

Toxic gluten peptides

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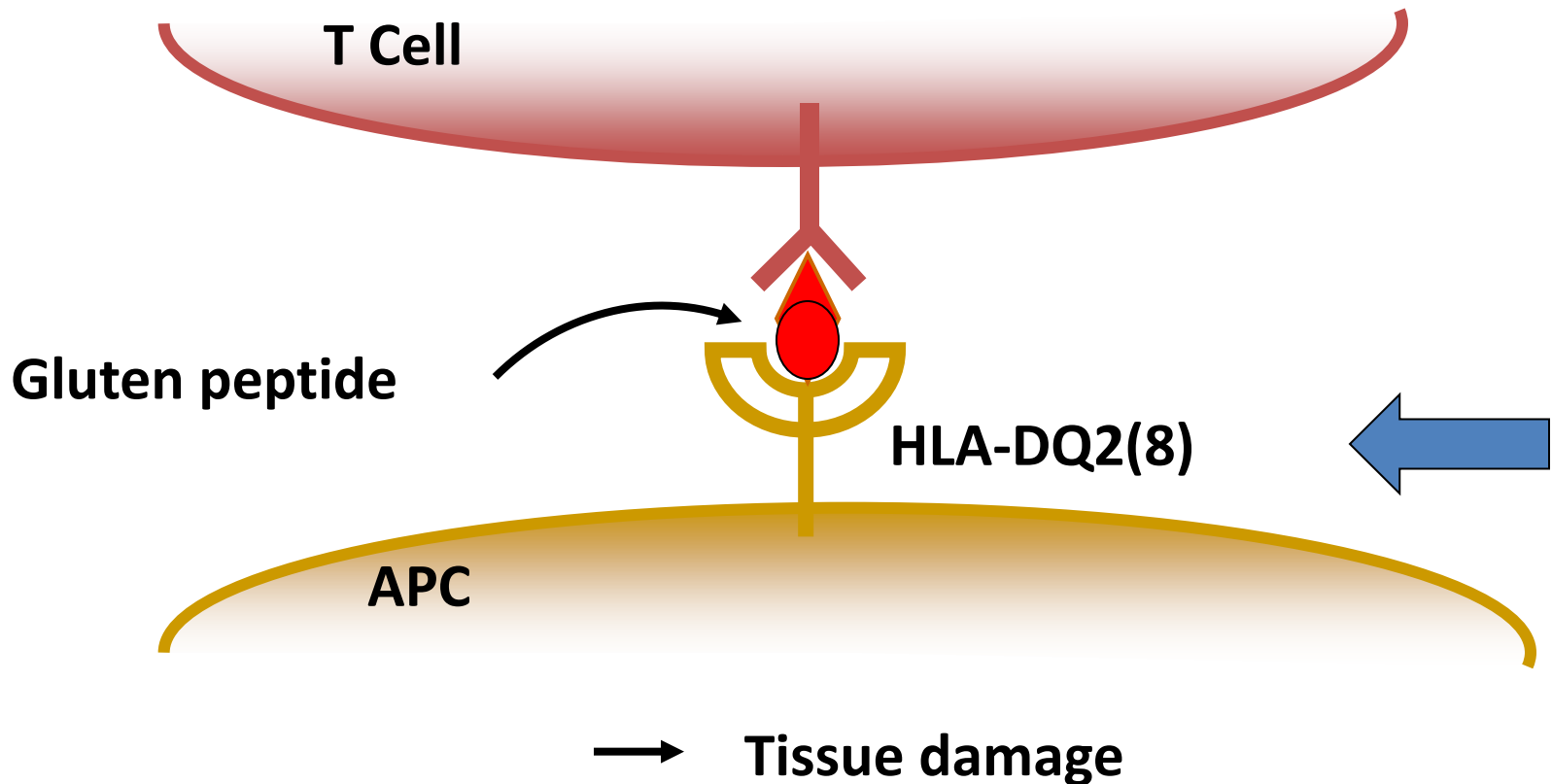
Celiac Disease Consortium

Gluten proteins in wheat

HLA-DQ2/8

T-cells

Gluten specific T cell response in the small intestine



Gluten and HLA-DQ2/8 are incompatible!!

