Logical Creations Education Research Institute
MADER E MILAT INTERNATIONAL JOURNAL OF NURSING AND ALLIED SCIENCES
E-ISSN: 2960-2181
Web: www.minasij.com | Email: editor@minasij.com
Volume-03 | Issue-03 | September-2025

HLA-DQ2 Heterozygosity in Symptomatic Adults from Balochistan: A Case Series Supporting Coeliac Disease Diagnosis

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DOI: 10.5281/zenodo.17461890

ABSTRACT

Background: Coeliac disease (CD) is an immune-mediated enteropathy triggered by gluten ingestion in genetically susceptible individuals. The presence of HLA-DQ2 and/or HLA-DQ8 haplotypes is a major genetic predisposing factor, with HLA-DQ2.5 showing the strongest association. In Pakistan, particularly in resource-limited regions such as Balochistan, CD remains underdiagnosed due to limited access to genetic testing and awareness of its clinical spectrum.

Objective: This case series aims to describe the clinical and genetic findings of three adult patients from Balochistan presenting with symptoms suggestive of coeliac disease, confirmed by the presence of HLA-DQ2 heterozygosity through whole blood genotyping.

Methods: Whole blood samples were collected from three symptomatic adults with chronic gastrointestinal complaints and malabsorptive features. HLA-DQA1 and HLA-DQB1 alleles were analyzed using standard genotyping techniques to determine the presence of HLA-DQ2 and HLA-DQ8 haplotypes. The allelic combinations were assessed to identify high-risk variants, particularly the DQ2.5 heterodimer.

Results: All three patients demonstrated heterozygous HLA-DQ2 haplotypes. One individual was identified as carrying the high-risk DQ2.5 combination (DQA1*05 and DQB1*02* alleles). Clinical features—including chronic diarrhea, weight loss, anemia, and fatigue—were consistent with coeliac disease in all cases. Symptomatic improvement was noted following the initiation of a gluten-free diet, further supporting the diagnosis.

Conclusion: This case series provides molecular evidence of HLA-DQ2 heterozygosity among symptomatic adults in Balochistan and reinforces the diagnostic relevance of HLA genotyping in suspected coeliac disease. Expanding access to genetic testing and increasing clinical awareness can enhance early detection and management of CD in underserved populations. Early identification of genetically at-risk individuals may significantly improve patient outcomes through timely dietary interventions and prevention of long-term complications.

Keywords: Celiac disease, HLA-DQ2, HLA-DQ8, HLA-DQ2.5, HLA-DQ2.2, Balochistan.

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Cite as: Mohammad Usman Tareen, Khan Mohammad Babar, Mohsin Ali Hassni, Abdul Malik, Sayyad Monawar Anwar, Aslam Buzdar (2025). HLA-DQ2 Heterozygosity in Symptomatic Adults from Balochistan: A Case Series Supporting Coeliac Disease Diagnosis. *Mader e Milat International Journal of Nursing and Allied Sciences, 3*(3), 16–25. https://doi.org/10.5281/zenodo.17461890

INTRODUCTION

Celia is an immune mediated illness of intestine cased with typical symptoms of diarrhea vomiting, constipation and weight loss. It is a genetic disease as evidence shows many biochemical pathways and cause have connection. Many genes very evaluated in past years but a detail analysis is pending to find out gaps and more understanding of genetic factors contributing in pathology of this diseases. This disease is life longing disorder in European population and effecting 1% of population (1,2). Celia diseases cases are also prevalent in Africa and Middle East. American population has prevalence of (5.6-11.1%)due to genetic and dietary changes.HLA-DQ2 and HLA-DQ8 are more prevalent in developed countries (3).The presence of HLA-DQ2 and/or HLA-DQ8 haplotypes is a key genetic marker, with HLA-DQ2.5 being the most strongly associated. In Pakistan, particularly in underserved regions like Balochistan, genetic screening for CD remains limited.

Tables should be numbered sequentially editable using Arabic numerals (e.g., Table 1, Table 2), and each table should have a descriptive title. The table number and title should be typed in bold, single-spaced, and centered across the top of the table, in 11-point Times New Roman, as shown below.

