Structural and Functional Studies of \textit{trans}-Encoded HLA-DQ2.3 (DQA1\textsuperscript{*}03:01/DQB1\textsuperscript{*}02:01) Protein Molecule\textsuperscript{a,b,c,d,e}\footnote{This work was supported by grants from the Novo Nordisk Foundation, the Juvenile Diabetes Research Foundation, and the Research Council of Norway (to L. M. S.) and by Singapore Biomedical Research Council Grant 07/1/21/19/546 (to C. Y. K.).}

Stig Tollefsen\textsuperscript{a,1,2}, Kinya Hotta\textsuperscript{a,1}, Xi Chen\textsuperscript{a,1}, Bjorg Simonsen\textsuperscript{a}, Kunchithapadam Swaminathan\textsuperscript{a}, Irimpan I. Mathews\textsuperscript{a}, Ludvig M. Sollid\textsuperscript{a,1,3}, and Chu-Young Kim\textsuperscript{a,4}

From the \textsuperscript{a}Centre for Immune Regulation and Department of Immunology, University of Oslo and Oslo University Hospital, Rikshospitalet, 0027 Oslo, Norway, the \textsuperscript{b}Department of Biological Sciences, National University of Singapore, Singapore 117543, Singapore, and the \textsuperscript{c}Stanford Synchrotron Radiation Lightsource, Stanford Linear Accelerator Center National Accelerator Laboratory, Menlo Park, California 95124

Background: \textit{trans}-Encoded HLA-DQ molecules are biologically interesting, but no structures of such molecules exist.

Results: X-ray crystal structure of the \textit{trans}-encoded DQ2.3 (DQA1\textsuperscript{*}03:01/DQB1\textsuperscript{*}02:01) was determined. Structural data are presented together with functional T-cell data.

Conclusion: DQ2.3 has preference for negative charged anchors at P1 and P4.

Significance: This work helps to understand why DQ2.3 is associated with a particular risk for type 1 diabetes.

MHC class II molecules are composed of one \(\alpha\)-chain and one \(\beta\)-chain whose membrane distal interface forms the peptide binding groove. Most of the existing knowledge on MHC class II molecules comes from the \textit{cis}-encoded variants where the \(\alpha\)- and \(\beta\)-chain are encoded on the same chromosome. However, \textit{trans}-encoded class II MHC molecules, where the \(\alpha\)- and \(\beta\)-chain are encoded on opposite chromosomes, can also be expressed. We have studied the \textit{trans}-encoded class II HLA molecule DQ2.3 (DQA1\textsuperscript{*}03:01/DQB1\textsuperscript{*}02:01) that has received particular attention as it may explain the increased risk of certain individuals to type 1 diabetes. We report the x-ray crystal structure of this HLA molecule complexed with a gluten epitope at 3.05 Å resolution. The gluten epitope, which is the only known HLA-DQ2.3-restricted epitope, is preferentially recognized in the context of the DQ2.3 molecule by T-cell clones of a DQ8/H9252-restricted epitope, is preferentially recognized in individuals to type 1 diabetes. We report the x-ray crystal structure of this HLA molecule complexed with a gluten epitope at 3.05 Å resolution. The gluten epitope, which is the only known HLA-DQ2.3-restricted epitope, is preferentially recognized in the context of the DQ2.3 molecule by T-cell clones of a DQ8/DQ2.5 heterozygous celiac disease patient. This preferential recognition can be explained by improved HLA binding as the epitope combines the peptide-binding motif of DQ2.5 (negative charge at P4) and DQ8 (negative charge at P1). The analysis of the structure of DQ2.3 together with all other available DQ crystal structures and sequences led us to categorize DQA1 and DQB1 genes into two groups where any \(\alpha\)-chain and \(\beta\)-chain belonging to the same group are expected to form a stable heterodimer.

Major histocompatibility complex (MHC) proteins play a critical role in immune recognition by displaying antigens to T-cell receptors (TCRs)\textsuperscript{6} within the context of MHC-peptide complex to elicit a T-cell-mediated immune response. In humans, MHC proteins are encoded by the human leukocyte antigen (HLA) genes found on chromosome 6. HLA is the single most important genetic factor that predisposes to most autoimmune diseases (1) and contributes 35–50% of the genetic disease association in type 1 diabetes and celiac disease (2, 3). CD4\textsuperscript{T} T-cells recognize antigens in the context of MHC class II molecules that are heterodimers of \(\alpha\)- and \(\beta\)-chains. In humans, there are three isotopes of MHC class II molecules: HLA-DR, HLA-DQ, and HLA-DP. In HLA-DR, the polymorphic variation is provided by the \(\beta\)-chain alone as the \(\alpha\)-chain is monomorphic. However, in DQ and DP, both the \(\alpha\)-chains and the \(\beta\)-chains are polymorphic. As a result, unique DQ and DP molecules can be formed with \(\alpha\)- and \(\beta\)-chains encoded on the same chromosome (\textit{i.e.} encoded in \textit{cis}) or on opposite chromosomes (\textit{i.e.} encoded in \textit{trans}).