HLA-DQ2 and HLA-DQ8 prefer peptides that contain amino acids with **negative charge**:

HLA-DQ2 XXXEEEXX

HLA-DQ8 EXXXXXXXXE

Gluten **does not contain** these amino acids:

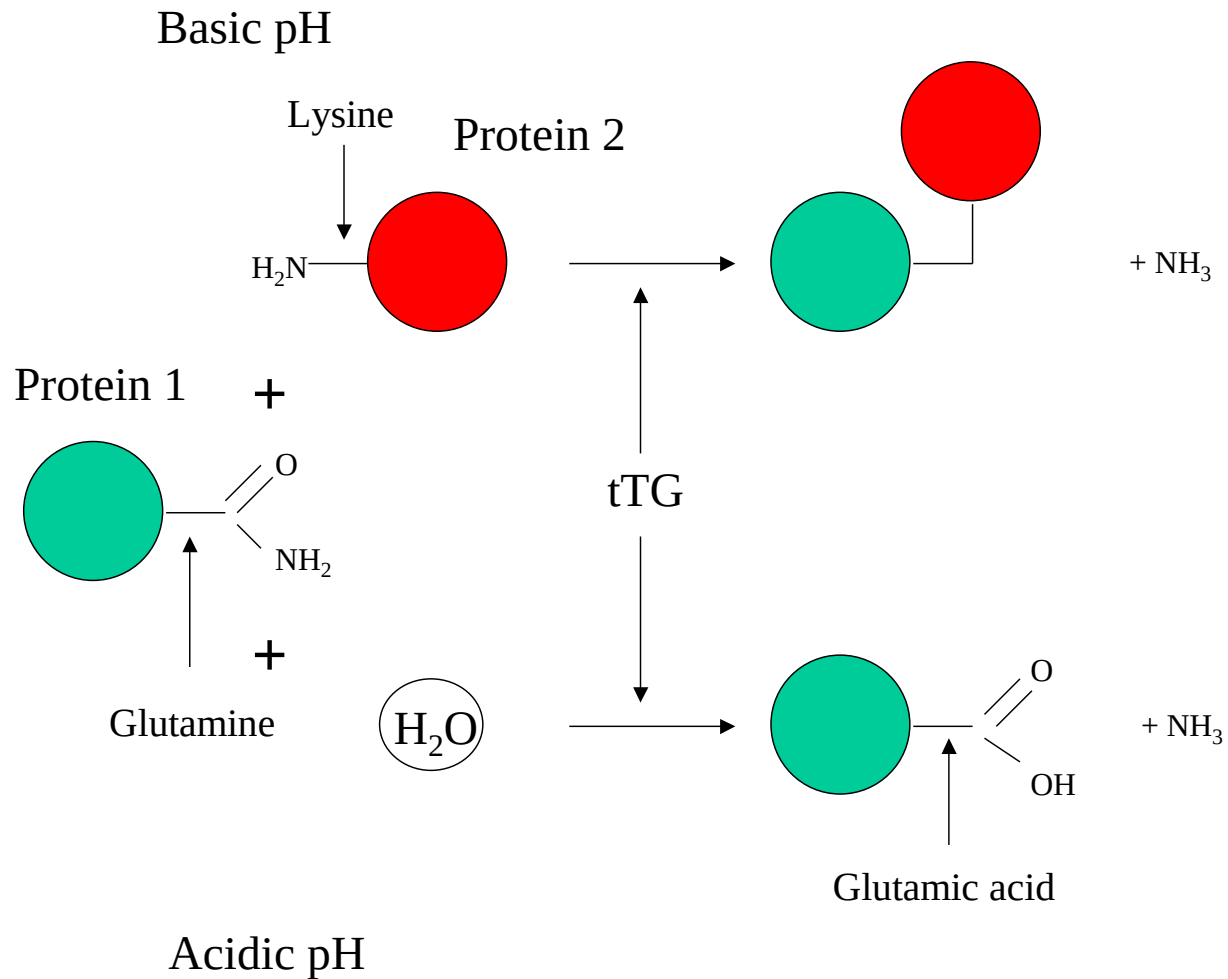
- LGQQQPFPPQQPYQPQPFPSQLPYLQLQPFPQPQL
- PQPQPQYSQPQQPISQQQQQQQQQQQQQQQQQQ

T cell stimulatory Gliadin peptide

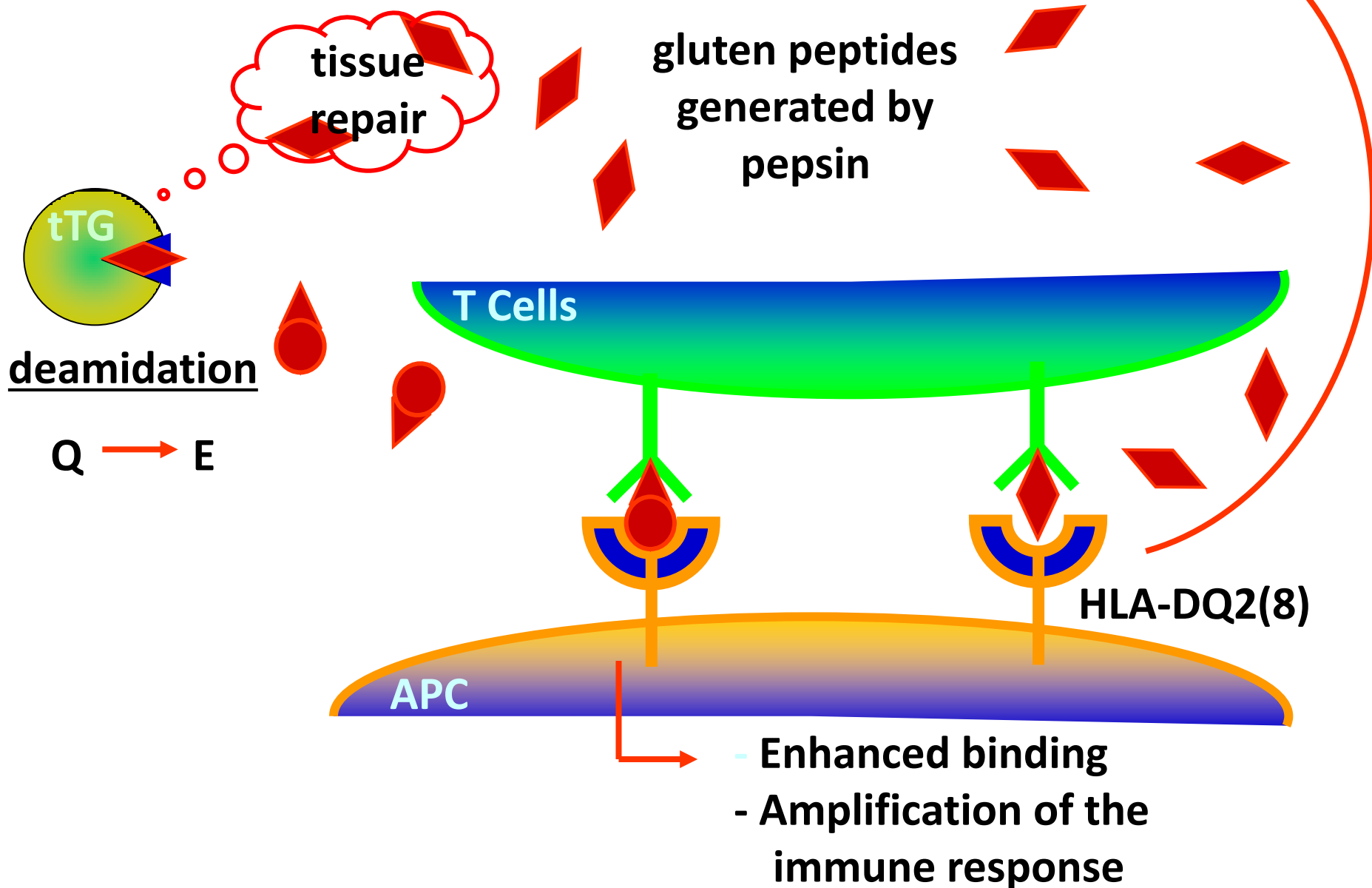
T cell recognition

SGQGSFQPSQQN	+
SG <u>E</u> GSFQPSQQN	+++
SGQGSFQPSQ <u>E</u> N	+++
SG <u>E</u> GSFQPSQ <u>E</u> N	+++

Tissue transglutaminase: autoantigen and gluten modifier



Tissue damage: release of intracellular tTG



The specificity of tTG is determined by proline, the 2nd most abundant aa in gluten

Characteristic gluten sequences:

QP	no modification
QXP	yes
QXXP	no
QXPY or QXPF	yes

LGQQQPFPPQQPYPQPQPFPSQLPYLQLQPFPPQPQL

LGQEQPFPPEQPYPQPQPFPSELPYLQLQPFPPQPQL

Predict toxic gluten sequences?

	Gluten	Hordein	Secalin	Avenin	Tcells
	Wheat	Barley	Rye	Oats	
Search					
Algorithm	46	60	33	0	yes

Specificity of tissue transglutaminase explains cereal toxicity in celiac disease.

Vader, de Ru, van der Wal, Kooy, Benckhuijsen, Mearin, Drijfhout, van Veelen, and Koning. J. Exp. Med. 195: 643-649 (2002).

Identification of T cell stimulatory peptides in cereals

Gliadin:

QLQPFPPQQLPYPPQ

PPQQLPY

PPQQLPYPPQ

Secalin:

