Update 2020: nomenclature and listing of celiac disease-relevant gluten epitopes recognized by CD4(+) T cells

Sollid, L.M.; Tye-Din, J.A.; Qiao, S.W.; Anderson, R.P.; Gianfrani, C.; Koning, F.

Immunogenetics (2020) 72:85–88
https://doi.org/10.1007/s00251-019-01141-w

REVIEW

Update 2020: nomenclature and listing of celiac disease–relevant gluten epitopes recognized by CD4$^+$ T cells

Ludvig M. Sollid[1] · Jason A. Tye-Din[2] · Shuo-Wang Qiao[1] · Robert P. Anderson[2] · Carmen Gianfrani[3] · Frits Koning[4]

Received: 16 October 2019 / Accepted: 16 October 2019 / Published online: 18 November 2019

Abstract

Celiac disease is caused by an abnormal intestinal T cell response to cereal gluten proteins. The disease has a strong human leukocyte antigen (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 with 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).

While the Table 1 list in all likelihood contains the most important and immunodominant epitopes, we strongly suspect that the list is not complete and that several additional epitopes are yet to be identified. Particularly relevant to this point are observations of T cell clones generated from T cell lines of gut biopsies of untreated celiac subjects (both young children shortly after serum IgA anti-TG2 seroconversion and adults), where approximately only half of the T cell clones could have their reactivities assigned to known gluten epitopes (Ráki et al. 2017). Of note, in contrast to most previous studies, this study reported on the reactivity of T cell lines and clones generated from celiac patients with active disease and not from patients in remission. A possible explanation for the wide breadth of epitope reactivity observed in this study could be that in active disease, there is an increased T cell infiltration both in small intestinal lamina propria and clonal expansions of gluten-reactive T cells, and therefore, more reactivities would 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 are likely additional epitopes to be defined, particularly as most gluten-epitope discovery in patients with celiac disease has focused on the majority of celiac patients who are positive for HLA-DQ2.5.

This article is part of the Topical Collection on *"Nomenclature, databases and bioinformatics in Immunogenetics"*.

✉ Ludvig M. Sollid
l.m.sollid@medisin.uio.no

[1] KG Jebsen Coeliac Disease Research Centre and Department of Immunology, Oslo University Hospital, Rikshospitalet, University of Oslo, Oslo, Norway

[2] Immunology Division, The Walter and Eliza Hall Institute of Medical Research, Parkville, Victoria, Australia

[3] Institute of Biochemistry and Cell Biology, National Research Council of Italy, Naples, Italy

[4] Department of Immunohematology and Blood Transfusion, Leiden University Medical Center, Leiden, The Netherlands