Background

The section Coeliac disease (CD) is an immune-mediated enteropathy activate by gluten consumption in genetically predisposed individuals. The presence of HLA-DQ2 and/or HLA-DQ8 haplotypes is a key genetic marker, with HLA-DQ2.5 being the most strongly associated. In Pakistan, particularly in underserved regions like Balochistan, genetic screening for CD remains limited.

Objective

To report a case series of three patients from Balochistan with clinical suspicion of coeliac disease and confirmed HLA-DQ2 heterozygosity through whole blood genotyping.

LITERATURE REVIEW

Review of Relevant Theories

The autoimmune enteropathy known as Coeliac Disease (CD) is widely understood through the lens of immune-genetic interaction theory, in which dietary gluten acts as the environmental trigger in genetically predisposed individuals. Central to this paradigm is the role of major histocompatibility complex (MHC) class II molecules, specifically the human leukocyte antigen (HLA)-DQ family. In CD, the most strongly associated haplotypes are those encoding the heterodimeric molecules HLA-DQ2.5 (encoded by HLA-DQA1*05* + *HLA-DQB1*02), and less frequently HLA-DQ8 (HLA-DQA1*03* + *HLA-DQB1*03:02) or, in some cases, HLA-DQ2.2 (HLA-DQA1*02* + *HLA-DQB1*02).

Mechanistically, the "gluten-HLA-T-cell" theory holds that gluten-derived, deamidated gliadin peptides bind preferentially to the antigen-binding groove of DQ2.5 (and to a lesser extent DQ8), leading to presentation to $CD4^+$ T cells in the lamina propria. This triggers a cascade of pro-

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inflammatory cytokine release (e.g., interferon-γ) and subsequent intestinal mucosal damage, characteristic intra-epithelial lymphocytosis and villous atrophy.

Another theoretical strand is the gene-dose effect: patients homozygous or compound heterozygous for high-risk HLA genotypes (e.g., DQ2.5/DQ2.5 or DQ2.5/DQ2.2) tend to have greater antigen-presenting capacity of the "permissive" heterodimer, thereby increasing the likelihood and severity of CD.

Finally, while HLA DQ2/DQ8 haplotypes are necessary but not sufficient for CD development (i.e., they exhibit high negative predictive value but low positive predictive value) — many carriers never develop disease — emerging models incorporate non-HLA genes, microbiome influence, and environmental cofactors (such as gluten load, infections, gut permeability) into a "multi-hit" theoretical framework for CD pathogenesis.

Existing Studies

A broad base of empirical studies supports the preponderant role of HLA DQ2 and/or DQ8 haplotypes in CD. For example, an early meta-analysis of children found HLA-DQB1*02 (which encodes the β-chain of DQ2) conferring an odds ratio (OR) of ~10.3, and DQB1*03:02 (DQ8) an OR ≈ 2.24 for CD risk. (PubMed) In adult populations, a systematic review and meta-analysis revealed that heterozygous HLA DQ2 carriers had an increased risk (OR ~1.54; 95% CI 0.86-2.73) though with substantial heterogeneity (I^2 ~94 %). A key large-cohort adult study of over 24,000 patients found that HLA-DQ2 homozygosity conferred very high odds for tTG-IgA positivity (OR ≈96.9; 95% CI 58.3–147.9), whereas simple DQ2.2 heterozygosity did *not* appear to raise risk significantly.

In Pakistani settings, the evidence is more limited but supportive. A study in Rawalpindi found that among 100 diagnosed CD patients vs 100 controls, HLA-DQ2 was present in 93% of cases and 20% of controls; of DQ2 positive patients, DQ2.5 subtype was seen in ~92% and DQ2.2 in ~8%. (JCPSP) Another Pakistani study in children (n=50) found 82% DQ2, 10% DQ8, and 2% DQ2/DQ8 in CD patients, compared to 8% DQ2 in controls, with statistically significant differences. (Pakistan Armed Forces Medical Journal) Regionally in the Middle East, a Saudi population study in healthy children found that 52.7% carried CD-predisposing HLA-DQ genotypes (heterozygous DQ2.5 ~28%, homozygous DQ2.5 ~2.6%).

Beyond genetics, one mechanistic study found that infants carrying HLA-DQ2 had significantly altered early gut microbiota composition (less Bifidobacterium, more Proteobacteria) compared to low-risk infants, suggesting a host-genotype–microbiota interaction in predisposition to CD.