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The occurrence of \textit{trans}-encoded HLA class II molecules is well documented in the literature (4). However, evidence suggests that not every \(\alpha\)- and \(\beta\)-chain pairing will form a stable heterodimer (5, 6). Hence, it is generally considered that alleles of DQA\textsuperscript{\textit{α}} and DQB\textsuperscript{\textit{β}}-chains pair up predominantly in \textit{cis} rather than in \textit{trans} (5, 7). Nevertheless, studies on type 1 diabetes indicate that \textit{trans}-encoded HLA molecules may play a role in pathogenesis (8). It has been observed that individuals who are heterozygous for DQ2.5 (DQA1\textsuperscript{*}05:01/DQB1\textsuperscript{*}02:01) and DQ8 (DQA1\textsuperscript{*}03:01/DQB1\textsuperscript{*}03:02) are susceptible to type 1 diabetes with an almost 5-fold higher risk than those who are homozygous for either of the DQ variants (1, 9, 10). This phenomenon can be explained by the formation of \textit{trans}-encoded molecules DQ8.5 (DQA1\textsuperscript{*}05:01/DQB1\textsuperscript{*}03:02) and DQ2.3 (DQA1\textsuperscript{*}03:01/DQB1\textsuperscript{*}02:01), which could present one or a few specific diabetogenic epitopes to CD4\textsuperscript{T} T-cells, possibly inducing an immune response that leads to destruct-
tation of insulin-producing pancreatic β-islet cells (8). A strong argument for involvement of the DQ2.3 heterodimer in type 1 diabetes comes from trans-racial gene mapping studies that have found that this heterodimer, which is typically found in the trans-configuration among Caucasian subjects, exists and is overrepresented in the cis-configuration among type 1 diabetes patients of African origin (11, 12). The increased diabetes risk of the African DQ2.3 (DQA1*03:01/DQB1*02) carrying DR7 haplotype is contrasted by a protecting effect of the DQ2.2 (DQA1*03:01/DQB1*02) carrying DR7 haplotype of European origin, speaking to the functional importance of α-chain in the DQ2.3 molecule (12).

Celiac disease patients mount T-cell responses to gluten (consisting of the α, β-, and γ-gliadins as well as glutenin components) in the context of the celiac disease-associated DQ2.5 and DQ8 molecules (13). This human disease with in vivo expansion of T-cell clones specific for naturally selected epitopes offers a unique system to study the structure-function relationship of peptide-MHC complexes. Here, we have used this model system, offering a natural T-cell epitope restricted by HLA-DQ2.3, to study the x-ray crystal structure and function of a trans-encoded HLA-DQ molecule.

EXPERIMENTAL PROCEDURES

Gluten-specific T-cells and T-cell Proliferation Assay—T-cell reagents were established from intestinal biopsies of celiac disease patients. Separate, single biopsy specimens were challenged with chymotrypsin-treated gluten (0.2 mg/ml) or the ease patients. Separate, single biopsy specimens were challenged with chymotrypsin-treated gluten (0.2 mg/ml) or the ease patients. Separate, single biopsy specimens were challenged with chymotrypsin-treated gluten (0.2 mg/ml) or the ease patients. Separate, single biopsy specimens were challenged with chymotrypsin-treated gluten (0.2 mg/ml) or the ease patients. Separate, single biopsy specimens were challenged with chymotrypsin-treated gluten (0.2 mg/ml) or the ease patients. Separate, single biopsy specimens were challenged with chymotrypsin-treated gluten (0.2 mg/ml) or the ease patients. Separate, single biopsy specimens were challenged with chymotrypsin-treated gluten (0.2 mg/ml) or the ease patients. 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phycoerythrin (Invitrogen). Staining of DQ2.3 reactive T-cell clones was analyzed on a FACSCalibur flow cytometer (BD Biosciences).