Table 1 List of celiac disease–relevant T cell epitopes

Epitope*	Previous names	Peptide-binding register† 1	2	3	4	5	6	7	8	9	Reference
DQ2.5 restricted epitopes											
DQ2.5-glia-α1a	DQ2-α-I, α9	P	F	P	Q	P	**E**	L	P	Y††	(Arentz-Hansen et al. 2000)
DQ2.5-glia-α1b	DQ2-α-III	P	Y	P	Q	P	**E**	L	P	Y	(Arentz-Hansen et al. 2002)
DQ2.5-glia-α2	DQ2-α-II, α2	P	Q	P	**E**	L	P	Y	P	Q	(Arentz-Hansen et al. 2000)
DQ2.5-glia-α3	glia-α20	F	R	P	**E**	Q	P	Y	P	Q	(Vader et al. 2002)
DQ2.5-glia-γ1	DQ2-γ-I	P	Q	Q	S	F	P	**E**	Q	Q	(Sjöström et al. 1998)
DQ2.5-glia-γ2	DQ2-γ-II, γ30	I	Q	P	**E**	Q	P	A	Q	L	(Qiao et al. 2005; Vader et al. 2002)
DQ2.5-glia-γ3	DQ2-γ-III	Q	Q	P	**E**	Q	P	Y	P	Q	(Arentz-Hansen et al. 2002)
DQ2.5-glia-γ4a	DQ2-γ-IV	S	Q	P	**E**	Q	**E**	F	P	Q	(Arentz-Hansen et al. 2002)
DQ2.5-glia-γ4b	DQ2-γ-VIIc	P	Q	P	**E**	Q	**E**	F	P	Q	(Qiao et al. 2005)
DQ2.5-glia-γ4c	DQ2-γ-VIIa	Q	Q	P	**E**	Q	P	F	P	Q	(Arentz-Hansen et al. 2002)
DQ2.5-glia-γ4d	DQ2-γ-VIIb	P	Q	P	**E**	Q	P	F	C	Q	(Qiao and Sollid 2019)
DQ2.5-glia-γ4e§		L	Q	P	**E**	Q	P	F	P	Q	(Qiao and Sollid 2019)
DQ2.5-glia-γ5	DQ2-γ-VI	Q	Q	P	F	P	**E**	Q	P	Q	(Arentz-Hansen et al. 2002)
DQ2.5-glia-ω1	DQ2-ω-I	P	F	P	Q	P	**E**	Q	P	F	(Tye-Din et al. 2010)
DQ2.5-glia-ω2	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	Q	Q	Q	**E**	S	P	F	(Stepniak et al. 2005; Vader et al. 2002)
DQ2.5-hor-1	Hor-α9, Hα9	P	F	P	Q	P	**E**	Q	P	F	(Tye-Din et al. 2010; Vader et al. 2003)
DQ2.5-hor-2	Hor-α2, Hα2	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§		P	Y	P	**E**	Q	P	Q	P	Y	(Hardy et al. 2015b)
DQ2.5-sec-1	Sec-α9, Sα9	P	F	P	Q	P	**E**	Q	P	F	(Tye-Din et al. 2010; Vader et al. 2003)
DQ2.5-sec-2	Sec-α2, Sα2	P	Q	P	**E**	Q	P	F	P	Q	(Vader et al. 2003)
DQ2.5-sec-3§		P	F	P	**E**	Q	P	E	Q	I	(Hardy et al. 2015b)
DQ2.5-ave-1a	Av-α9A	P	Y	P	E	Q	**E**	E	P	F	(Arentz-Hansen et al. 2004; Vader et al. 2003)
DQ2.5-ave-1b	Av-α9B, 1490	P	Y	P	E	Q	**E**	Q	P	F	(Arentz-Hansen et al. 2004; Vader et al. 2003)
DQ2.5-ave-1c§		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-α1§		Q	G	S	V	Q	P	Q	Q	L	(Dørum et al. 2014)
DQ2.2-glia-α2§		Q	Y	S	Q	P	**E**	Q	P	I	(Dørum et al. 2014)
DQ8 restricted epitopes											
DQ8-glia-α1	DQ8-α-I	**E**	G	S	F	Q	P	S	Q	**E**	(van de Wal et al. 1998)
DQ8-glia-γ1a	DQ8-γ-Ia	**E**	Q	P	Q	Q	P	F	P	Q	(Tollefsen et al. 2006)
DQ8-glia-γ1b	DQ8-γ-Ib	**E**	Q	P	Q	Q	P	Y	P	**E**	(Tollefsen et al. 2006)
DQ8-glia-γ2§		P	Q	Q	S	F	P	**E**	Q	**E**	(Petersen et al. 2016)
DQ8-glut-H1	HMW-glutenin	Q	G	Y	Y	P	T	S	P	Q	(van de Wal et al. 1999)
DQ8.5 restricted epitopes											
DQ8.5-glia-α1	DQ8-α-I	**E**	G	S	F	Q	P	S	Q	**E**	(Kooy-Winkelaar et al. 2011)
DQ8.5-glia-γ1		P	Q	Q	S	F	P	**E**	Q	**E**	(Kooy-Winkelaar et al. 2011)
DQ8.5-glut-H1	HMW-glutenin	Q	G	Y	Y	P	T	S	P	Q	(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; ave, avenin

† Glutamate residues (E) formed by TG2-medited 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).

This notion of additional unreported epitopes may have translational consequences. For example, there are efforts to produce celiac disease–safe grains by the removal of culprit gluten gene sequences—for instance, by employing RNAi or CRISPR/Cas9 technology (Gil-Humanes et al. 2010; Jouanin et al. 2019; Sanchez-Leon et al. 2018). The successful removal from wheat of all sequences that give rise to the current Table 1 wheat epitopes may not necessarily produce wheat that would be safe for celiac disease patients. Future studies will be needed to determine if this is the case.

