Understanding the role of HLA-DQ genes in celiac disease: Implications for type 1 diabetes

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CELIAC DISEASE
- Enteropathy precipitated by ingestion of wheat gluten proteins. Complete recovery on a gluten-exclusion diet.
- Inappropriate immune response to gluten in the gut → Loss of villi of the small intestine (malabsorption). Infiltration of lymphocytes in lamina propria and epithelium.
- Prevalence: 1:100.
- Familial clustering (10% of 1st degree rel. affected). MZ twin concordance rate ~ 75%.
- Very strong HLA association.

GLUTEN PROTEINS
- rich in Glutamine and Proline residues

GENETIC AND ENVIRONMENTAL FACTORS INVOLVED IN DEVELOPMENT OF CELIAC DISEASE

Genes
- HLA >50%
- 5q32
- 2q33

Environment
- Gluten

HLA-DR PHENOTYPES OF CELIAC PATIENTS

Norway
Italy-Bologna
Spain
Italy-Rome

HLA ASSOCIATION CELIAC DISEASE

- most are DR4(DQ8)
**HLA ASSOCIATION IN CELIAC DISEASE AND TYPE 1 DIABETES**

Celiac disease:
- DQ2 (DQA1*05/DQB1*02): ♦ ♦ ♦ ♦
- DQ8 (DQA1*03/DQB1*0302): ♦ ♦ ♦ ♦ (majority of DQ2- pts are DQ8+)

No increased risk of DQ2/DQ8 heterozygotes

Type 1 diabetes:
- DQ8 (DQA1*03/DQB1*0302): ♦ ♦ ♦ ♦
- DQ2 (DQA1*05/DQB1*02): ♦ ♦ ♦ ♦
- DQ2/DQ8 heterozygotes: ♦ ♦ ♦ ♦ ♦ (role of trans-dimers?)
- DQ6 (DQA1*0102/DQB1*0602): ÈÈÈÈ

**THE CELIAC LESION**

**T CELL RECOGNITION AND DQ2 BINDING OF DQ2-α-I GLADIIN EPITOPE VARIANTS**

$\text{QLQPFPQQLPY}$

<table>
<thead>
<tr>
<th>Gladin</th>
<th>peptide-binding register P1-P9</th>
<th>IC50 (μM)</th>
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<tbody>
<tr>
<td>α-I</td>
<td>PFPQPELPYP QPELPYPQPE LPYPQPQPF</td>
<td>nd</td>
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<tr>
<td>γ-I</td>
<td>FFPQQPPELPYP QPPELPYPQPE LPYPQPQPF</td>
<td>1.5</td>
</tr>
<tr>
<td>γ-II</td>
<td>FFPQQPPELPYP QPPELPYPQPE LPYPQPQPF</td>
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</tr>
<tr>
<td>γ-III</td>
<td>LFPQQPPELPYP QPPELPYPQPE LPYPQPQPF</td>
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<td>γ-IV</td>
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<tr>
<td>γ-VI</td>
<td>FFPQQPPELPYP QPPELPYPQPE LPYPQPQPF</td>
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<tr>
<td>γ-VII</td>
<td>FFPQQPPELPYP QPPELPYPQPE LPYPQPQPF</td>
<td>1.5</td>
</tr>
</tbody>
</table>

**GENERATION OF T CELL EPITOPES IN THE GUT**

Transglutaminase (QXPY)

After transglutaminase treatment

$\text{QLQPFPQQLPY}$

Proline spacing and glutamine deamidation at P4, P6 (and P7)

**SEVERAL DQ2 RESTRICTED GLUTEN T CELL EPITOPES**

Qiao et al. J Immunol 2005

**Gliadin-specific, HLA-DQ(α*0501,β*0102) Restricted T Cells Isolated from the Small Intestinal Mucosa of Celiac Disease Patients**

By Knut E. A. Lundin, Helge Scoll, Torbjørn Hansen, Gunnar Paulsen, Trond S. Halsen, Olav Fausa, Erik Thornby, and Ludvig M. Solid

DEAMIDATED GLUTEN PEPTIDE CAUGHT IN THE ACT

Kim et al. PNAS, 2004

X-ray crystal structure (2.2 Å resolution)

DQ8 RESTRICTED GLUTEN T CELL EPITOPE:
importance of deamidation at P1 and P9

Suri et al. JCI, 2005 (commentary by Ploegh)

THE DQ8 PEPTIDE SIGNATURE

Deamidation at P1 and/or P9
The peptide variant with deamidation at P4 only is not recognised

Tollefsen et al, JCI 2006

T CELL RESPONSE TO AN α-GLIADIN (A1133612)

DQ2 and DQ8 restricted T cells
- recognise peptides in different regions of the α-glaidin
- have different requirements for deamidation:
  - DQ2: P4, P6, P7
  - DQ8: P1, P9

T CELL RESPONSE TO A γ-GLIADIN (M36999)

DQ2 and DQ8 restricted T cells recognise peptides within the same region.

Q:
Can DQ2 and DQ8 restricted T cell respond to the same peptide when bound in the same register?
**PEPTIDE RECOGNITION IN CONTEXT OF DQ2 OR DQ8**

- These T cells have different preferences for deamidation of the peptides.
- DQ2 restricted T cells prefer negative charge at P1.
- DQ8 restricted T cells require negative charge at P4.
- Peptides with negative charge at P1 and P4 are recognized by both DQ2 and DQ8 restricted T cells.

**Question:**
Can peptides with the combined DQ2 and DQ8 signatures be presented by trans-encoded heterodimers?

**CIS- AND TRANS-ENCODED HETERODIMERS IN DQ2/DQ8 HETEROZYGOTES**

Trans-encoded heterodimers can present peptides.
Better presentation of peptide with the combined DQ2 and DQ8 signatures when presented by one of the trans-encoded heterodimers.

**WHY NOT A DQ2/DQ8 HETEROZYGOUS EFFECT IN CELIAC DISEASE?**

Many of the DQ2 restricted gluten T cell epitopes carry Proline at P1.
Accommodation of Proline at P1 is unique to DQ2.
DQ8 is likely unable to present peptides with Proline at P1.
Epitopes with Proline at P1 cannot be presented by DQ2/DQ8 trans-encoded heterodimers.
DQ8 AND DQ2 HLA ASSOCIATION IN TYPE 1 DIABETES

Can be explained by an immune response to a single peptide or a limited set of peptides that:

- carry a DQ8 signature (neg charge at P1 and/or P9)
- carry a DQ2 signature (neg. charge at P4; ??? and/or P6, P7)
- are better presented by DQ2/DQ8 trans encoded heterodimers (sp. DQA1*0301/DQB1*0201)

_reverse immunogenetics approach_