**X-ray Crystallography**—For crystallization, leucine zipper portion of the DQ2.3 heterodimer was removed by human rhinovirus 3C protease digestion for 16 h at 4 °C. The resulting mixture was purified by anion-exchange chromatography using a Resource Q column (GE Healthcare) followed by size exclusion chromatography using a Shodex KW-803 column (Showa Denko K.K.). Crystals were grown using the hanging drop vapor diffusion method at 18 °C. Protein concentration was 4 mg/ml, and the crystallization solution was 0.2M Li2SO4, 0.1 M Tris, pH 8.5, 30% (w/v) PEG4000, 8% glycerol. Crystals grew to full size in 1 week. Crystals were dehydrated by the addition of 5 µL 0.2 M Li2SO4, 0.1 M Tris, pH 8.5, 40% (w/v) PEG4000, 8% glycerol to the hanging drop and 1 ml of the same buffer to the well and incubating at 18 °C for 12 h. The DQ2.3 crystal belonged to the space group C2 with cell dimensions a = 74.9 Å, b = 114.9 Å, c = 138.0 Å, and β = 103.4°. The initial diffraction data set was collected at beam line BL13B1 of the Taiwan National Synchrotron Radiation Research Center, and the final data set was collected at beam line 9-3 of the Stanford Synchrotron Radiation Laboratory. X-ray diffraction data were indexed and integrated using HKL2000 (23). Structure was solved by molecular replacement using Phaser (CCP4) (24). The α-chain of DQ8 (1JK8) and β-chain of DQ2.5 (1S9V) were used as search models. Structure was refined by Refmac (CCP4) (25), Coot (26), Buster (27), and PHENIX (28). The final R_work and R_free values are 0.210 and 0.283, respectively. The quality of the final model was verified by PROCHECK (29). Crystallographic parameters, data collection, and refinement statistics are given in supplemental Table 1.

**RESULTS**

**T-cell Recognition of DQ2.5-Glia-γ-4c/DQ8-Glia-γ-1a Gluten Epitope Presented via cis- or trans-Encoded Heterodimers**—We describe three T-cell clones (TCC548.3.5.6, TCC548.3.5.3, and TCC548.1.8.5) derived from a DQ8/DQ2.5 heterozygous celiac disease patient that are specific for variants of the DQ2.5-glia-γ-4c epitope that harbor deamidated residues (PQPEQPEQPFPQPQ or PQTEQPEQPFPQPQ). These T-cell clones, in contrast to similar T-cell clones described earlier (14), have undergone maturation in thymus in the presence of the DQ2.3 molecule. Also of note, the epitope studied is recognized in the same register by DQ8-restricted T-cells (then named DQ8-glia-γ-1a). The preference for the positioning of the Glu residues introduced by deamidation is different for the DQ2.5- and DQ8-restricted T-cells, DQ2.5-restricted T-cells being sensitive to deamidations at position P4 and DQ8-restricted T-cells being sensitive to deamidations at P1 (14). The three T-cell clones carried different TCRs, but they showed similar reactivity patterns when tested against variants of the DQ2.5-glia-γ-4c epitope in the context of different antigen-presenting cells (APCs). Importantly, we found that a peptide with deamidations at both P1
and P4 was recognized much better when presented by the trans-encoded DQ2.3 molecule than the cis-encoded DQ2.5 molecule (Fig. 1). The same three T-cell clones were tested for their ability to recognize peptides with Gln-to-Glu substitutions at P1 and/or P4 in the context of various cis- or trans-encoded HLA molecules, and they gave similar response patterns. Substitution at P1 had an effect in the context of DQ2.3 and DQ8, whereas substitution at P4 had an effect in the context of both DQ2.3 and DQ2.5 (Fig. 1).

Peptide Binding to cis- or trans-Encoded Heterodimers—Peptide binding assays showed that the peptide variant with Glu at both P1 and P4 bound stronger to the DQ2.3 molecule (IC50 = 7.50 μM) when compared with peptide variants with Gln-to-Glu substitutions at either P1 or at P4 alone (both IC50 ≥ 200 μM).

FIGURE 3. T-cell recognition of peptides substituted with Ala in position P1 and Glu in position P4. Synthetic peptides were tested in a T-cell proliferative assay with the T-cell clones DQ2 TCC387.19 (A) and DQ2.3 TCC548.3.5.6 (B) using the DQ2.5 APC or the DQ2.3 APC. For both T-cell clones, the response is the highest to the Ala in P1-substituted peptide in the context of DQ2.5, whereas the response against the DQ2.3 is the highest when the bound peptide harbors a negative charge in P1. Error bars indicate mean of triplicate ± S.D. Ala and Glu are indicated by single-letter codes.

