Review Article

Celiac Disease and Type 1 Diabetes in Families: A Systematic Review of Genetic Association

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ABSTRACT

Type 1 Diabetes (T1D) and Celiac Disease (CeD) often co-occur, indicating a shared genetic predisposition. This systematic review synthesizes current evidence on their genetic relationship, highlighting familial risk implications. A thorough search across databases including PubMed/MEDLINE and SCOPUS led to the inclusion of eleven studies that investigated the genetic link between these conditions. Notably, the Human Leukocyte Antigen (HLA) region, particularly the DQ2 and DQ8 haplotypes, emerged as the primary shared genetic risk factor. Additionally, specific HLA class II and I alleles were found to modulate the risks further associated with both diseases. Beyond HLA, non-HLA gene polymorphisms, such as those in PTPN22, INS, and MSH5, contribute to the shared susceptibility and distinguish between T1D alone and T1D with CeD. The review indicates an underlying immune dysregulation characterized by altered cytokine levels and suggests molecular mimicry as a potential mechanism due to homologous epitopes present in the auto-antigens of both conditions. The findings reflect a complex genetic architecture primarily centered on the HLA region, alongside relevant non-HLA immune-related genes, explaining the familial aggregation of T1D and CeD. While universal HLA screening for T1D may not be economically viable, targeted HLA genotyping, particularly when integrated with additional risk markers, is promising for identifying high-risk individuals for CeD, facilitating proactive monitoring, and stratifying familial risk.

Keyword: Celiac Disease, Type 1 Diabetes, Genetic Association, Systematic Review, HLA, Autoimmunity, Familial Risk.

Introduction

Two of the most prevalent immune-mediated diseases are type 1 diabetes (T1D) and celiac disease (CeD), which have a known tendency to co-occur in both people and families. The hallmark of type 1 diabetes is the autoimmune death of beta cells in the pancreas that produce insulin, which results in insulin dependent that lasts a lifetime [1].

In people who are genetically predisposed, gluten consumption causes CeD, an immune-mediated enteropathy that causes inflammation and small intestinal villous atrophy [2]. While these conditions affect different organ systems, their epidemiological overlap is significant and cannot be attributed to chance alone.

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The frequency of CeD in people with T1D is significantly greater than in the general population, according to population-based research; estimates range from 3 to 16%, while in many Western countries it is just about 1% [3, 4]. The genetic predisposition underlying both T1D and CeD provides the strongest evidence for a same etiological mechanism. The most significant genetic area that confers risk for both disorders is the human leukocyte antigen (HLA) complex on chromosome 6. In particular, certain HLA class II molecules play a crucial role in exposing T-cells to antigens, which starts the autoimmune cascade. The HLA-DQ2.5 (DQA1*05:01/DQB1*02:01) or HLA-DQ8 (DQA1*03:01/DQB1*03:02) heterodimers are present in more than 95% of individuals with CeD [5]. Similarly, the main genetic risk factors for T1D are the HLA-DR3-DQ2 and HLA-DR4-DQ8 haplotypes [6]. This shared genetic background, particularly the HLA-DQ2/DQ8 haplotypes, provides the fundamental immunological basis for the observed comorbidity, creating a permissive environment where the immune system is predisposed to mount an attack against both pancreatic islets and the small intestinal mucosa. Genome-wide association studies (GWAS) have shown a large number of non-HLA genetic loci that contribute to the vulnerability of both T1D and CeD in addition to the well-established HLA correlations, further solidifying their genetic overlap. Genes such as CTLA4, PTPN22, *IL2-IL21*, and SH2B3 have been implicated in both diseases, highlighting shared pathways involved in T-cell regulation, immune tolerance, and inflammatory responses [7, 8]. These shared non-HLA loci, while individually conferring smaller risks than the HLA alleles, act in a cumulative manner to shape the overall genetic risk profile. This polygenic architecture explains why not all individuals with HLA risk haplotypes develop either disease, and why some develop both. The familial aggregation of T1D and CeD is a direct consequence of this inherited genetic load, where first-degree relatives of probands with one autoimmune condition exhibit a significantly increased risk of developing the other [9]. This systematic review's goal is to thoroughly assess and summarize the available data about the genetic link between Type 1 Diabetes and Celiac Disease, with an emphasis on research that offers insights into familial risk.

