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Update 2020: Nomenclature and listing of celiac disease-relevant gluten epitopes recognized by CD4+ T cells --Manuscript Draft--

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Abstract:	Celiac disease is caused by an abnormal intestinal T-cell response to cereal gluten proteins. The disease has a strong HLA association, and CD4 + T cells recognizing gluten epitopes presented by disease-associated HLA-DQ allotypes are considered to be drivers of the disease. This paper provides an update of the currently known HLA-DQ restricted gluten T-cell epitopes with their names and sequences.
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24 **Update 2020: Nomenclature and listing of celiac disease-relevant gluten epitopes recognized by CD4⁺ T cells**
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Abstract

Celiac disease is caused by an abnormal intestinal T-cell response to cereal gluten proteins. The disease has a strong HLA association, and CD4⁺ T cells recognizing gluten epitopes presented by disease-associated HLA-DQ allotypes are considered to be drivers of the disease. This paper provides an update of the currently known HLA-DQ restricted gluten T-cell epitopes with their names and sequences.

Keywords

Celiac disease, Gluten, T cell, Epitopes, HLA-DQ2, HLA-DQ8

This report provides an update of a listing of HLA-DQ-restricted epitopes recognized by CD4⁺ T cells of celiac disease patients as reported in 2012. The criteria used for epitope definition are unaltered from the first report, and we refer to this publication for details (Sollid et al. 2012). Table 1 contains the 9-mer core region of the epitopes. As was also mentioned in the first report, we emphasize that most CD4⁺ T cells recognize peptides longer than 9 amino acids by involvement of N- and C-terminal flanking residues. Consequently, peptides with an identical 9-mer sequence, but with different flanking regions, can thus elicit differential reactivities by T-cell clones specific for the same epitope.

In adults, gluten-specific T-cell responses are either dependent on or strongly enhanced by deamidation of gluten (Sollid et al. 2012). An early report indicated that deamidation dependency in children was less prominent compared to what had been observed in adults (Vader et al. 2002). Three subsequent reports, however, indicated that also in children gluten-specific T cells chiefly recognize epitopes that are deamidation dependent (Camarca et al. 2017; Hardy et al. 2015a; Ráki et al. 2017).

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21 While the Table 1 list in all likelihood contains the most important and immunodominant epitopes, we strongly suspect that the list
22 is not complete and that several additional epitopes are yet to be identified. Particularly relevant to this point are observations of
23 T-cell clones generated from T-cell lines of gut biopsies of untreated celiac subjects (both young children shortly after serum IgA
24 anti-TG2 seroconversion and adults), where approximately only half of the T-cell clones could have their reactivities assigned to
25 known gluten epitopes (Ráki et al. 2017). Of note, in contrast to most previous studies, this study reported on the reactivity of T-
26 cell lines and clones generated from celiac patients with active disease and not from patients in remission. A possible explanation
27 for the wide breadth of epitope reactivity observed in this study could be that in active disease there is both an increased T-cell
28 infiltration in small intestinal lamina propria and clonal expansions of gluten-reactive T cells, and therefore more reactivities would
29 likely be represented in the generated T-cell lines and T-cell clones. Also for epitopes restricted by HLA-DQ8 and HLA-DQ2.2, there
30 are likely additional epitopes to be defined, particularly as most gluten-epitope discovery in patients with celiac disease has
31 focused on the majority of celiac patients who are positive for HLA-DQ2.5.
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42 This notion of additional unreported epitopes may have translational consequences. For example, there are efforts to produce
43 celiac disease-safe grains by the removal of culprit gluten gene sequences – for instance, by employing RNAi or CRISPR/Cas9
44 technology (Gil-Humanes et al. 2010; Jouanin et al. 2019; Sanchez-Leon et al. 2018). The successful removal from wheat of all
45 sequences that give rise to the current Table 1 wheat epitopes may not necessarily produce a wheat that would be safe for celiac
46 disease patients. Future studies will be needed to determine if this is the case.
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52 Interest in the recent publication of the first reference wheat genome (International Wheat Genome Sequencing 2018) highlights
53 the importance of celiac disease-relevant gluten epitopes to the scientific, medical, and agricultural communities. If more epitopes
54 are to be identified and the listing of epitopes to be entirely complete – if indeed this is at all achievable given the complexity of
55 the gluten proteome – more effort in working with selected T-cell reagents would be warranted.
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Table 1 List of celiac disease-relevant T-cell epitopes