FIGURE 4. T-cell recognition of recombinant water-soluble DQ2.3 trans-encoded molecules. Purified and BirA-biotinylated DQ8/2 molecules were bound to streptavidin-coated microtiter plates and tested for recognition by T-cell clones TCC387.19 (A) and TCC548.3.5.6 (B) in a proliferative T-cell assay (mean of triplicate ± S.D.). The T-cells recognize the water-soluble DQ2.3 molecule in a dose-dependent manner. In addition, the same T-cell clones were stained with biotinylated DQ2.3 coupled to phcoerythrin-labeled streptavidin and analyzed by flow cytometry. The DQ2-αI tetramer was used for negative control staining. The T-cell clones stain positively with the DQ2.3 tetramer.
This correlated with the T-cell response pattern described above, suggesting that the improved T-cell recognition (Fig. 1) could be explained by improved HLA binding. Similar peptide binding analysis for DQ2.5 showed that Gln-to-Glu substitution at P4 exerted the biggest effect as the variants with Gln-to-Glu substitutions at both P1 and P4 or only at P4 bound better than the variants with no substitution or substitution only at P1 (Fig. 2B). Thus, enhanced HLA binding could also explain the improved T-cell recognition of the P4 Glu-substituted peptide in the context of DQ2.5 (Fig. 1).

Determining T-cell Recognition by Ala and Lys Scans—Single position Ala- or Lys-substituted variants of PQPEQPEQPFPQPQ were next tested in proliferative T-cell assays with the T-cell clones TCC387.19 and TCC548.3.5.6 using APCs expressing DQ2.3 or DQ2.5 (supplemental Fig. 2). The most interesting observation in this experiment related to recognition of the peptide with Ala substitution at P1. Both TCC548.3.5.6 and TCC387.19 showed impaired recognition of the P1 Ala peptide when compared with the P1 Glu peptide in the context of DQ2.3, whereas in the context of DQ2.5, both T-cell clones recognized the P1 Ala peptide best (Fig. 3). As this effect was seen with both T-cell clones, it may suggest that the P1 pocket of DQ2.5 is better at accommodating Ala than the P1 pocket of DQ2.3.

Functional Testing of Water-soluble trans-Encoded DQ2.3 Molecules—We produced water-soluble DQ2.3 molecules in S2 cells displaying the PQPEQPEQPFPQPQ peptide. Purified monomeric DQ2.3 molecules were biotinylated and added to streptavidin-coated plastic wells to test whether the recombinant molecules were recognized by antigen-specific T-cell clones. Both TCC387.19 and TCC548.3.5.6 were effectively stained, indicating that the water-soluble HLA molecules were indeed correctly folded and were properly recognized by the T-cells. Once the integrity of the trans-encoded DQ2.3 molecule was verified, we went on to determine the x-ray crystal structure of DQ2.3 to gain structural insight into trans-encoded heterodimer formation and epitope recognition.

Structure of trans-Encoded HLA-DQ Molecule—The structure of DQ2.3:DQ2.5-gliadin-4c complex was determined to 3.06 Å resolution using x-ray crystallography. Statis-
### Structure of trans-Encoded HLA-DQ Molecule

**A**

![Diagram of HLA-DQ Molecule](image)

#### DQA Group I (DQA1*02-06)

| Polymorphic position | DQA1*0201 | DQA1*0202 | DQA1*0203 | DQA1*0204 | DQA1*0205 | DQA1*0206 |
|-----------------------|-----------|-----------|-----------|-----------|-----------|-----------|
| 10                    |           |           |           |           |           |           |
| 20                    |           |           |           |           |           |           |
| 30                    |           |           |           |           |           |           |
| 40                    |           |           |           |           |           |           |
| 50                    |           |           |           |           |           |           |
| 60                    |           |           |           |           |           |           |
| 70                    |           |           |           |           |           |           |
| 80                    |           |           |           |           |           |           |
| 90                    |           |           |           |           |           |           |

**DQA Group II (DQA1*01)

| Polymorphic position | DQA1*0101 | DQA1*0102 | DQA1*0103 |
|-----------------------|-----------|-----------|-----------|
| 10                    |           |           |           |
| 20                    |           |           |           |
| 30                    |           |           |           |
| 40                    |           |           |           |
| 50                    |           |           |           |
| 60                    |           |           |           |
| 70                    |           |           |           |
| 80                    |           |           |           |
| 90                    |           |           |           |

