT3	Hyper-IgE recurrent infection syndrome 1	17	42322474	rs113994139	NC_000017.11:42322473:C:T	SNV	missense variant	p
NM_139276.3(STAT3):c.1145 G > A (p. Arg382Gln)	STAT3	Hyper-IgE recurrent infection syndrome 1	17	42329642	rs113994136	NC_000017.11:42329641:C:T	SNV	missense variant	p
NM_139276.3(STAT3):c.1144 C > T (p. Arg382Trp)	STAT3	Hyper-IgE recurrent infection syndrome 1	17	42329643	rs113994135	NC_000017.11:42329642:G:A	SNV	missense variant	p
NM_139276.3(STAT3):c.1003 C > T (p. Arg335Trp)	STAT3	Hyper-IgE recurrent infection syndrome 1	17	42333719	rs193922716	NC_000017.11:42333718:G:A	SNV	missense variant	p/Lp
NM_139276.3(STAT3):c.1907C>T (p. Ser636Phe)	STAT3	Hyper-IgE recurrent infection syndrome 1	17	42322476		NC_000017.11:42322475:G:A	SNV	missense variant	P
NM_139276.3(STAT3):c.1397 A > G (p. Asn466Ser)	STAT3	Hyper-IgE recurrent infection syndrome 1	17	42325030	rs1057521091	NC_000017.11:42325029:T:C	SNV	missense variant	P
NM_139276.3(STAT3):c.994 C > T (p. His332Tyr)	STAT3	Hyper-IgE recurrent infection syndrome 1	17	42333728	rs2144827923	NC_000017.11:42333727:G:A	SNV	missense variant	P/Lp
NM_001253697.2(ERBIN):c.1588 G > T (p. Asp530Tyr)	ERBIN	Atopy	5	66044296	rs748519248	NC_000005.10:66044295:G:T	SNV	missense variant	VUS

(Continues)

TABLE 1 | (Continued)

Name	Gene (s)	Condition(s)	GRCh38 Chromosome	GRCh38Location	dbSNP ID	Canonical SPDI	Variant type	Molecular consequence	Germline classification
NM_015599.3(PGM3):c.421dup (p. Ile141fs)	PGM3	Immunodeficiency 23	6	83187043 - 83187044	rs2128504331	NC_000006.12:83187043:TT:TTT	Duplication	frameshift variant	P
NM_015599.3(PGM3):c.1474 C > T (p. Arg492Ter)	PGM3	Immunodeficiency 23| Severe combined immunodeficiency disease	6	83170370	rs144104577	NC_000006.12:83170369:G:A	SNV	nonsense	P/Lp
NM_015599.3(PGM3):c.-2-195C > G	PGM3	Immunodeficiency 23	6	83191209	N/A	NC_000006.12:83191208:G:C	SNV	Nonsense, intron variant	P
NM_015599.3(PGM3):c.322_323insGATTG (p. Asp108fs)	PGM3	Immunodeficiency 23	6	83188680 - 83188681	N/A	NC_000006.12:83188680:CAAT:CAATCCAAT	Insertion	frameshift variant	P
NM_015599.3(PGM3):-c.1198_1202dup (p. Ala402fs)	PGM3	Immunodeficiency 23	6	83174413 - 83174414	N/A	NC_000006.12:83174413:GCTTT:GCTTTGCTTT	Duplication	frameshift variant	P
NM_015599.3(PGM3):c.-2-185C > T	PGM3	Immunodeficiency 23| Severe combined immunodeficiency disease	6	83191199	rs565900346	NC_000006.12:83191198:G:A	SNV	Nonsense, intron variant	P/Lp
NM_015599.3(PGM3):c.398_413del (p. Ser133fs)	PGM3	Immunodeficiency 23	6	83187052 - 83187067	rs1404084330	NC_000006.12:83187051:TGTGAAAGTTTCTCACTG:TG	Deletion	frameshift variant	P/Lp
NM_001282933.2(ZNF341):-c.1054 T > C (p. Cys352Arg)	ZNF341	Hyper-IgE recurrent infection syndrome 3, autosomal recessive	20	33761887	rs2122686345	NC_000020.11:33761886:T:C	SNV	missense variant	Lp
NM_006846.4(SPINK5):c.891 C > T (p. Cys297 =)	SPINK5	Increased circulating IgE level, Netherton syndrome	5	148097875	rs752941297	NC_000005.10:148097874:C:T	SNV	synonymous variant	P/Lp

(Continues)

TABLE 1 | (Continued)

Name	Gene (s)	Condition(s)	GRCh38 Chromosome	GRCh38Location	dbSNP ID	Canonical SPDI	Variant type	Molecular consequence	Germline classification
NM_004612.4(TGFBR1):c.1460 G > A (p. Arg487Gln)	TGFBR1	Loeys-Dietz syndrome	9	99149253	rs113605875	NC_000009.12:99149252:G:A	SNV	missense variant	P
NM_004612.4(TGFBR1):c.934 G > A (p. Gly312Ser)	TGFBR1	Loeys-Dietz syndrome	9	99142664	rs760079636	NC_000009.12:99142663:G:A	SNV	missense variant	P/Lp

Note: STAT3: signal transducer and activator of transcription 3; IL: interleukin; gp130: Glycoprotein 130; ZNF341: Zinc Finger Protein 341; PGM3: Phosphoglucomutase 3; ERBB2IP: Erbb2 interacting protein; TGFβ: Transforming Growth Factor Beta; CARD11: Caspase recruitment domain-containing protein 11; SNV: Single Nucleotide Variants; Canonical SPDI: NCBI's SPDI notation describes variants as a sequence of four attributes: sequence, position, deletion and insertion; GRCh38: Genome Reference Consortium Human Reference [5]; dbSNP: Database for Single Nucleotide Polymorphisms; P: Pathogenic; LP: Likely pathogenic.

expression levels and impaired autoinduction of *STAT3* observed in *ZNF341*-deficient lymphocytes [17].