From a diagnostic viewpoint, studies show that HLA-DQ typing has strong value in *excluding* CD (because absence of DQ2/DQ8 argues strongly against CD), but more limited value for *confirming* CD, given the large number of carriers who never manifest disease. For example, one review of adults pointed out that the positive predictive value is low, and HLA testing must not be used in isolation for diagnosis.

Identification of Gaps

Despite considerable research, several gaps remain relevant to the context of symptomatic adult populations in underserved regions such as Balochistan. First, there is a paucity of data from Pakistan overall — one bibliographic review noted only 34 articles on CD in Pakistan (14 pediatric, 14 adult) and none from Balochistan; moreover, most were small case-series or reports, with limited genotyping data.

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Second, while the dose-effect of HLA DQ2.5 homozygosity vs heterozygosity is fairly well described, less is known about heterozygous DQ2 carriage (especially in populations outside Europe) and how this relates to clinical manifestation in adults. For example, the meta-analysis cited earlier found heterozygous DQ2 risk to be non-significant (OR ~1.54; CI crossing unity) although fixed-effect model gave significance.

Third, most studies focus on children or mixed age populations; the adult symptomatic population (particularly in under-resourced regions) has been less examined with respect to HLA genotype, clinical correlation, and utility of genotyping as a diagnostic adjunct. Fourth, virtually no studies have specifically addressed heterozygosity for DQ2 (non-homozygous, non-compound high-risk) in adult symptomatic cases from Balochistan or similar underserved areas, nor the diagnostic yield of genotyping in such a context. Fifth, there is limited integration of genotyping with clinical, serologic, histologic and environmental data (such as gluten exposure, local diet, microbiome) in these populations, limiting full contextual understanding. Finally, although the negative predictive value of HLA typing is well-established, its cost-effectiveness, feasibility and acceptability in resource-limited settings are underexplored.

Conceptual Framework

Based on the above theoretical and empirical foundations, a conceptual framework for investigating HLA-DQ2 heterozygosity in symptomatic adults in Balochistan can be proposed as follows:

1. **Genetic predisposition node**: HLA-DQ genotype (presence/absence of DQ2/DQ8; subtype DQ2.5 vs DQ2.2; zygosity status heterozygous/homozygous).
2. **Environmental/Exposure node**: gluten ingestion (typical dietary pattern in the region), co-factors (infections, gut microbiota, nutritional status).
3. **Immune activation node**: presentation of deamidated gliadin peptides via HLA-DQ2/DQ8 → $CD4^+$ T-cell activation → cytokine release (IFN-γ etc) → intestinal mucosal injury (villous atrophy, crypt hyperplasia).
4. **Clinical manifestation node**: symptoms (GI complaints, malabsorption, anemia), serologic markers (anti-tTG, anti-endomysial), histologic findings (Marsh classification).
5. **Diagnostic utility node**: genotyping adds value in symptomatic adults in underserved setting by aiding in risk stratification and decision-making (e.g., whether to proceed to biopsy/gluten challenge).
6. **Contextual/moderator node**: demographic and regional factors (age, gender, nutritional state, local healthcare access, ethnicity), which may modulate the pathway from genotype to phenotype.

In this framework, one hypothesises that in symptomatic adults in Balochistan, presence of HLA-DQ2 (even if heterozygous) interacts with high gluten exposure, possible nutritional deficiencies and enteric stress, culminating in overt CD. Genotyping thereby plays a role not only in exclusion but also in supporting diagnosis, especially when serology/histology are ambiguous or biopsy resources limited.

Summary

In summary, the existing literature robustly supports the centrality of HLA-DQ2 (particularly DQ2.5) and DQ8 haplotypes in coeliac disease risk, with clear mechanistic grounding and empirical confirmation in diverse populations. Yet, gaps remain in adult populations from under-researched regions such as Balochistan, especially concerning heterozygous DQ2 status, genotype-phenotype correlation, and diagnostic utility of genotyping. Employing the above conceptual framework, research

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Volume-03 | Issue-03 | September-2025

(such as your proposed case series) can contribute valuable local data to inform both understanding of CD genetics in Pakistan and practical diagnostic strategies in resource-limited contexts.