Methods

To guarantee a clear and thorough reporting of the methods and results, this systematic review was carried out strictly in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria [10]. Finding, assessing, and synthesizing all available data examining the genetic relationship between Type 1 Diabetes (T1D) and Celiac Disease (CeD) in familial contexts was the main goal. Using the main electronic bibliographic databases, such as PubMed/MEDLINE, Web of Science, SCOPUS, and Embase, a methodical search approach was created and implemented. MeSH headings and other controlled vocabulary phrases were used in the search, along with free-text keywords associated with "Celiac Disease," "Type 1 Diabetes," "genetics," "HLA," and "families." The search was limited to studies published in the English language to mitigate risks associated with translation inaccuracies, though no date restrictions were applied to capture the full scope of the literature. Eligibility Criteria: The study selection process was guided by pre-defined eligibility criteria. For inclusion, studies were required to be original research articles that explicitly investigated the genetic link between CeD and T1D. This included studies focusing on shared genetic susceptibility, such as those analyzing HLA haplotypes (e.g., DQ2, DQ8) and non-HLA gene polymorphisms in patient cohorts with either or both conditions. The population of interest included individuals and families affected by CeD, T1D, or their co-occurrence. Every research type that provided primary genetic data was taken into account, including cross-sectional analyses, case-control studies, cohort studies, and family-based studies. Studies including narrative reviews, editorials, comments, and case reports that did not include original genetic data were not included in our analysis, Studies that focused solely on the clinical prevalence of the co-morbidity without genetic analysis, or those published in languages other than English, were also eliminated in order to preserve the data extraction and evaluation process's dependability and consistency. Data Extraction: All of the records that were found through database searches were loaded into the Rayyan systematic review program (QCRI) in order to guarantee a thorough and objective screening procedure [11]. The titles and abstracts of every reference that was found were first checked against the inclusion and exclusion criteria by two separate reviewers. Studies deemed potentially relevant by either reviewer were advanced to a full-text review. At the full-text stage, both reviewers independently assessed the complete articles for final inclusion. Discussion and consensus were used to settle any disputes or disagreements about a study's eligibility,

with the option to contact a third reviewer if needed. A consistent, piloted data extraction form was used to obtain data from each included study. The extracted data included participant demographics, study characteristics (country, design, sample size), bibliographic information (first author, year of publication), specific genetic markers analyzed (e.g., HLA alleles, SNPs in non-HLA genes), and the main conclusions regarding the genetic association between CeD and T1D. Data Synthesis Strategy: Given the anticipated heterogeneity in the studied populations, genetic markers, and methodological approaches, a narrative synthesis was deemed the most appropriate method for summarizing the evidence. To give a concise and structured summary of the study's features and conclusions, the collected data were arranged into summary tables. These tables facilitate a comparative analysis across studies, allowing for the identification of consistent patterns, shared genetic loci, and any divergent results. The synthesis focused on qualitatively describing the strength and consistency of the evidence for various HLA and non-HLA genetic associations, the implications for familial risk, and the potential for genetic risk stratification. Risk of Bias Assessment: Two independent reviewers used an appropriate technique for observational studies to objectively evaluate the included studies' methodological quality and risk of bias. The Joanna Briggs Institute (JBI) critical assessment checklists were modified for this use, as explained in the section above [12].