1.6 | Homozygous Mutations in Phosphoglucomutase 3 (PGM3)

Mutations in genes responsible for encoding various signaling molecules, such as *PGM3*, have also been associated with immune dysregulation syndromes that share clinical features with HIES. *PGM3* is essential for protein glycosylation and proper functioning of immune cells. Defects in *PGM3* disrupt immune cell signaling and function, leading to impaired host defense mechanisms and susceptibility to infections [18].

1.7 | ERBIN Disrupt Regulation of TGFβ Signaling via STAT3

Erbb2 interacting protein (*ERBB2IP*), also known as ERBIN, is a protein encoded by the *ERBB2IP* gene in humans. ERBIN is crucial for mediating the interaction between *STAT3* and TGFβ (Transforming Growth Factor Beta) signaling pathways. Mutations in the *ERBB2IP* gene can contribute to an epithelial-specific predisposition to allergic diseases and connective tissue disorders. Studies show that ERBIN mutations enhance TGFβ signaling and inhibit *STAT3* from negatively regulating this pathway. This mechanism likely accounts for the clinical similarities observed in disorders involving *STAT3* and TGFβ signaling. The excessive TGFβ signaling, which increases IL-4 receptor expression, supports the use of precision-based therapies that block the IL-4 receptor to treat atopic diseases. Significant allergic diseases have been observed in Loeys–Dietz syndrome (LDS), a condition associated with various connective tissue abnormalities, and linked to loss-of-function mutations in *STAT3*, *TGFBR1*, and *TGFBR2* [19, 20].

The main genetic changes involve loss-of-function mutations in the *STAT3*/ERBIN/SMAD2/3 complex. TGF-β activates SMAD3, which moves into the nucleus to promote Th2-biased lymphocyte responses. The *STAT3*-ERBIN complex inhibits TGF-β signaling by trapping SMAD3 in the cytoplasm. The *ERBB2IP* variant disrupts the formation of the STAT3-ERBIN-SMAD2/3 complex, leading to increased TGF-β signaling via SMAD3. Recently it has been proved that, Dupilumab, a drug used to treat severe allergic conditions, can block the IL-4–mediated effects of abnormal TGF-β signaling [21].

1.8 | Elevated IgE From Attenuated CARD11 Signaling

Caspase recruitment domain-containing protein 11 or CARD-containing MAGUK protein 1, a large scaffold and membrane associated protein is encoded by *CARD11* gene. Pathogenic hypomorphic mutations in *CARD11* are associated with several human-inborn errors of immunity including severe combined immunodeficiency (SCID), since both T cell and B cell functions are critical for adaptive immunity. CARD11 is activated after T cell receptor or B cell receptor stimulation. After

receptor stimulation, CARD11 is phosphorylated by PKC-θ (in T cells) or PKC-β (in B cells) at serine residues within the inhibitory domain. The phosphorylation induces formation of filamentous CARD11 multimers that recruit BCL10 and MALT1, which in turn as a complex activates NF-κB [22]. Missense variants causing *CARD11* deficiency may affect the protein function rather than the expression and can result in a phenotype combining the atopic skin disease and the features of CID [23].

1.9 | Comèl–Netherton Syndrome Associated With Mutations in the SPINK5 Gene

A similar phenotype to HIES may be produced by genetic skin disorder of Comèl–Netherton syndrome characterized by generalized exfoliative erythroderma, ichthyosiform dermatitis, trichorrhexis invaginata, hypernatremic dehydration, failure to thrive, and recurrent respiratory infections. An ichthyosis syndrome is caused by mutations in *SPINK5* encoding, a serine protease essential for skin barrier integrity [24].

These mutations lead to increased protease activity, resulting in fewer layers of the outer skin, contrary to other forms of ichthyosis where there are too many layers. The severity of the disease can vary based on the type of mutation, with complete *SPINK5* gene deletions linked to severe cases, and mutations causing alternate splicing or premature stop codons leading to varying levels of severity [25, 26].

Treatment is tailored to the individual patient's needs. There is no cure, but management strategies aim to alleviate symptoms and prevent complications. Topical keratolytic agents, oral antihistamines, systemic antibiotics, topical steroids and oral retinoids, intravenous immunoglobulin therapy have shown varying success. Very recently a successful clearance of the skin lesions, and a significant decrease in total IgE levels has been achieved after treatment with a purified, recombinant DNA-derived chimeric IgG monoclonal antibody protein of infliximab infusions [27]. Figure 2 provides a comprehensive summary of the latest reported changes in this context related to the aforementioned genes (Figure 2).