Epitope*	Previous names	Peptide-binding register†									Reference
		1	2	3	4	5	6	7	8	9	
<u>DQ2.5 restricted epitopes</u>											
DQ2.5-glia- α 1a	DQ2- α -I, α 9	P	F	P	Q	P	E	L	P	Y ^{††}	(Arentz-Hansen et al. 2000)
DQ2.5-glia- α 1b	DQ2- α -III	P	Y	P	Q	P	E	L	P	Y	(Arentz-Hansen et al. 2002)
DQ2.5-glia- α 2	DQ2- α -II, α 2	P	Q	P	E	L	P	Y	P	Q	(Arentz-Hansen et al. 2000)
DQ2.5-glia- α 3	glia- α 20	F	R	P	E	Q	P	Y	P	Q	(Vader et al. 2002)
DQ2.5-glia- γ 1	DQ2- γ -I	P	Q	Q	S	F	P	E	Q	<u>Q</u>	(Sjöström et al. 1998)
DQ2.5-glia- γ 2	DQ2- γ -II, γ 30	I	Q	P	E	Q	P	A	Q	L	(Qiao et al. 2005; vader et al. 2002)
DQ2.5-glia- γ 3	DQ2- γ -III	<u>Q</u>	Q	P	E	Q	P	Y	P	<u>Q</u>	(Arentz-Hansen et al. 2002)
DQ2.5-glia- γ 4a	DQ2- γ -IV	S	Q	P	E	Q	E	F	P	Q	(Arentz-Hansen et al. 2002)
DQ2.5-glia- γ 4b	DQ2- γ -VIIc	P	Q	P	E	Q	E	F	P	Q	(Qiao et al. 2005)
DQ2.5-glia- γ 4c	DQ2- γ -VIIa	<u>Q</u>	Q	P	E	Q	P	F	P	Q	(Arentz-Hansen et al. 2002)
DQ2.5-glia- γ 4d	DQ2- γ -VIIb	P	Q	P	E	Q	P	F	C	<u>Q</u>	(Qiao and Sollid 2019)
DQ2.5-glia- γ 4e ^S		L	Q	P	E	Q	P	F	P	<u>Q</u>	(Qiao and Sollid 2019)
DQ2.5-glia- γ 5	DQ2- γ -VI	<u>Q</u>	Q	P	F	P	E	Q	P	Q	(Arentz-Hansen et al. 2002)
DQ2.5-glia- ω 1	DQ2- ω -I	P	F	P	Q	P	E	Q	P	F	(Tye-Din et al. 2010)
DQ2.5-glia- ω 2	DQ2- ω -II	P	Q	P	E	Q	P	F	P	W	(Tye-Din et al. 2010)
DQ2.5-glut-L1	glutenin-17	P	F	S	E	Q	E	Q	P	V	(Vader et al. 2002)
DQ2.5-glut-L2	glutenin-156	F	S	<u>Q</u>	Q	Q	E	S	P	F	(Stepniak et al. 2005; vader et al. 2002)

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DQ2.5-hor-1	Hor- α 9, H α 9	P F P Q P E Q P F	(Tye-Din et al. 2010; Vader et al. 2003)
DQ2.5-hor-2	Hor- α 2, H α 2	P Q P E Q P F P Q	(Vader et al. 2003)
DQ2.5-hor-3a	hor-I-DQ2	P I P E Q P Q P Y	(Tye-Din et al. 2010)
DQ2.5-hor-3b ^s		P Y P E Q P Q P Y	(Hardy et al. 2015b)
DQ2.5-sec-1	Sec- α 9, S α 9	P F P Q P E Q P F	(Tye-Din et al. 2010; Vader et al. 2003)
DQ2.5-sec-2	Sec- α 2, S α 2	P Q P E Q P F P Q	(Vader et al. 2003)
DQ2.5-sec-3 ^s		P F P E Q P E Q I	(Hardy et al. 2015b)
DQ2.5-ave-1a	Av- α 9A	P Y P E Q E E P F	(Arentz-Hansen et al. 2004; Vader et al. 2003)
DQ2.5-ave-1b	Av- α 9B, 1490	P Y P E Q E Q P F	(Arentz-Hansen et al. 2004; Vader et al. 2003)
DQ2.5-ave-1c ^s		P Y P E Q E Q P I	(Hardy et al. 2015b)

DQ2.2 restricted epitopes

DQ2.2-glut-L1	glutenin-17	P F S E Q E Q P V	(Bodd et al. 2012)
DQ2.2-glia- α 1 ^s		Q G S V Q P Q Q L	(Dørum et al. 2014)
DQ2.2-glia- α 2 ^s		Q Y S Q P E Q P I	(Dørum et al. 2014)

DQ8 restricted epitopes

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DQ8-glia- α 1	DQ8- α -I	E G S F Q P S Q E	(van de wal et al. 1998)
DQ8-glia- γ 1a	DQ8- γ -Ia	E Q P <u>Q</u> Q P F P Q	(Tollefsen et al. 2006)
DQ8-glia- γ 1b	DQ8- γ -Ib	E Q P <u>Q</u> Q P Y P E	(Tollefsen et al. 2006)
DQ8-glia- γ 2 [§]		P Q Q S F P E Q E	(Petersen et al. 2016)
DQ8-glut-H1	HMW-glutenin	<u>Q</u> G Y Y P T S P <u>Q</u>	(van de wal et al. 1999)

DQ8.5 restricted epitopes

DQ8.5-glia- α 1	DQ8- α -I	E G S F Q P S Q E	(Kooy-winkelaar et al. 2011)
DQ8.5-glia- γ 1		P Q Q S F P E Q E	(Kooy-winkelaar et al. 2011)
DQ8.5-glut-H1	HMW-glutenin	<u>Q</u> G Y Y P T S P <u>Q</u>	(Kooy-winkelaar et al. 2011)

* In the names of the epitopes, the following short terms denote the proteins of origin. glia- α : α -gliadin; glia- γ : γ -gliadin; glia- ω : ω -gliadin, glut-L: low molecular weight glutenin, glut-H: high molecular weight glutenin; hor: hordein, sec: secalin and ave: avenin.

† Glutamate residues (E) formed by TG2-mediated deamidation that are important for recognition by T cells are shown in *bold*. Additional glutamine residues also targeted by TG2 are *underlined*.

§ Epitope added to the table since the first report (Sollid et al. 2012).

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