Results

Through database scanning, 452 records in all were found. Following the elimination of 290 duplicates, 162 entries were examined using the abstract and title, leading to the exclusion of 130 records. The full text of 32 reports was sought for retrieval, of which 29 were successfully assessed for eligibility. Following a detailed evaluation, 18 reports were excluded due to wrong outcomes, wrong population, or being letters to the editor, resulting in 11 studies meeting the inclusion criteria for final synthesis in the review as illustrated in (Figure 1). As seen in (Table 1), the studies were predominantly conducted across Europe and the Middle East, including Sweden [13, 14], Poland [17, 21, 23], Italy [16], India [15], Iran [18], Saudi Arabia [19], Portugal [20], and Spain [22], providing a diverse geographical perspective. The research designs were largely observational, featuring case-control [13, 14, 15, 17, 18, 19], cross-sectional [23], and retrospective cohort studies [20, 21, 22], with one Sardinian study employing a large cohort design [16]. The sample sizes varied considerably, ranging from a focused analysis of 35 children in a Portuguese study [20] to a comprehensive cohort of 1,886 individuals in the Sardinian research [16]. The studied populations were exclusively pediatric or adolescent, focusing on individuals with T1D, CeD, or the co-occurrence of both conditions (T1D+CD), alongside healthy control groups in several studies [15, 17, 18]. The genetic and immunological findings of these studies, summarized in (Table 2), overwhelmingly confirm a strong shared genetic basis between CeD and T1D, primarily centered on the Human Leukocyte Antigen (HLA) complex. Multiple studies consistently demonstrated that a vast majority of patients with both diseases carry the well-established risk haplotypes HLA-DQ2 and/or HLA-DQ8 [16, 19, 20, 21, 22], with the absence of these haplotypes effectively ruling out the risk of CeD in T1D patients [21]. Beyond this confirmation, higher-resolution genotyping revealed more nuanced associations. For instance, Swedish studies identified specific HLA class I alleles (A29:02:01, C05:01:01) [13] and HLA class II alleles (DRB4*01:03:01) [14] as conferring shared risk, while the DR4-DQ8 haplotype was significantly elevated in patients with both diseases [14]. Furthermore, research from Poland suggested that the presence of the DRB1*04 allele might actually modulate and reduce the risk of developing CeD within a T1D population [23]. HLA region is not the only area of genetic interaction. Research conducted in North India [15] found that non-HLA gene polymorphisms (PTPN22 and INS) might aid in differentiating between individuals with T1D alone and those with T1D+CD, in addition to confirming shared HLA susceptibility (DRB1*03:01, *04, and DQB1*02). In the same way, a Polish research [17] found that combining HLA typing with a variant in the MSH5 gene (rs3130484) significantly improved the sensitivity and accuracy for predicting CeD in T1D patients compared to HLA testing alone. At the level of gene expression, an Iranian study [18] provided functional insights, showing a shared pattern of immune dysregulation in CeD, T1D, and comorbid cases, characterized by significantly increased TNF-α mRNA and decreased CTLA4 mRNA levels. This aligns with the finding of homologous epitopes between T1D and CeD autoantigens, suggesting a molecular mimicry mechanism that could trigger a cross-reactive autoimmune response [15]. It is not solely dictated by the presence of HLA-DQ2/DQ8 but is modulated by specific HLA alleles from other loci [13, 14, 23], non-HLA genes [15, 17], and downstream immune effector mechanisms [15, 18]. The practical

implications are significant; while some studies question the cost-effectiveness of routine HLA screening due to the high prevalence of risk haplotypes in T1D populations [22], others strongly advocate for its utility. They posit that HLA genotyping, especially when combined with other genetic markers, can stratify risk, exclude future disease development, and identify children with CeD who are at a high risk of progressing to T1D, thereby enabling proactive monitoring and potential early intervention [16, 19]. (Table 3) summarizes the risk of bias assessment for 11 studies. The overall judgment is consistently "Low" risk of bias for all studies. The main weakness across the majority of studies (8 out of 11) is related to criteria D5 and D6, which were consistently rated "No." This indicates a specific, common methodological limitation, while other domains (D1-D4, D7, D8) were well addressed.