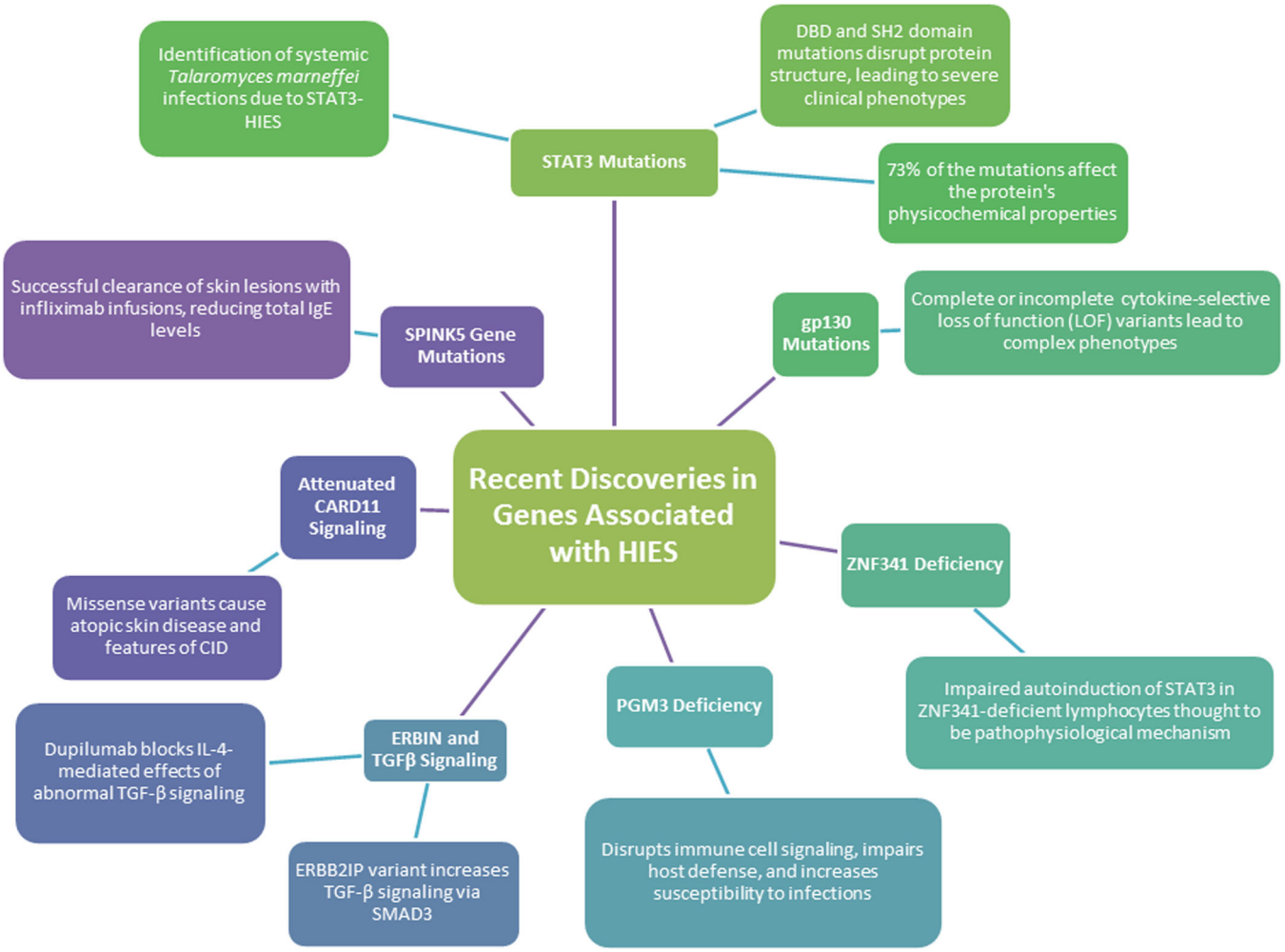

FIGURE 2 | Recent Genetic Discoveries in HIES: Unveiling New Gene Mutations and Their Roles in Immune Dysregulation. STAT3: signal transducer and activator of transcription 3; DBD: DNA binding domain; SH2: Src Homology 2; IL: interleukin; gp130: Glycoprotein 130; ZNF341: Zinc Finger Protein 341; PGM3: Phosphoglucomutase 3; ERBB2IP: Erbb2 interacting protein; TGFβ: Transforming Growth Factor Beta; SMAD: small mother against decapentaplegic; CID: combined immunodeficiency; CARD11: Caspase recruitment domain-containing protein 11.

1.10 | DOCK8 Mutations and Defective Cytoskeletal Regulation

In addition to mutations in the *STAT3* gene, mutations in dedicator of cytokinesis 8 (*DOCK8*) gene have also been identified in patients with high level of IgE. *DOCK8* is involved in regulating the cytoskeleton and has a pivotal role in lymphocyte migration, attachment, and the formation of immune synapses. Malfunctioning *DOCK8* leads to disrupted interactions between T and B cells, hindered movement (compromised trafficking) of immune cells, and weakened responses to pathogens. Individuals with *DOCK8* deficiency frequently experience narrow range of infections, eczema, and high IgE levels, resembling the clinical features of HIES [28].

Although, based on the latest International Union of Immunological Societies (IUIS) classification, *DOCK8* deficiency is classified as a CID (generally less profound than SCID), patients with such disorder mostly share the same clinical manifestation with HIES, but viral infections including *severe wart* and *molluscum contagiosum* are more common [29, 30]. However, we mention it here because it should be still considered as a differential diagnosis with the *STAT3*-related disorders.

1.11 | Why Tyk2 is Not Faulty Anymore?

Further research post 2015 revealed that *TYK2* deficiency primarily leads to mycobacterial and viral infections, rather than HIES. Seven additional *TYK2*-deficient patients from different ethnic groups were identified, all showing mycobacterial and/or viral infections but no HIES features. Impaired responses to IL-12 and IFN-α/β (important cytokines) account for the infections seen in *TYK2* deficiency. Interestingly, these patients lacked the typical HIES symptoms, such as high serum IgE levels and staphylococcal abscesses [31].