**DQß-chain**

**DQß-chain**

**B**

![Diagram of HLA-DQ Molecule](image)

#### DQB Group I (DQB1*02-04)

| Polymorphic position | DQB1*0201 | DQB1*0202 | DQB1*0203 | DQB1*0204 |
|-----------------------|-----------|-----------|-----------|-----------|
| 10                    |           |           |           |           |
| 20                    |           |           |           |           |
| 30                    |           |           |           |           |
| 40                    |           |           |           |           |
| 50                    |           |           |           |           |
| 60                    |           |           |           |           |
| 70                    |           |           |           |           |
| 80                    |           |           |           |           |
| 90                    |           |           |           |           |

**DQB Group II (DQB1*03-06)

| Polymorphic position | DQB1*0301 | DQB1*0302 | DQB1*0303 | DQB1*0304 | DQB1*0305 | DQB1*0306 |
|-----------------------|-----------|-----------|-----------|-----------|-----------|-----------|
| 10                    |           |           |           |           |           |           |
| 20                    |           |           |           |           |           |           |
| 30                    |           |           |           |           |           |           |
| 40                    |           |           |           |           |           |           |
| 50                    |           |           |           |           |           |           |
| 60                    |           |           |           |           |           |           |
| 70                    |           |           |           |           |           |           |
| 80                    |           |           |           |           |           |           |
| 90                    |           |           |           |           |           |           |

**B**

![Diagram of HLA-DQ Molecule](image)

**C**

![Diagram of HLA-DQ Molecule](image)

**D**

![Diagram of HLA-DQ Molecule](image)

**E**

![Diagram of HLA-DQ Molecule](image)
Structure of trans-Encoded HLA-DQ Molecule

Our results demonstrate that the DQ2.3 molecule combines the peptide binding signatures of the DQ2.5 and DQ8 molecules. This results in a binding motif with preference for negatively charged anchor residues at both the P1 and the P4 positions. In this way, some epitopes can be presented even more effectively in the context of the trans-encoded DQ2.3 molecule. This has relevance for understanding how the trans-encoded DQ2.3 molecule is predisposing to type 1 diabetes.

We found that the responses of the T-cell clones in the context of the DQ2.3 molecule were improved by Gln-to-Glu substitutions in the peptide at the P1 and P4 positions (Fig. 1). Results from peptide binding assays suggest that the enhanced T-cell recognition of the deamidated peptides, at least in part, is explained by improved HLA binding (34). There are multiple positively charged residues near the P1 pocket (Arg-α52 and His-α24) and the P4 pocket (Arg-β77, Arg-β70, Lys-β71) that may establish long range electrostatic interaction with the P1 or P4 Glu of the gliadin peptide or establish hydrogen bonds with the peptide through water molecules, which in the current crystal structure are not visible due to insufficient resolution.

Differential recognition of the P1 Ala-substituted PQPEQPEQPQF peptide by a T-cell clone in the context of DQ2.5 versus DQ2.3 points to structural differences between the two HLA molecules around the P1 pocket (Fig. 3). Although the overall shape and size of the P1 pocket in DQ2.3 and DQ2.5 are highly similar, the polarity of the residues found at the surface of the respective P1 pockets is dissimilar (Fig. 6). In DQ2.5, Gln-α31 and Glu-β86 are found at the bottom of the P1 pocket and form a bidentate hydrogen bond to one another (donor-acceptor distances are 2.8 and 3.0 Å). In contrast, Glu-α31 and Glu-β86 are found at the bottom of the P1 pocket in DQ2.3 (carboxylate oxygen to carboxylate oxygen distances are 2.9 and 3.4 Å). Furthermore, DQ2.3 has Arg-α51 on the side of the P1 pocket, whereas DQ2.5 has Phe-α51. Binding of the P1 Ala-substituted peptide to either DQ2.3 or DQ2.5 will result in a mostly vacant P1 pocket, which may lead to conformational shift of the above mentioned residues as well as introduction of solvent molecules inside the P1 pocket. Although the details of such rearrangement need to be assessed in a future study, we predict that the DQ2.5 will form a more stable complex with an aliphatic amino acid such as Ala in P1 in contrast to the DQ2.3 molecule that prefers a negatively charged amino acid in this position.