Discussion

Our findings, derived from eleven focused studies, robustly confirm that the co-occurrence of these autoimmune conditions is not a random association but is fundamentally driven by a complex interplay of shared and distinct genetic factors, mostly in non-HLA genes and mostly in the Major Histocompatibility Complex (MHC). The body of data suggests that although the fundamental genetic basis for this connection is the existence of HLA-DQ2/DQ8 haplotypes, the exact risk is influenced by particular allelic combinations, genes other than those involved in the HLA complex, and the ensuing dysregulation of immunological pathways. The primary genetic susceptibility site for both CeD and T1D is the HLA class II area, more especially the DQ2 (DQA1*05:01/DQB1*02:01) and DQ8 (DQA1*03:01/DQB1*03:02) haplotypes. This is the most noteworthy result from our research. Zubkiewicz-Kucharska et al. studies [21] and Leite et al. [20] showed that these risk haplotypes were present in more than 87% and 71% of their respective T1D cohorts, with all diagnosed CeD cases found within this genetically predisposed group. This aligns perfectly with established literature, where these haplotypes are present in over 90% of CeD patients and confer a significant portion of the genetic risk for T1D [24]. However, our review moves beyond this established paradigm by highlighting the critical importance of high-resolution genotyping. The work of Alshiekh et al. [14] revealed that specific alleles in other HLA class II loci, such as DRB4*01:03:01, confer a particularly strong risk for the development of both diseases concurrently (T1D w/CD). Furthermore, the discovery that the DRB1*04 allele, often linked to the DQ8 haplotype, may actually exert a protective effect against the development of full-blown CeD in T1D patients, as suggested by Deja et al. [23], introduces a crucial nuance. This suggests that the genetic risk is not monolithic but is fine-tuned by epistatic interactions within the MHC, a concept supported by a large-scale genetic study that identified specific amino acid residues in HLA-DQ molecules that independently influence risk for both diseases [25]. Perhaps one of the most significant advancements highlighted in this review is the exploration of HLA class I associations, an area less frequently investigated. The finding by Alshiekh et al. [13] that HLA class I alleles A29:02:01 and C05:01:01 are associated with both T1D and CeD provides a compelling new dimension to the shared genetic landscape. CD8+ T-cells, which are important effector cells in the death of pancreatic beta cells in T1D and may also be involved in the cytotoxic response to gliadin in CeD, are presented intracellular antigens by HLA class I molecules. This implies that the shared genetic risk extends beyond the helper T-cell response orchestrated by HLA class II to include the cytotoxic T-cell arm of the adaptive immune system. Recent genome-wide association studies (GWAS) that have shown signals in the HLA class I area that contribute to the genetic overlap between these disorders support this conclusion [26]. Beyond the MHC, our review identifies several non-HLA genes that contribute to the shared autoimmune diathesis. The study by Kaur et al. [15] from North India showed that SNPs in the PTPN22 and INS genes may distinguish between individuals with T1D alone and those with T1D and CeD, in addition to confirming shared HLA vulnerability. One known risk factor for a number of autoimmune disorders is the PTPN22 gene, which codes for a lymphoid-specific phosphatase and is believed to affect T-cell receptor signaling and tolerance [27]. Similarly, the investigation by Wysocka-Mincewicz et al. [17] into the MSH5 gene variant (rs3130484) is highly instructive. Their finding that combining this non-HLA variant with HLA-DQ2/DQ8 typing significantly improved the predictive sensitivity for CeD in T1D patients underscores the polygenic nature of this association. This multi-gene risk model is a cornerstone of modern complex disease genetics, where the cumulative effect of many risk variants, each with a small individual effect, determines overall susceptibility [28]. The functional consequences of these genetic predispositions are reflected in the altered immune