Interest in the recent publication of the first reference wheat genome (International Wheat Genome Sequencing 2018) highlights the importance of celiac disease–relevant gluten epitopes to the scientific, medical, and agricultural communities. If more epitopes are to be identified and the listing of epitopes to be entirely complete—if indeed this is at all achievable given the complexity of the gluten proteome—more effort in working with selected T cell reagents would be warranted.

References

Arentz-Hansen H, Körner R, Molberg Ø, Quarsten H, Vader W, Kooy YM, Lundin KEA, Koning F, Roepstorff P, Sollid LM, McAdam SN (2000) The intestinal T cell response to α-gliadin in adult celiac disease is focused on a single deamidated glutamine targeted by tissue transglutaminase. J Exp Med 191:603–612

Arentz-Hansen H, McAdam SN, Molberg Ø, Fleckenstein B, Lundin KE, Jorgensen TJ, Jung G, Roepstorff P, Sollid LM (2002) Celiac lesion T cells recognize epitopes that cluster in regions of gliadins rich in proline residues. Gastroenterology 123:803–809

Arentz-Hansen H, Fleckenstein B, Molberg Ø, Scott H, Koning F, Jung G, Roepstorff P, Lundin KE, Sollid LM (2004) The molecular basis for oat intolerance in patients with celiac disease. PLoS Med 1:e1

Bodd M, Kim CY, Lundin KE, Sollid LM (2012) T-cell response to gluten in patients with HLA-DQ2.2 reveals requirement of peptide-MHC stability in celiac disease. Gastroenterology 142:552–561

Camarca A, Auricchio R, Picascia S, Fierro O, Maglio M, Miele E, Malamisura B, Greco L, Troncone R, Gianfrani C (2017) Gliadin-reactive T cells in Italian children from preventCD cohort at high risk of celiac disease. Pediatr Allergy Immunol 28:362–369

Dørum S, Bodd M, Fallang LE, Bergseng E, Christophersen A, Johannesen MK, Qiao SW, Stamnaes J, de Souza GA, Sollid LM (2014) HLA-DQ molecules as affinity matrix for identification of gluten T cell epitopes. J Immunol 193:4497–4506

Gil-Humanes J, Piston F, Tollefsen S, Sollid LM, Barro F (2010) Effective shutdown in the expression of celiac disease-related wheat gliadin T-cell epitopes by RNA interference. Proc Natl Acad Sci U S A 107:17023–17028

Hardy MY, Girardin A, Pizzey C, Cameron DJ, Watson KA, Picascia S, Auricchio R, Greco L, Gianfrani C, La Gruta NL, Anderson RP, Tye-Din JA (2015a) Consistency in polyclonal T-cell responses to gluten between children and adults with celiac disease. Gastroenterology 149:1541–1552 e2

Hardy MY, Tye-Din JA, Stewart JA, Schmitz F, Dudek NL, Hanchapola I, Purcell AW, Anderson RP (2015b) Ingestion of oats and barley in patients with celiac disease mobilizes cross-reactive T cells activated by avenin peptides and immuno-dominant hordein peptides. J Autoimmun 56:56–65

International Wheat Genome Sequencing CI (2018) Shifting the limits in wheat research and breeding using a fully annotated reference genome. Science 361

Jouanin A, Schaart JG, Boyd LA, Cockram J, Leigh FJ, Bates R, Wallington EJ, Visser RGF, Smulders MJM (2019) Outlook for coeliac disease patients: towards bread wheat with hypoimmunogenic gluten by gene editing of α- and γ-gliadin gene families. BMC Plant Biol 19:333

Kooy-Winkelaar Y, van Lummel M, Moustakas AK, Schweizer J, Mearin ML, Mulder CJ, Roep BO, Drijfhout JW, Papadopoulos G, van Bergen J, Koning F (2011) Gluten-specific T cells cross-react between HLA-DQ8 and the HLA-DQ2α/DQβ transdimer. J Immunol 187:5123–5129