However, there are indeed cases where patients exhibit clinical and laboratory phenotypes consistent with HIES, but genetic tests do not reveal any known mutations. This suggests that there could be undiscovered genes associated with HIES. The genetic heterogeneity and the presence of patients with HIES symptoms but without identified genetic mutations highlight the complexity of this syndrome and indicate that our understanding of its genetic basis is still incomplete. Therefore, further research is needed to uncover these potential undiscovered genes and to deepen our understanding of the genetic underpinnings of HIES. This could potentially lead to more accurate diagnosis and better treatment strategies for patients with this syndrome.

1.12 | Impact on Th17 Cell Differentiation

T helper 17 (Th17) cells represent a subset of T cells essential for defending the host against external pathogens and for preserving immunity in mucosal and mucocutaneous regions through generating interleukin 17 (IL-17) [32]. The disruption of *STAT3* signaling in HIES impacts the differentiation and activity of Th17 cells [33]. The hindered differentiation of Th17 cells leads to decreased secretion of IL-17 and IL-22, crucial for maintaining the integrity of epithelial barriers and defending against fungal and bacterial infections [34, 35]. Changes in Th17 cell reactions contribute to the increased vulnerability of individuals with HIES to frequent skin and lung infections which are mostly caused by a narrow spectrum of pathogens [33].

CD4 + T cells with one mutated copy of *STAT3* gene (heterozygous *STAT3* mutations) fail to produce interleukin 17-secreting cells (also known as Th17 cells) duo to the lack of retinoid-related orphan receptor γt, which is crucial for the development of Th17 cells [36]. Sharma and colleagues showed a significant decrease in Th17 cell levels in all cases with *STAT3* pathogenic variants [37].

1.13 | Impaired Regulatory T Cell Function

Another molecular mechanism linked to HIES involves abnormalities in regulatory T (Treg) cells, which play a critical role in preserving immune tolerance and controlling exaggerated immune reactions [7]. Malfunctioning Treg cells contribute to the uncontrolled immune activation and inflammation seen in HIES, resulting in the emergence of allergic symptoms, autoimmune conditions, and inflammatory issues [33, 38].

Dendritic cells (DCs) play a central role in coordinating different forms of immunity and tolerance. Myeloid and monocyte-derived DCs showed a reduced ability to respond to IL-10, failing to become tolerogenic (FoxP3 +), and to increase the expression of Programmed cell death 1 (PD-1) and Immunoglobulin-like transcript 4 (ILT4) compared to control DCs. These deficiencies in DC function might contribute to the inflammation observed in hyper-IgE syndromes [5].

1.14 | Clinical Spectrum and Variability

HIES is characterized by a variety of clinical manifestations stemming from defects in both innate and adaptive immunity. The clinical presentation of HIES is diverse and can include recurrent skin infection and recurrent pneumonias, parenchymal lung abnormalities including bronchiectasis and pneumatocele, moderate to severe eczema, elevated levels of serum IgE more than 2000 IU/mL and, eosinophilia (Table 1) [39]. Non-immunological or somatic manifestations such as connective tissue abnormalities, coronary vasculature anomalies (aneurysms), to less extent trauma fractures, dental abnormalities, joint may stretch beyond the normal range, skull malformation as well as scoliosis can also be developed in patients with HIES. Clinical features of HIES with autosomal dominant inheritance pattern with approximate frequency have been depicted in Figure 3.

1.15 | Immunological Abnormalities and Defect in Humoral Immunity of HIES

In HIES, there is an abnormal production of IgE, leading to significantly increased levels in the bloodstream, often reaching thousands of times above the normal range. The precise mechanism behind the disruption of IgE regulation in HIES remains incompletely understood, but it is believed to involve aberrant signaling pathways downstream of cytokine receptors,