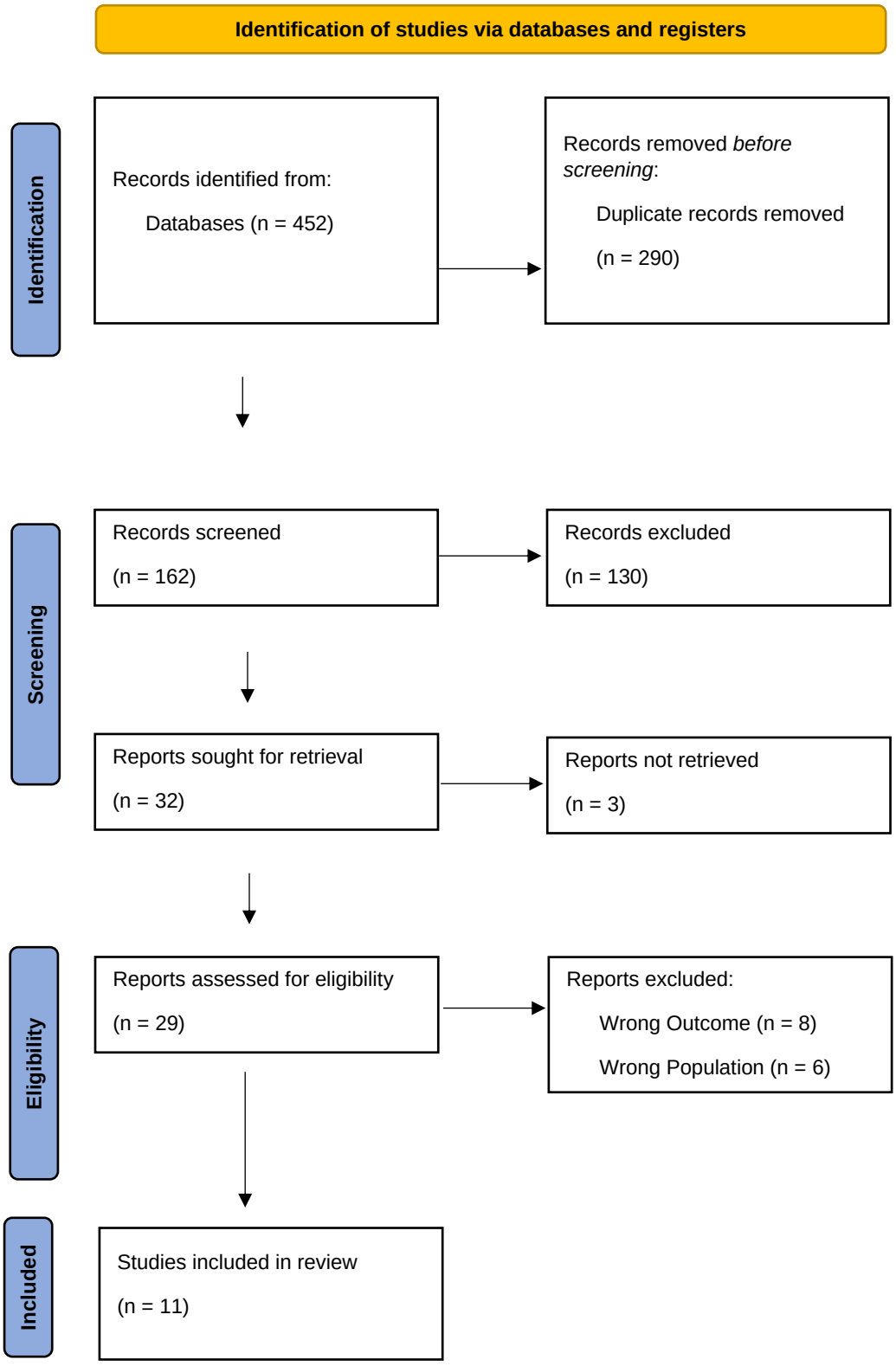

Figure 1: PRISMA Flow Diagram of the Study Selection Process.

Table 1: Demographic and study characteristics of the included studies.

Study (Author, Year) [Ref]	Country	Study Design	Sample Size	Study Population Description	Key Demographics (Age, Gender)
Alshiekh S, 2021 [13]	Sweden	Case-Control	294	Children from a high-risk birth cohort: 68 with T1D, 219 with CD, 7 with T1D+CD.	NM (Children from a birth cohort)
Alshiekh S, 2021 [14]	Sweden	Case-Control	294	Children from a high-risk birth cohort: 68 with T1D, 219 with CD, 7 with T1D+CD.	NM (Children from a birth cohort)
Kaur N, 2024 [15]	India (North)	Case-Control	300	100 with T1D, 50 with T1D+CD, 150 healthy controls.	NM
Schirru E, 2024 [16]	Italy (Sardinia)	Cohort	1,886	822 with CD, 1,064 with T1D, 627 controls. 76 had both CD and T1D (CD-T1D).	NM
Wysocka-Mincewicz M, 2022 [17]	Poland	Case-Control	799	248 pediatric T1D patients (20 with CD), 551 healthy controls.	Pediatric population
Malekahmadi S, 2024 [18]	Iran	Case-Control	104	29 CD, 29 T1D, 16 CD+T1D, 30 healthy controls.	NM
Al-Hussaini A, 2024 [19]	Saudi Arabia	Case-Control	291	67 T1D with CD (cases), 224 T1D without CD (controls).	Mean age: Cases 15y, Controls 18.29y
Leite L, 2021 [20]	Portugal	Retrospective	35	Children with T1D diagnosed under 6 years of age.	Median age: ~47 months; 72% Female
Zubkiewicz-Kucharska A, 2022 [21]	Poland	Retrospective	166	Children and adolescents with T1D (16 with CD).	91 girls, 75 boys; Pediatric population
Roldán Martín MB, 2021 [22]	Spain	Retrospective	296	T1D patients aged <18 years (23 with CD).	148 girls, 148 boys; Pediatric population
Deja G, 2020 [23]	Poland	Cross-Sectional	145	Three T1D groups: Newly diagnosed (n=92), with CD+villous atrophy (n=30), with potential CD (n=23).	Pediatric population