METHODOLOGY

Methodology HLA-DQA1 and HLA-DQB1 alleles were typed using whole blood samples from three symptomatic individuals. Allelic combinations were assessed for the presence of HLA-DQ2 and DQ2.5 haplotypes.

Research Design

This descriptive case series was conducted at a tertiary care diagnostic facility in Balochistan, Pakistan, between January and September 2025. The study aimed to evaluate the presence of HLA-DQ2 haplotypes in patients with clinical suspicion of coeliac disease.

Data Collection Methods

Three symptomatic individuals (two males, one female) aged 13 to 56 years were included based on clinical features suggestive of coeliac disease, such as chronic diarrhea, weight loss, abdominal discomfort, and/or iron deficiency anemia. All patients were residents of Balochistan and had no prior diagnosis of autoimmune enteropathy.

Sample Collection

Whole blood samples (3–5 mL) were collected in EDTA tubes under aseptic conditions. Samples were stored at 2–8°C and processed within 24 hours of collection.

HLA Genotyping Procedure

Genomic DNA was extracted using a silica-based column purification method. HLA-DQA1 and HLA-DQB1 alleles were typed using PCR sequence-specific oligonucleotide (PCR-SSO) hybridization, followed by Luminex-based multiplex bead array analysis. Allele assignment was performed using commercial software aligned with WHO HLA nomenclature standards.

Interpretation Criteria

HLA-DQ2 positivity was defined by the presence of DQA1*05:01 and DQB1*02:01 alleles. The DQ2.5 haplotype was considered high-risk for coeliac disease.

Ethical Considerations

Written informed consent was obtained from all participants. Bolan Medical College, Hospital Ethical Committee of research have approved this study.

Data Analysis

The Data is analyzed using SPSS and Excel.

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DATA ANALYSIS AND RESULTS

Results

Table 01. All three patients from Balochistan carried HLA-DQ2 haplotypes—one with the high-risk DQ2.5 genotype.

Case	Age / Sex	Specimen	HLA-DQA1 Alleles	HLA-DQB1 Alleles	HLA-DQ2 Status	Interpretation
1	56 / Male	Whole Blood	05:01, 05:01	02:01, 03:01	Heterozygous DQ2	Genotype consistent with coeliac disease
2	31 / Female	Whole Blood	01:01, 05:01	02:01, 05:03	Heterozygous DQ2	Genotype consistent with coeliac disease
3	13 / Male	Whole Blood	05:01	02:01	Heterozygous DQ2.5	High-risk genotype for coeliac disease

Robustness Test

This section consists of one or more test to check the robustness of the results, to ensure that the results are robust and meaningful.

Analysis

- **Case 1 (56-year-old male)** carried *DQA1*05:01 homozygously* and *DQB1*02:01/03:01*, confirming heterozygous DQ2 status. This genotype supports a moderate to high risk for coeliac disease.
- **Case 2 (31-year-old female)** showed *DQA1*01:01/05:01* and *DQB1*02:01/05:03*, also consistent with heterozygous DQ2. Although DQA1*01:01 and DQB1*05:03 are not risk alleles, the presence of DQA1*05:01 and DQB1*02:01 confirms genetic predisposition.
- **Case 3 (13-year-old male)** carried *DQA1*05:01** and *DQB1*02:01**, forming the high-risk **DQ2.5 heterodimer**, which is the strongest genetic marker for coeliac disease. This genotype is known to present immunogenic gluten peptides to T cells, triggering intestinal inflammation.
- All three patients from Balochistan demonstrated the presence of HLA-DQ2 haplotypes, with one carrying the high-risk DQ2.5 genotype (DQA1*05:01* + *DQB1*02:01), which is strongly associated with gluten-sensitive enteropathy.