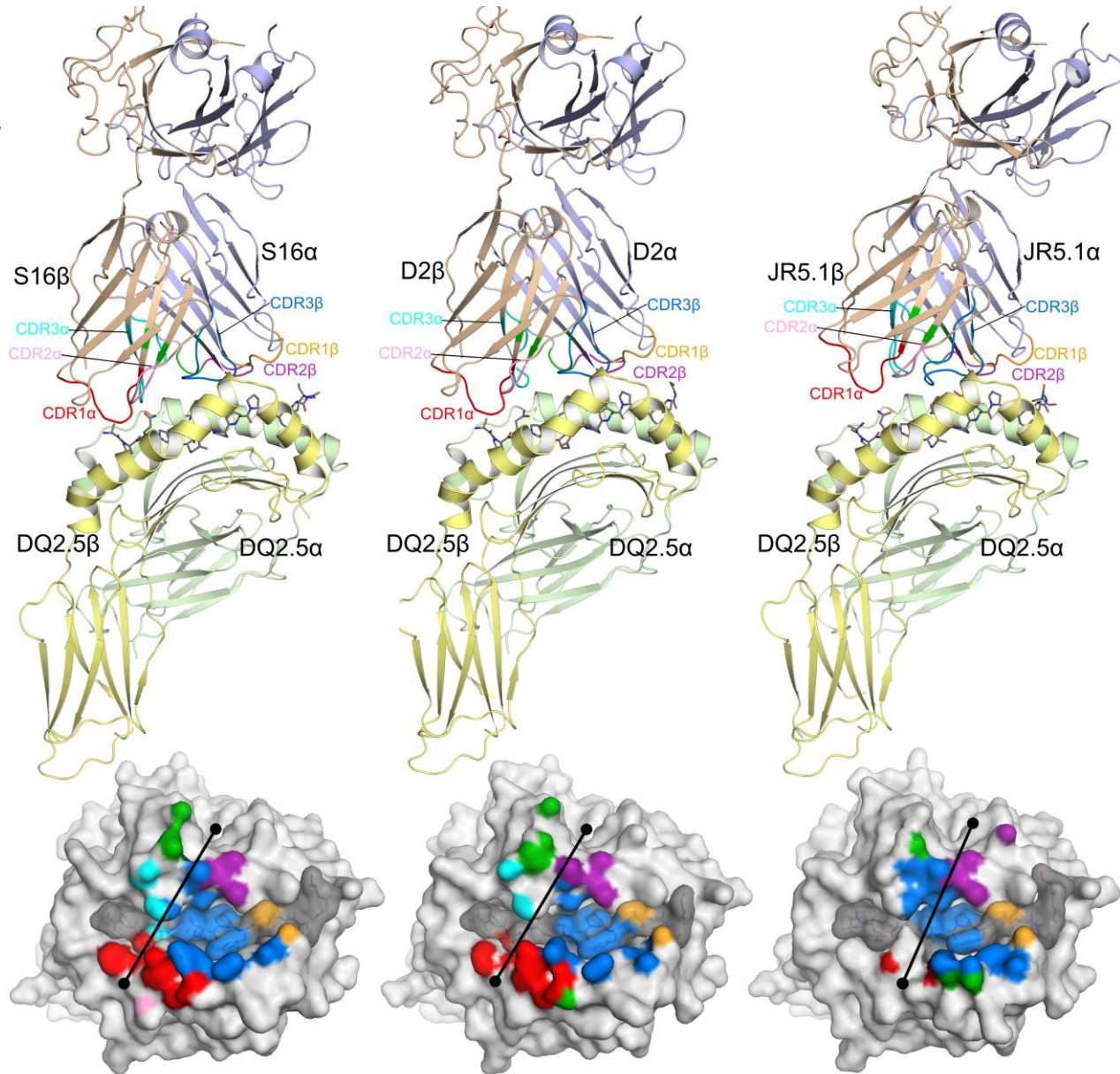
PQQPFPPQQPFPPSQ

PPQQLPY

PPQQPFPPQ

DQ2-glia- α 2 recognition

TRAV26-01
TRBV7-02⁺



T cell receptor

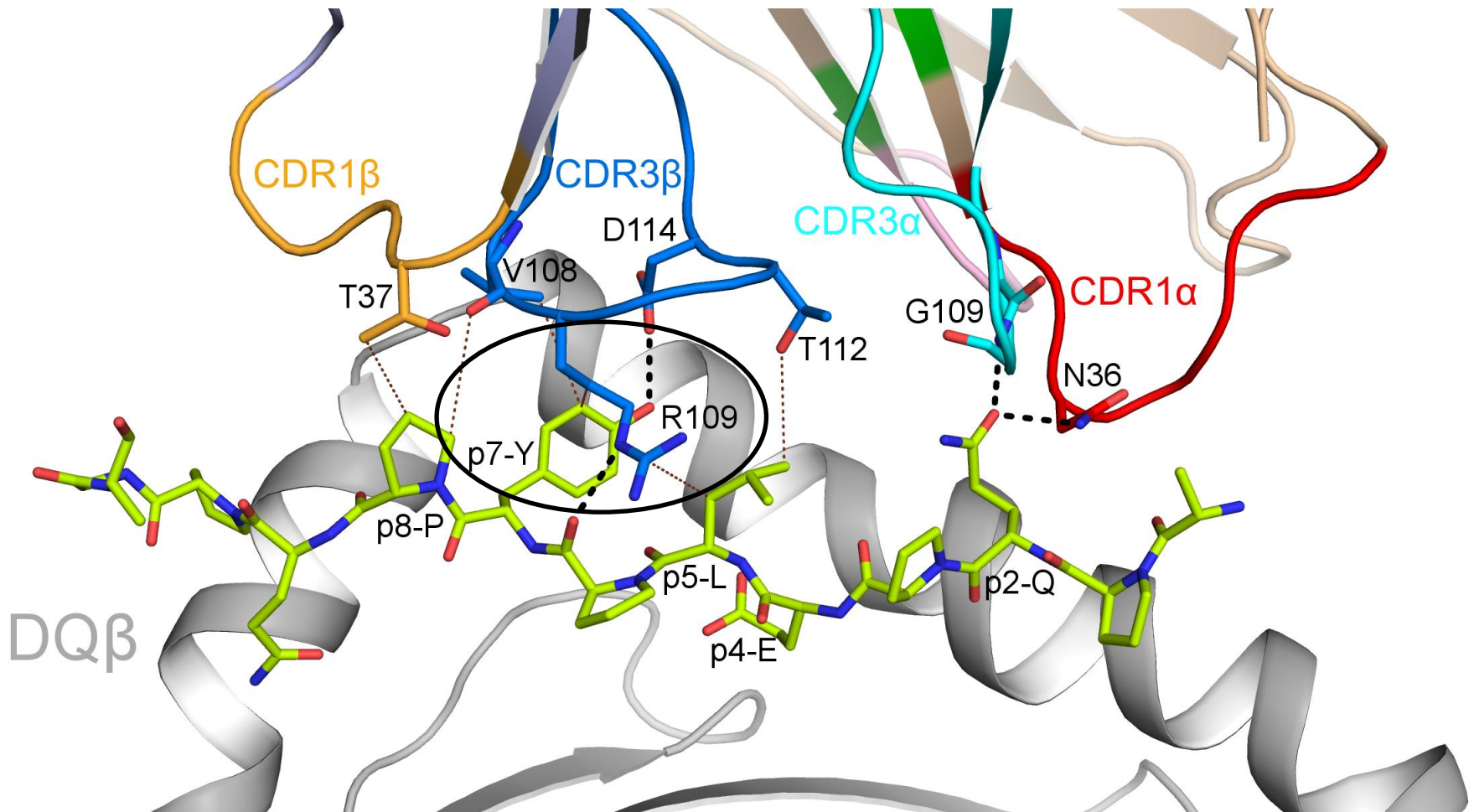
Peptide

DQ2

Conserved β -chain footprint

Petersen et al, NMSB 2014

DQ2-glia- α 2 recognition



Gluten is complex: a heterogeneous mixture of proteins

- Gliadins

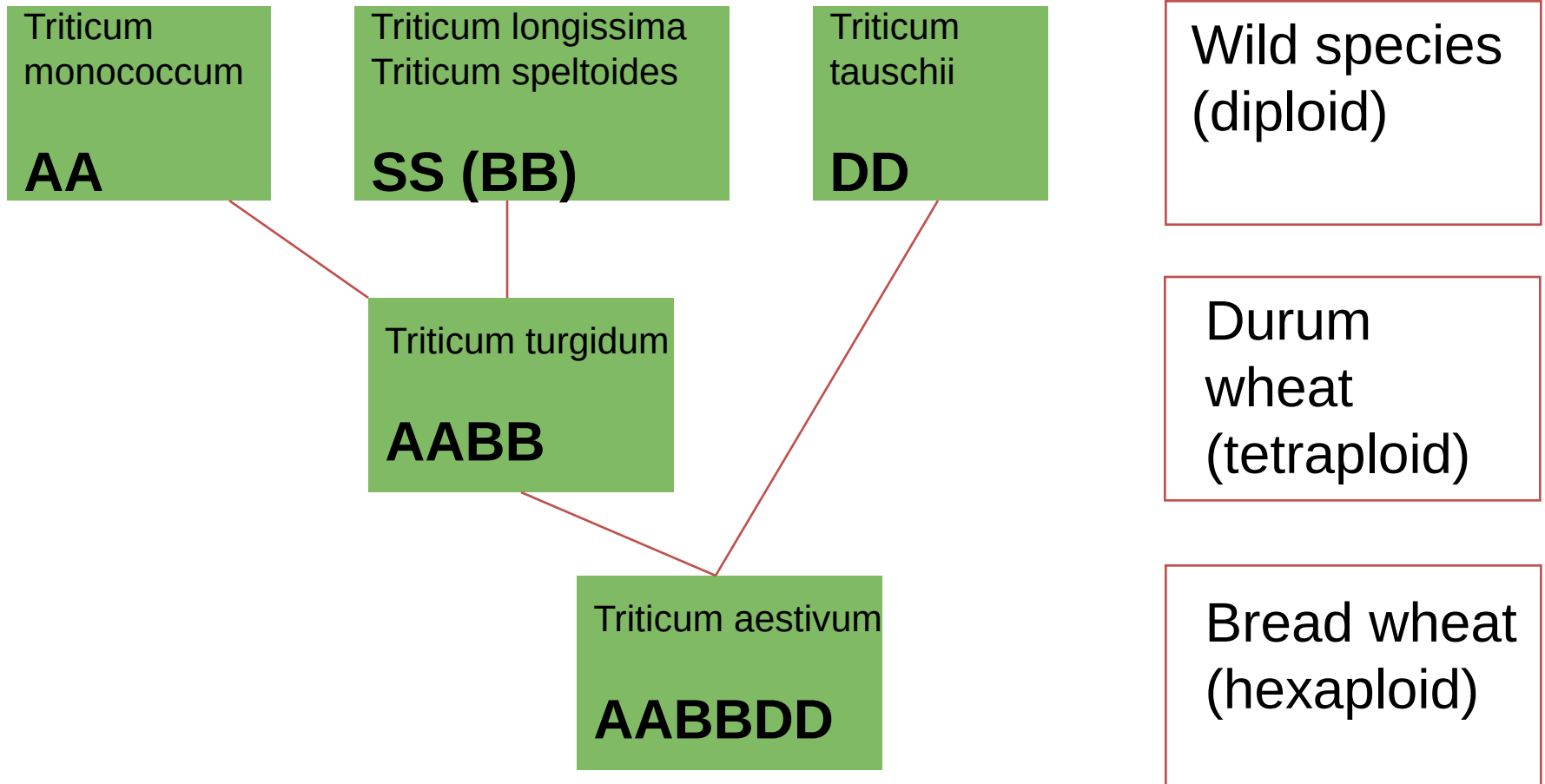
- Alpha-gliadins
- Gamma-gliadins
- Omega-gliadins

$\alpha/\omega > \gamma > \text{LMW} > \text{HMW}$

- Glutenins

- Low Molecular Weight Glutenins
- High Molecular Weight Glutenins

Wheat is complex: three genomes



Systematic analysis alpha-gliadins

- 3022 expressed α -gliadin sequences
- Assigned to A, B or D genome
- Tested all potential T cell stimulatory peptides for HLA-DQ-binding and T cell recognition

No alpha-gliadins exist
that lack all T cell stimulatory epitopes

	DQ2- α 1	DQ2- α 2	DQ2- α 3	DQ8- α 1
A	+	-	+	-
B/S	-	-	-	+
D	+	+	+	+

The same is true for the gamma gliadins

Nomenclature and listing of celiac disease relevant gluten T-cell epitopes restricted by HLA- DQ molecules

Ludvig M. Sollid & Shuo-Wang Qiao &
Robert P. Anderson & Carmen Gianfrani & Frits Koning

Immunogenetics 2012; 64:455–460

Bona fide toxicity of gluten for patients with celiac disease

- Well defined
- Mechanism underlying toxicity clear
- Ill understood phenomenon of non-celiac gluten sensitivity
 - No mechanism firmly established
- Claims that gluten stimulates innate immunity
 - No mechanism firmly established