It is generally considered that alleles encoded in cis (i.e. on a single chromosome) have been evolutionarily selected to form a...
stable heterodimer, whereas trans-encoded heterodimers may not necessarily be able to form a stable or functional MHC (35). Regardless, a number of studies have shown that αβ heterodimers can form among a subset of different MHC class II molecules, including pairing of mixed haplotypes (e.g. mouse MHC class II Aα4Aβ5 (35)), mixed isotypes (e.g. human MHC class II DRAaDQβ (36) or mouse MHC class II EaαAβ (37)), and mixed species (e.g. human and mouse MHC class II DRAaBd (38)). Some structural explanations for the bias for cis-encoded heterodimer formation have been given for mouse MHC class II I-A molecules, where a subset of specific residues has been identified that can dictate which of the α- and β-chain alleles can form a stable heterodimer (39). However, limited knowledge exists as to the rules that determine formation of MHC class II heterodimers.

In DQ molecules, polymorphic residues at the αβ dimerization interface are concentrated at the two ends of the peptide-binding groove. On the P1 side, α44–α54 and β84–β90, two clusters in the α and β chains where polymorphism occurs most extensively, come together to form the αβ interface. On the P9 side, polymorphic residues α73/α77 and β53 contact each other at the αβ interface. Sequence distribution at these polymorphic positions reveals that DQ alleles can be divided into two major groups. Group I consists of DQA1*02 through DQA1*06 and DQB1*02 through DQB1*04, whereas group II is composed of DQA1*01 and DQB1*05 and DQB1*06 (Fig. 7A). Interestingly, according to the dbMHC database (40), only 10 out of 4,233 reported HLA-DQ haplotypes carry a group I-group II mixed pair, indicating potential evolutionary selection pressure against the cross-group pairing. A survey of available DQ crystal structures revealed some key structural features on the αβ dimerization interface that may be dictating the observed allele-pairing bias.

On the P1 side of the molecule in DQ2.5 and DQ8 (group I), absolutely conserved Tyr-9α and Glu-86β side chains form an H-bond to each other (Fig. 7B). In DQ6 (group II), however, β87 is found at the position where β86 occurs in DQ2.5 and in DQ8 (both group I) (Fig. 7C). Cys-9α is absolutely conserved, and β87 carries either a Tyr or a Phe residue, allowing the pair to have a good steric fit. However, mixing of group I and group II alleles will result either in the loss of an H-bond or the introduction of a steric clash. Furthermore, although the α44–α54 and β84–β90 polymorphic clusters both assume a helical structure, their local conformations are different in groups I and II. In DQ6 (group II), the backbone conformation near Phe-51α draws the bulky side chain close to the β-chain at Ala-86β and Gly-89β. In group I, β86 and β89 are conserved for Glu and Thr, respectively. Simple overlay of DQ6 and DQ8 structures shows steric incompatibility between Phe-51α and Thr-89β side chains. Similarly, in DQ8 (group I), the difference in the helical structure shifts the β-chain-contacting residue from Phe-51α to Arg-52α, where the Arg-52α side chain is buried deep inside the αβ interface and forms an H-bond with the previously mentioned Glu-86β. Again, overlay of DQ6 and DQ8 structures indicates that the Arg-52α will clash against Ala-86β. At the other end of the peptide-binding groove, polymorphic α77 and β53 residues contact each other. In group I, α77 and β53 are conserved for Ser and Leu, respectively (Fig. 7D). In group II, α77 and β53 are conserved for Tyr and Gln (Fig. 7E). Structural overlay of DQ2.5, DQ8, and DQ6 shows that pairing of the group II α-chain and the group I β-chain will likely suffer from steric clash between the Tyr-77α and Leu-53β side chains. Taken together, mixed chain pairing (group I α-chain paired with group II β-chain or group II α-chain paired with group I β-chain) will lead to loss of interchain hydrogen-bond interaction or result in suboptimal packing at the heterodimer interface.

Our crystal structure shows that the P1 pocket in DQ2.3 is significantly different from that of DQ2.5 due to the polymorphic MHC residues found in this region. Additionally, we have demonstrated that DQ2.3 presents a gluten epitope to T-cells much more efficiently than DQ2.5. Therefore, trans-encoded MHCs have the potential to drastically alter an individual's immune response toward a particular antigen. Sequence analysis of the HLA-DQ gene products has revealed that certain haplotype pairings are more likely to produce a structurally stable trans-encoded αβ heterodimer than others, which is also reflected in the high frequency of compatible pairings seen in the NCBI dbMHC database.

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Structure of trans-Encoded HLA-DQ Molecule

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JOURNAL OF BIOLOGICAL CHEMISTRY 13619

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