Discussion

This case series from Balochistan provides a rare glimpse into the genetic landscape of coeliac disease (CD) in a region where diagnostic infrastructure is limited and awareness remains low. All three symptomatic patients demonstrated heterozygous HLA-DQ2 haplotypes, with one carrying the high-risk DQ2.5 genotype (DQA1*05:01* + *DQB1*02:01), which is globally recognized as the strongest genetic marker for CD**(4)**. The presence of DQ2.5 in the youngest patient (13-year-old male) is

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particularly noteworthy. This genotype is known to present deamidated gluten peptides to CD4+ T cells, triggering the autoimmune cascade that leads to villous atrophy**(5)**. Its identification in a pediatric patient from Balochistan suggests that CD may be underdiagnosed in younger populations due to lack of genetic screening and limited access to gastroenterology services. Case 1 and Case 2 also carried DQ2 alleles, though not the full DQ2.5 heterodimer. Their genotypes still support moderate risk, especially when clinical symptoms such as chronic diarrhea, weight loss, and iron deficiency anemia are present. As Singh et al. noted, even partial DQ2 positivity warrants clinical vigilance, particularly in populations with limited biopsy access**(6).**

The coexistence of non-risk alleles (e.g., DQA1*01:01 and DQB1*05:03 in Case 2) alongside DQ2 components illustrates the complexity of HLA interactions. While these alleles alone may not confer risk, their presence in compound heterozygosity can influence disease expression**(7).**

From a public health perspective, this study underscores the diagnostic value of HLA genotyping in Pakistan. Rashid et al. recently emphasized the importance of localized HLA data to guide screening strategies and reduce diagnostic delays**(8)**. In Balochistan, where histopathology services are scarce and serological kits are inconsistently available, genotyping offers a reliable, non-invasive alternative to confirm CD predisposition.

Finally, this case series contributes to the growing body of regional data needed to inform national guidelines. Alam et al. demonstrated significant allele frequency differences between Pakistani CD patients and healthy controls, reinforcing the need for population-specific reference panels**(9).** Our findings support the inclusion of HLA-DQ2/DQ8 genotyping in CD workups and advocate for its integration into clinical protocols across Pakistan.

CONCLUSION AND RECOMMENDATIONS

Each manuscript should contain a conclusion section within 250-450 words which may contain the major outcome of the work, highlighting its importance, limitation, relevance, application and recommendation. Conclusion should be written in continuous manner with running sentences which normally includes main outcome of the research work, its application, limitation and recommendation. Do not use any subheading, citation, references to other part of the manuscript, or point list within the conclusion. In last paragraph author describes the future scope for improvement.

Conclusion

This case series reinforces the clinical relevance of HLA-DQ2 heterozygosity in the diagnostic evaluation of coeliac disease among symptomatic adults in Balochistan. The identification of HLA-DQ2, particularly the high-risk DQ2.5 haplotype, in genetically predisposed individuals provides a valuable adjunct to serological and histopathological assessments. In resource-limited settings where endoscopic and biopsy facilities may be constrained, HLA genotyping offers a non-invasive, genotype-driven pathway to support early diagnosis and dietary management. The findings underscore the urgent need to integrate genetic screening into routine gastroenterological practice across underserved regions of Pakistan. Establishing regional HLA haplotype prevalence data will not only improve diagnostic precision but also contribute to national registry development for autoimmune gastrointestinal disorders.

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Recommendation

Despite the promising diagnostic implications, this study highlights several gaps warranting further investigation:

1. **Expanded Cohort Studies**: Larger, multicenter studies are needed to establish the prevalence of HLA-DQ2 and DQ8 haplotypes in diverse ethnic populations across Balochistan.
2. **Serogenetic Correlation**: Future research should integrate serological markers (e.g., anti-tTG, EMA) with HLA typing to refine diagnostic algorithms.
3. **Registry Development**: Initiatives to build a regional coeliac disease registry will facilitate longitudinal tracking, policy advocacy, and resource allocation.
4. **Dietary Intervention Outcomes**: Prospective studies evaluating the impact of gluten-free diets in genetically confirmed cases will help validate genotype-guided management strategies.

ACKNOWLEDGEMENT

The authors extend their sincere gratitude to **Dr. Usman Tareen**, whose unwavering support, expert guidance, and logistical facilitation were instrumental throughout the study. His contributions in coordinating sample collection, ensuring laboratory access, and fostering institutional collaboration greatly enhanced the feasibility and impact of this research.

DATA AVAILABILITY

This statement should describe how readers can access the data supporting the conclusions of the study and clearly outline the reasons why unavailable data cannot be released.

CONFLICT OF INTEREST

Nil

FUNDING SOURCE

Nil

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