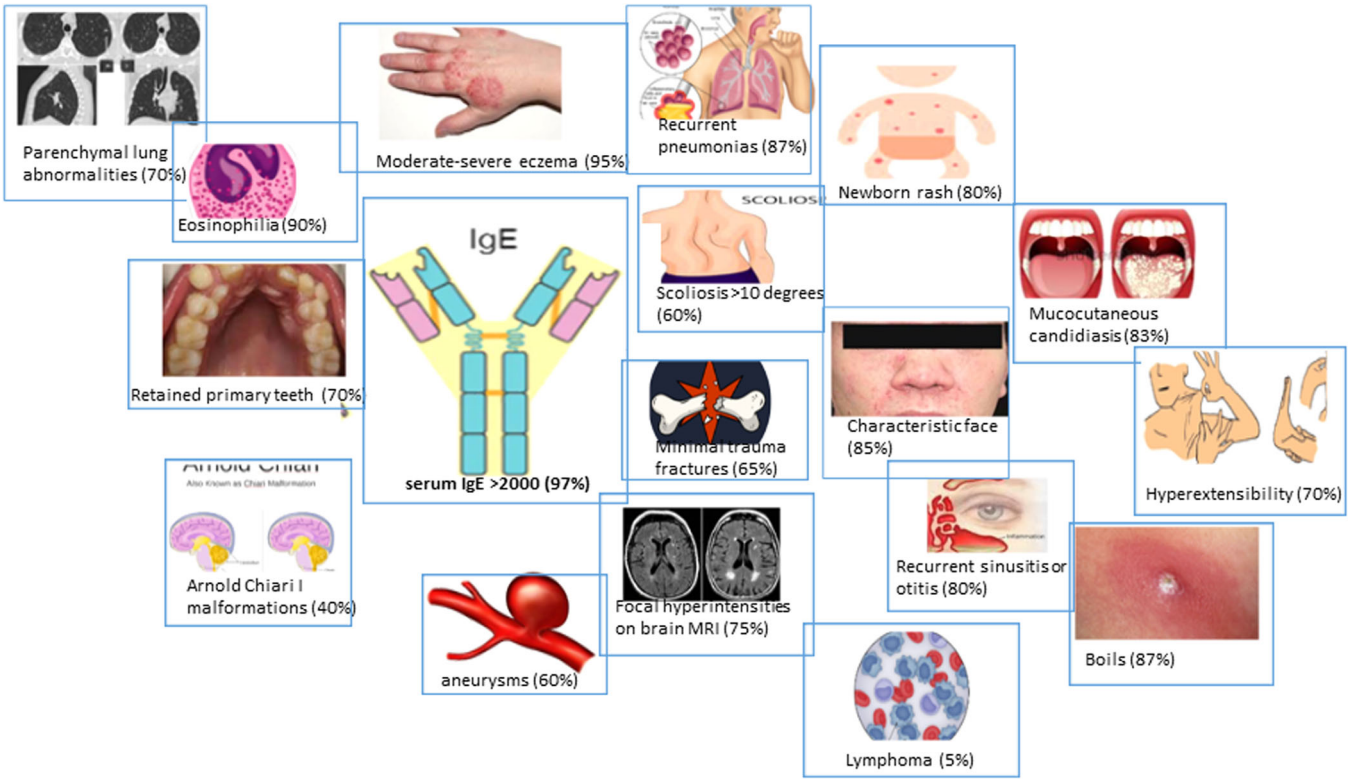

FIGURE 3 | Clinical features of HIES with autosomal dominant inheritance pattern.

particularly interleukin-4 (IL-4) and interleukin-13 (IL-13), which are key regulators of IgE production, so that targeting them using monoclonal antibody of Dupilumab mitigate atopic dermatitis manifestations [40].

Patients with HIES commonly exhibit significant deficiencies in neutrophil chemotaxis (the ability of immune cells to move toward infection) and phagocytosis, key aspects of their immune response. In HIES, malfunctioning neutrophils struggle to effectively migrate to infection sites due to compromised chemotaxis. Additionally, their reduced ability to phagocyte pathogens impairs the clearance of harmful pathogens. Consequently, individuals with HIES face increased susceptibility to recurrent skin and lung infections, including staphylococcal abscesses and pneumonia [41, 42].

Dysregulated cytokine production is another key immunological abnormality observed in HIES. Cytokines are signaling molecules that regulate immune responses and inflammation. In HIES, there is dysregulation of cytokine production, particularly involving IL-17 and interferon-gamma (IFN-γ) [43, 44]. Defective IL-17 production in HIES contributes to the development of eczema-like dermatitis and susceptibility to cutaneous infections. Conversely, dysregulated IFN-γ production leads to impaired Th1 responses and increased susceptibility to intracellular pathogens such as mycobacteria [44, 45].

The immune system deficiencies observed in HIES stem from genetic mutations that impact crucial signaling pathways responsible for immune control. Mutations in genes like *STAT3* lead to disrupted cytokine signaling and hindered differentiation of Th17 cells [44, 46]. Indeed, one of the immune defects in HIES is the malfunction of antibodies, specifically immunoglobulins. While the levels of these immunoglobulins might appear normal, their function can be impaired. For instance, after vaccination, a healthy immune system typically produces a robust antibody response to help protect against the specific disease. However, in patients with HIES, this antibody response might be insufficient or absent. This can leave these patients more susceptible to the disease the vaccine was designed to protect against. In such cases, patients with antibody dysfunction are often treated with Intravenous Immunoglobulin (IVIG) therapy. IVIG is a treatment that boosts antibody levels in people with immunodeficiencies, autoimmune diseases, or inflammatory conditions. IVIG treatment can replace the missing antibodies and protect against a range of infections. Therefore, regular IVIG therapy, such as monthly infusions, can help manage the antibody dysfunction in these patients [47].

Comprehending the immunological deficiencies associated with HIES is crucial for uncovering how the disease develops and for creating specific treatments. Approaches focusing on re-establishing immune capabilities, such as hematopoietic stem cell transplantation (HSCT), cytokine replacement therapy, and gene therapy, offer hope for enhancing outcomes in individuals with HIES [48, 49]. Furthermore, next generation sequencing (NGS), a progress in genetic sequencing methods, has facilitated the discovery of new genetic mutations linked to HIES [50, 51].

1.16 | Diagnostic Approaches and Challenges

Although the presence of repeated staphylococcal skin abscesses, pneumonia leading to pneumatocele formation, and

increased serum IgE levels are typical indicators of HIES, diagnosing the condition can be difficult due to the diverse range of clinical manifestations and symptoms that overlap with other immunodeficiency disorders [52].

Various diagnostic criteria have been suggested to assist in diagnosing HIES, with notable ones established by the National Institutes of Health (NIH) and the International Union of Immunological Societies (IUIS). The NIH criteria for diagnosing HIES encompass a history marked by recurring skin abscesses or pneumonia, distinctive facial features (like coarse facial appearance and retention of primary teeth), increased levels of serum IgE (> 2000 IU/mL), and other associated clinical features such as eczema, skeletal abnormalities, or recurrent infections [53]. The IUIS criteria incorporate similar clinical features but also include laboratory evidence of impaired neutrophil chemotaxis or deficient antibody responses. While these diagnostic criteria provide a framework for identifying patients with HIES, clinicians must carefully consider the full spectrum of clinical manifestations and perform comprehensive evaluations to confirm the diagnosis [29]. A practical diagnostic guidelines for clinicians could be "Mutations in STAT3 and diagnostic guidelines for hyper-IgE syndrome" written by Cristina Woellner et al [54].