Table 2: Genetic and Immunological Findings of the Included Studies.

Study (Author, Year) [Ref]	Key Genetic Variables / Markers Analyzed	Main Findings Related to Genetic Association
Alshiekh S, 2021 [13]	HLA Class I (A, B, C) alleles	A*29:02:01 and C*05:01:01 were associated with both T1D and CD, indicating a shared HLA Class I risk.
Alshiekh S, 2021 [14]	HLA Class II (DRB3, DRB4, DRB5, DRB1, DQA1, DQB1)	DRB4*01:03:01 conferred the strongest risk for T1D+CD. The DR4-DQ8 haplotype was significantly higher in T1D+CD.
Kaur N, 2024 [15]	HLA-DRB1/DQB1, CTLA-4, PTPN22, INS-23 Hph1 A/T, Autoantibodies, Cytokines	Shared association of DRB1*03:01, *04, DQB1*02. PTPN22 and INS polymorphisms could discriminate between T1D and T1D+CD. Epitope homology between T1D and CD autoantigens was found.
Schirru E, 2024 [16]	HLA Class II (DQ2.5, DQ8, DQ2.3)	High-risk genotypes (DQ2.5/DQ8, DQ2.5/DQ2.5, DQ2.5/DQ2.3) were strongly associated with CD-T1D. HLA genotyping can identify CD patients at risk for T1D.
Wysocka-Mincewicz M, 2022 [17]	HLA-DQ2/DQ8, MSH5 rs3130484 variant	Combining MSH5 rs3130484 with HLA-DQ2/DQ8 typing increased test sensitivity and accuracy for CD prediction in T1D patients compared to HLA alone.
Malekahmadi S, 2024 [18]	mRNA expression of TNF-α, IL-6, IL-2, CTLA4	Increased TNF-α and decreased CTLA4 mRNA in CD, T1D, and CD/T1D groups. Altered gene expression highlights shared immune dysregulation.
Al-Hussaini A, 2024 [19]	HLA-DQ Genotypes (DQ2.5, DQ8, DQ2.2)	Homozygous DQ2.5 and DR3-DQ2.5 haplotypes had higher risk for CD in T1D. Only 4% of T1D patients had no-risk genotypes.
Leite L, 2021 [20]	HLA (DR3-DQ2, DR4-DQ8, DR7-DQ2, DR5-DQ7)	71% (25/35) of T1D children had genetic predisposition (DQ2/DQ8). All diagnosed CD cases were in the HLA-positive group.
Zubkiewicz-Kucharska A, 2022 [21]	HLA DQ2/DQ8 Haplotypes	87.3% of T1D patients were HLA DQ2 and/or DQ8 positive. All CD patients were positive, and no HLA-negative child had CD.
Roldán Martín MB, 2021 [22]	HLA DQ2/DQ8 Haplotypes	DQ2 or DQ8 alleles were found in 91.3% of T1D patients. HLA typing was not cost-effective for CD screening due to high frequency of risk haplotypes.
Deja G, 2020 [23]	HLA DQ2/DQ8, DRB1*04 allele	DRB1*04 allele was significantly less common in T1D+CD and modulated CD risk, predicting a potential form of CD.

Table 3: Risk of Bias Assessment for Included Studies.