Petersen J, Kooy-Winkelaar Y, Loh KL, Tran M, van Bergen J, Koning F, Rossjohn J, Reid HH (2016) Diverse T cell receptor gene usage in HLA-DQ8-associated celiac disease converges into a consensus binding solution. Structure 24:1643–1657

Qiao SW, Sollid LM (2019) Two novel HLA-DQ2.5-restricted gluten T-cell epitopes in the DQ2.5-glia-γ4 epitope family. Immunogenetics https://doi.org/10.1007/s00251-019-01138-5

Qiao SW, Bergseng E, Molberg Ø, Jung G, Fleckenstein B, Sollid LM (2005) Refining the rules of gliadin T cell epitope binding to the disease-associated DQ2 molecule in celiac disease: importance of proline spacing and glutamine deamidation. J Immunol 175:254–261

Ráki M, Dahal-Koirala S, Yu H, Korponay-Szabo IR, Gyimesi J, Castillejo G, Jahnsen J, Qiao SW, Sollid LM (2017) Similar responses of intestinal T cells from untreated children and adults with celiac disease to deamidated gluten epitopes. Gastroenterology 153:787–798 e4

Sanchez-Leon S, Gil-Humanes J, Ozuna CV, Gimenez MJ, Sousa C, Voytas DF, Barro F (2018) Low-gluten, nontransgenic wheat engineered with CRISPR/Cas9. Plant Biotechnol J 16:902–910

Sjöström H, Lundin KEA, Molberg Ø, Körner R, McAdam SN, Anthonsen D, Quarsten H, Noren O, Roepstorff P, Thorsby E, Sollid LM (1998) Identification of a gliadin T-cell epitope in coeliac disease: general importance of gliadin deamidation for intestinal T-cell recognition. Scand J Immunol 48:111–115

Sollid LM, Qiao SW, Anderson RP, Gianfrani C, Koning F (2012) Nomenclature and listing of celiac disease relevant gluten T-cell epitopes restricted by HLA-DQ molecules. Immunogenetics 64:455–460

Stepniak D, Vader LW, Kooy Y, van Veelen PA, Moustakas A, Papandreou NA, Eliopoulos E, Drijfhout JW, Papadopoulos GK, Koning F (2005) T-cell recognition of HLA-DQ2-bound gluten peptides can be influenced by an N-terminal proline at p-1. Immunogenetics 57:8–15

Tollefsen S, Arentz-Hansen H, Fleckenstein B, Molberg Ø, Ráki M, Kwok WW, Jung G, Lundin KE, Sollid LM (2006) HLA-DQ2 and -DQ8 signatures of gluten T cell epitopes in celiac disease. J Clin Invest 116:2226–2236

Tye-Din JA, Stewart JA, Dromey JA, Beissbarth T, van Heel DA, Tatham A, Henderson K, Mannering SI, Gianfrani C, Jewell DP, Hill AV, McCluskey J, Rossjohn J, Anderson RP (2010) Comprehensive, quantitative mapping of T cell epitopes in gluten in celiac disease. Sci Transl Med 2:41ra51

Vader W, Kooy Y, van Veelen P, de Ru A, Harris D, Benckhuijsen W, Pena S, Mearin L, Drijfhout JW, Koning F (2002) The gluten response in children with celiac disease is directed toward multiple gliadin and glutenin peptides. Gastroenterology 122:1729–1737

Vader LW, Stepniak DT, Bunnik EM, Kooy YM, de Haan W, Drijfhout JW, van Veelen PA, Koning F (2003) Characterization of cereal toxicity for celiac disease patients based on protein homology in grains. Gastroenterology 125:1105–1113

van de Wal Y, Kooy YM, van Veelen PA, Pena SA, Mearin LM, Molberg Ø, Lundin KEA, Sollid LM, Mutis T, Benckhuijsen WE, Drijfhout JW, Koning F (1998) Small intestinal T cells of celiac disease patients recognize a natural pepsin fragment of gliadin. Proc Natl Acad Sci U S A 95:10050–10054

van de Wal Y, Kooy YM, van Veelen P, Vader W, August SA, Drijfhout JW, Pena SA, Koning F (1999) Glutenin is involved in the gluten-driven mucosal T cell response. Eur J Immunol 29:3133–3139