HIES can pose difficulties in diagnosis as its clinical features often resemble those of other immunodeficiency disorders and syndromes. Disorders such as *DOCK8* deficiency, *PAX1* deficiency, Arp2/3-mediated filament branching defect, Hypereosinophilic syndrome due to somatic mutations in *STAT5b* may exhibit eosinophilia, atopic dermatitis, and immunological abnormalities, complicating the distinction from HIES based solely on clinical presentation [29].

Likewise, the conditions known as Immune-dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome are among primary immunodeficiency disorders (PID) associated with elevated serum IgE levels [55]. Lack of Tregs (CD4 + CD25 + FOXP3 +) as functional defect in IPEX can provoke elevated serum IgE levels in affected individuals [29].

Other syndromes characterized by elevated IgE levels, such as Churg-Strauss syndrome, a condition which is also known as eosinophilic granulomatosis with polyangiitis (EGPA) [56] and allergic bronchopulmonary aspergillosis (ABPA) [57] may mimic some aspects of HIES.

Additionally, Atopic Dermatitis (AD) and HIES are both immunological disorders that can present with similar symptoms. However, they are distinct conditions that require different treatment approaches. Therefore, it's crucial to accurately distinguish between them [58, 59]. Differential diagnoses should be carefully considered and ruled out through extensive clinical assessments, immunological examinations, and genetic analyses.

1.17 | Management Strategies and Therapeutic Interventions

Several practical guidelines exist for managing the clinical manifestations of patients with HIES. Practice Guidelines for the Treatment of Aspergillosis [60], Diagnosis and Management Guidelines for Primary Immunodeficiency [61, 62], and guidelines for managing skin problems [63–65] can aid clinicians in the effective management of patients with HIES.

Effective management of HIES involves a comprehensive strategy that tackles infections, immune system abnormalities, and the overall well-being of those impacted. The use of preventive antimicrobial treatment is crucial in reducing both the frequency and intensity of infections in individuals with HIES. Specifically, prophylactic or preventive use of antibiotics like trimethoprim-sulfamethoxazole (TMP-SMX) has been effective in warding off bacterial infections, especially those originating from *Staphylococcus aureus*, a typical pathogen in HIES [42].

Moreover, clinicians may recommend antifungal treatments to avert fungal infections like candidiasis [66, 67].

Immunomodulatory treatment is frequently utilized in individuals with HIES. Methotrexate and corticosteroids, such as prednisone or methylprednisolone, may be prescribed to manage eczema-like skin inflammation and reduce overall systemic inflammation in HIES patients [68, 69].

Monoclonal antibodies like mepolizumab, omalizumab, reslizumab, and benralizumab have shown efficacy in managing allergic and eosinophilic inflammation in HIES and associated conditions [70]. Other appraisal among biologics demonstrated that dupilumab offer the best efficacy, safety, and dosing intervals for atopic dermatitis [71]. More recently, substantial relief of *STAT3*-HIES–related dermatitis, have been reported in three children who were treated with dupilumab, an antagonist of the IL-4 receptor α chain [72]. Dupilumab effectively treats eczematoid dermatitis, reduces the need for topical treatments, and helps manage asthma and allergic bronchopulmonary aspergillosis (ABPA). However, responses to biologics vary by patient and condition [70]. These therapies are generally well-tolerated, with minimal adverse effects noted in studies [70, 73–75].

While prolonged corticosteroid use can lead to notable side effects, it should be administered judiciously and closely monitored for adverse reactions. Additionally, alternative immunomodulatory treatments like mycophenolate mofetil have demonstrated potential in addressing the inflammatory symptoms of HIES. When choosing immunomodulatory treatment, it is essential to tailor the approach according to the severity of the disease, organ participation, and treatment response [76, 77].

HSCT stands as a potential cure for immunological aspects of diseases like HIES, Omenn syndrome, Wiskott-Aldrich Syndrome, and IPEX syndrome, characterized by immune system abnormalities and recurrent, life-threatening infections despite standard medical interventions. HSCT aims to replace the defective immune system with healthy stem cells from a donor, restoring proper immune function. Recent reports suggest that HSCT has also been performed successfully in some cases of autosomal dominant HIES [78, 79]. It is also important to note that, basically, HSCT is more often done for autosomal recessive *Dock 8* deficiency cases because it is associated with T-lymphocyte deficiency and is more severe and fatal [80].

Besides above mentioned approaches, supportive care measures are crucial for managing HIES. This encompasses tackling issues like recurrent skin infections, pulmonary problems, skeletal anomalies, and growth delays. Regular monitoring for disease progression, immune status, and potential complications is vital for prompt intervention and optimizing long-term results. Genetic counseling and psychosocial assistance also form vital aspects of HIES management, providing patients and families with information, support, and emotional aid to navigate the challenges linked with the condition [81].

1.18 | Long-Term Outcomes and Prognosis

HIES is associated with a range of long-term complications that can significantly impact patients' quality of life and overall prognosis [82]. These recurrent infections can result in progressive lung damage, bronchiectasis, and respiratory insufficiency, contributing to morbidity and mortality in HIES patients. Chronic inflammation and tissue damage associated with recurrent infections may also predispose individuals to the development of autoimmune diseases, connective tissue disorders, and malignancies, further complicating the clinical course of HIES [83–85].