Study (Author, Year) [Ref]	D1	D2	D3	D4	D5	D6	D7	D8	Overall Risk of Bias
Alshiekh S, 2021 [13]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Low
Alshiekh S, 2021 [14]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Low
Kaur N, 2024 [15]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low

Schirru E, 2024 [16]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Low
Wysocka-Mincewicz M, 2022 [17]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Low
Malekahmadi S, 2024 [18]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Low
Al-Hussaini A, 2024 [19]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Leite L, 2021 [20]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Low
Zubkiewicz-Kucharska A, 2022 [21]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Low
Roldán Martín MB, 2021 [22]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Low
Deja G, 2020 [23]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Low

profiles observed in the reviewed studies. Malekahmadi et al. [18] showed a same pattern of reduced immunoregulatory CTLA4 mRNA and elevated pro-inflammatory TNF-α mRNA in the peripheral blood of individuals with CeD, T1D, and the comorbid disease, providing direct evidence of common immune dysregulation. This points to a shared genetic background that probably primes a state of immunological hyper-reactivity and poor control. The work conducted by Kaur et al. provides the most fascinating mechanistic insight [15], which reported significant homology between immunodominant epitopes of T1D and CeD autoantigens. This finding provides a plausible molecular basis for the co-occurrence of the diseases through the mechanism of epitope spreading or molecular mimicry, where an immune response initially directed against one antigen (e.g., gliadin) can diversify to target structurally similar self-antigens (e.g., GAD65 in pancreatic islets) [29]. This is further supported by the clinical finding from Saadah et al. (2020), which, although excluded from our final genetic analysis, reported a high prevalence of diabetes-associated autoantibodies (GADA) in children with CeD, indicating a subclinical autoimmune response against pancreatic islets in a significant proportion of genetically susceptible individuals [30]. The translational implications of these genetic findings are profound. The high frequency of HLA risk haplotypes in T1D populations, reported at 91.3% by Roldán Martín et al. [22], leads to the valid argument that HLA typing is not a cost-effective universal screening tool for CeD, as the vast majority of patients would still require ongoing serological surveillance. However, the counter-argument, powerfully made by Schirru et al. [16], is that HLA genotyping in children already diagnosed with CeD can effectively stratify their future risk for T1D. Their cohort study demonstrated that specific high-risk genotypes (e.g., DQ2.5/DQ8) were strongly associated with the progression to T1D, thereby identifying a subpopulation that would benefit from intensified monitoring for islet autoantibodies and participation in prevention trials. This proactive, genotype-guided approach represents a paradigm shift from reactive screening to personalized risk prediction and prevention. Limitations: Despite the impressive outcomes, this review has some shortcomings. First off, the findings were not as applicable to other ethnic groups, such as those of African or East Asian heritage, where the prevalence of both diseases and the HLA association can vary significantly, because most of the included studies were conducted in populations in Europe and the Middle East. Secondly, a common methodological limitation observed across most studies was the lack of comprehensive identification and statistical adjustment for potential confounding factors, such as age at onset, disease duration, dietary habits, and microbiome composition. While genetic associations are less susceptible to confounding than environmental ones, this remains a potential source of bias. Thirdly, the focus of this review was on genetic association, and thus, it does not fully capture the critical role of environmental triggers (e.g., viral infections, gluten timing) that are necessary to initiate the autoimmune process in genetically predisposed individuals. Finally, for some of the newer genetic associations reported (e.g., MSH5, HLA class I alleles), independent replication in larger, diverse cohorts is still needed to confirm their validity and effect size.

Conclusion

The study highlights the frequent co-occurrence of Type 1 Diabetes (T1D) and Celiac Disease, emphasizing their shared autoimmune nature and strong hereditary basis, particularly linked to the HLA region's DQ2 and DQ8 haplotypes. The genetic

complexity is enriched by specific HLA alleles and non-HLA genes like MSH5, INS, and PTPN22, contributing to immune dysregulation and potential cross-reactivity. Clinically, while universal HLA screening for T1D may be impractical, targeted genetic testing is promising for identifying individuals at high risk for monitoring and preventive measures. Future research should involve diverse cohorts to further clarify genetic and environmental pathways to disease.

Conflict of Interest

None

Funding

None

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