Regarding to immunological abnormalities, patients with HIES are prone to developing eczema-like dermatitis, autoimmune cytopenia, lymphadenopathy, enteropathy, and other autoimmune manifestations [86, 87]. Chronic skin inflammation and dermatological complications may lead to pruritus, pain, and disfigurement, affecting patients' self-esteem and psychosocial well-being. Pruritus itself can lead to poor sleep quality, daytime tiredness [72]. Additionally, skeletal abnormalities, such as scoliosis, osteopenia, and fractures can impair mobility, exacerbate pain, and increase the risk of musculoskeletal complications [88].

The prognosis of HIES varies depending on several factors, including the specific genetic mutation underlying the disease, the severity of clinical manifestations, the presence of comorbidities, and the effectiveness of therapeutic interventions. Patients with milder forms of HIES and less severe immunological abnormalities generally have better long-term outcomes compared to those with severe, refractory disease. Despite advances in medical management, the prognosis of HIES remains variable [88, 89]. Long-term benefits in HIES include stabilization of severe pulmonary involvement and elimination of recurrent skin infections and abscesses. Successful outcomes depend on early intervention and suitable donor matches. However, HSCT carries significant risks such as graft-versus-host (GVHD), transplant-related complications, and long-term immune and nonimmune issues [90].

1.19 | Emerging Therapeutic Targets and Future Directions

Recent progress in understanding the pathophysiology of HIES has illuminated new immunological pathways and potential treatment targets. A significant focus of current research involves uncovering the role of specific cytokines and signaling pathways in the development of HIES. For instance, IL-6 has emerged as a crucial cytokine involved in regulating inflammatory responses and the differentiation of immune cells. Aberrant IL-6 signaling has been linked to the development of HIES. Targeting the IL-6 signaling pathway through monoclonal antibodies or small molecule inhibitors shows promise as a therapeutic approach for managing inflammatory symptoms of HIES and enhancing clinical outcomes. Clinical trials investigating the effectiveness and safety of IL-6 inhibitors in HIES are presently underway [91].

Another area of research focuses on the identification of genetic modifiers and epigenetic factors that modulate disease severity and clinical phenotypes in HIES [92]. Genome-wide association studies (GWAS) and methods in functional genomics have pinpointed genes and regulatory components that could impact immune dysregulation and inflammatory reactions in HIES [93]. By understanding the genetic and epigenetic aspects contributing to the pathophysiology of HIES, scientists aspire to pinpoint new targets for treatment and create personalized therapeutic plans tailored to each patient [92]. Furthermore, the progression of CRISPR/Cas9 gene editing presents the possibility of precisely addressing mutations responsible for diseases of inborn errors of immunity like AD-HIES, offering a potentially curative path for specific patients with genetic deficiencies in their immune system [94].

In recent times, Gene therapy is emerging as a promising option for conditions like HIES particularly for patients without suitable donors. Gene therapy shows potential in rectifying genetic mutations and restoring normal immune functions in those affected [95]. The approach involves modifying patient-derived hematopoietic stem cells (HSCs) outside the body using lentiviral or adeno-associated viral vectors carrying healthy copies of the flawed gene. These altered HSCs are reintroduced into patients to replenish the immune system with genetically corrected cells. Animal studies on HIES have displayed promising outcomes, indicating the viability and effectiveness of gene therapy in rectifying immunological abnormalities and enhancing survival rates [96]. Currently, clinical trials are underway to assess the safety and effectiveness of different interventions for HIES, offering a promising prospect for a curative treatment option for affected individuals. But, so far no intervention based on gene therapy has been registered for treatment of HIES [97, 98].

Enthusiasm for creating new biological treatments for HIES is increasing. These biologics, like monoclonal antibodies directed at particular cytokines or immune cell populations, provide precise and powerful immune regulation, potentially offering better safety and effectiveness than standard therapies [99].

Emerging therapies, including gene therapy and targeted immunomodulation, are under investigation to provide more definitive treatments. As of now, no gene therapies have advanced to clinical trials specifically for HIES, and targeted immunomodulation therapies like omalizumab are not approved for HIES treatment, though some off-label use has been reported [100]. Table 2 summarize the clinical trials therapies and their current status:

TABLE 2 | Summary of clinical trials for HIES and various immunodeficiency treatments and their current status (https://clinicaltrials.gov).

NCT number	Study title	Study status	Study results	Conditions	Interventions	Sponsor	Phases	Enrollment	Locations	Start date	Completion date
NCT00260702	Omalizumab to Treat HIES	Completed	No	HIES	Omalizumab	NIAID	1	1	US	2005	2010
NCT02996448	Safety, Tolerability, and Immunogenicity of One Dose of NDV 3 A Vaccine in People With STAT3-Mutated HIES	Terminated	Yes	HIES	NDV-3A	NIAID	2	3	US	2016	2018
NCT00033982	Posaconazole to Treat Invasive Fungal Infections	Completed	No	CGD, HIES	Posaconazole	NIAID	3	50	US	2002	2007
NCT01852370	Sequential Cadaveric Lung and Bone Marrow Transplant for Immune Deficiency Diseases	Enrolling_by_invitation	No	SCID, SCN, CGD, HIES, Hyper IgM Deficiencies, WAS, MSMD, CVID	CD3/CD19 negative allogeneic hematopoietic stem cells	Paul Szabolcs	1, 2	16	US	2013	2026
NCT02629419	CAMB/MAT2203 in Patients With Mucocutaneous Candidiasis	Completed	Yes	CMCC	Amphotericin B	MTNB	2	4	US	2016	2022
NCT01176006	Pilot Study of Reduced-Intensity Hematopoietic Stem Cell Transplant of DOCK8 Deficiency	Recruiting	No	DOCK8 Deficiency	Reduced-intensity hematopoietic stem cell, TBI, Donor peripheral blood stem cell mobiliation and collection, bone marrow harvest Procedure DRUG: fludarabine, cyclophospha-mide, busulfan	NCI	2	108	US	2010	2026

Note: SCID: Severe Combined Immunodeficiency; CGD: Chronic Granulomatous Disease; WAS: Wiskott-Aldrich Syndrome; CVID: Common Variable Immune Deficiency; MSMD: Mendelian Susceptibility to Mycobacterial Disease; NIAID: National Institute of Allergy and Infectious Diseases; MTNB: Matinas BioPharma Nanotechnologies Inc.; NCI: National Cancer Institute; TBI: Total Body Irradiation; US: United States; SCN:Severe Chronic Neutropenia; SCID: Severe combined immunodeficiency; CMCC: Chronic mucocutaneous candidiasis.

To make the future research section more impactful, it could emphasize the need for large-scale, multicenter studies to better understand and manage HIES. Collaborative efforts across institutions need to focus on standardizing diagnostic tools to help identification of HIES earlier and more accurately, testing new therapies, like biologics and gene treatments, in larger and more diverse groups of patients, investigating how genetic and environmental factors influence the severity of the condition, allowing for more personalized care, creating patient registries and biobanks to track long-term data and support future research, exploring innovative treatments, such as targeted immune therapies and advanced stem cell techniques.

1.20 | Epidemiology, Global Burden and Causes of Death

HIES is rare and due to its rarity, accurate epidemiological data on HIES prevalence rates are limited. HIES can affect individuals of all ethnicities, and genders. The estimated prevalence of HIES ranges from 1 in 100,000 to 1 in 1,000,000 individuals worldwide with equal sexual preponderance. On the other hand the incidence of HIES is about 6 to 10 cases per year, making it a highly uncommon condition [58].

However, these prevalence estimates may be conservative, as under diagnosis and misdiagnosis of HIES can occur due to its variable clinical presentation and overlapping features with other immunodeficiency disorders. Furthermore, advances in genetic testing and increased awareness of HIES may lead to higher reported prevalence rates in the future. Despite its rarity, HIES has been reported in populations worldwide, suggesting a global distribution of the syndrome [101–104]. However, comprehensive epidemiological studies investigating the geographic distribution of HIES on a global scale are limited, highlighting the need for further research to elucidate regional variations in disease prevalence and incidence.

Geographic distribution patterns of HIES may vary, with some regions reporting higher concentrations of cases than others. Studies have suggested that consanguinity and genetic founder effects may contribute to the clustering of HIES cases in certain populations or communities. For example, higher prevalence rates of HIES have been reported in regions with a high prevalence of consanguineous marriages, such as certain Middle Eastern countries and communities with close-knit social structures [105, 106]. Another factor that impact the prevalence of HIES is that there are patients who show clinical and laboratory characteristics that align with HIES, yet no known mutations are detected in their genetic tests. This implies that there might be genes related to HIES that have not yet been discovered [58, 107].

The primary factors leading to mortality in individuals with HIES involve respiratory failure stemming from frequent pneumonia episodes, resulting in complications like pneumatocele and lymphoma [108]. Additionally, the presence of cystic lungs predisposes them to secondary infections by Gram-negative bacteria and fungi, contributing to mortality through pulmonary fungal invasion and widespread dissemination throughout the body [58]. Pulmonary fungal vascular invasion with fatal hemorrhage, metastatic fungal disease to the brain caused by Aspergillus fumigatus and Scedosporium prolificans, renal tubular injury more likely resulted from amphotericin B toxicity, glomerulosclerosis and kidney angiomyolipomas were reported as causes of death in HIES patients [108].

2 | Conclusion

Despite its rarity, HIES imposes a significant burden on affected individuals, their families, and healthcare systems. The complex medical and immunological manifestations of HIES, including recurrent infections, dermatological complications, pulmonary complications, and immunological abnormalities, can lead to chronic morbidity, impaired quality of life, and increased healthcare utilization. Individuals with HIES may require lifelong medical management, including antimicrobial prophylaxis, immunomodulatory therapy, and supportive care measures, placing a substantial burden on patients and their families in terms of treatment adherence, healthcare costs, and psychosocial impact. The diagnosing and managing of HIES can be quite challenging because of its varied presentation or heterogeneous nature. Its diagnosis and management may pose challenges for healthcare providers, leading to delays in diagnosis, misdiagnosis, and suboptimal care. However there are some treatment targets and management approaches, providing optimism for enhanced outcomes and quality of life. Also, ongoing research needs to be considered to elucidate the distribution and burden of the syndrome across diverse populations. Finally, it worth to mention that addressing the global burden of HIES requires a multifaceted approach involving increased awareness, improved access to diagnostic and therapeutic resources, newborn screening, and enhanced support services for affected individuals and their families.

Author Contributions

Mohammad Salehi: methodology, conceptualization, investigation, resources, writing – original draft, writing – review and editing, visualization. **Zeinab Neshati:** supervision, validation, writing – review and editing. **Hamid Ahanchian:** supervision, writing–review and editing. **Rana Tafrishi:** writing – review and editing. **Alireza Pasdar:** conceptualization, methodology, supervision, validation, writing – review and editing. **Mojtaba Safi:** supervision. **Ehsan Ghayoor Karimiani:** supervision.

Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. The datasets (Table 1) generated during the current study are available from the corresponding author upon request.

Transparency Statement

The lead author Zeinab Neshati, Rana Tafrishi affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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