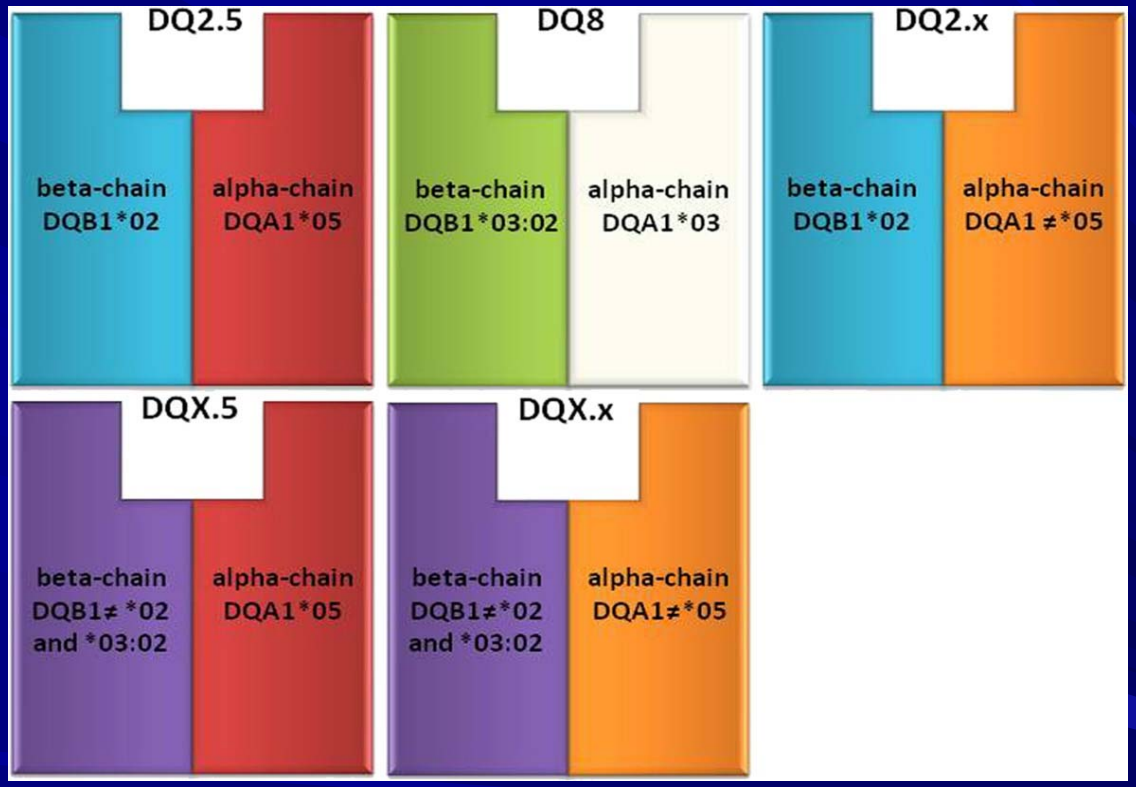
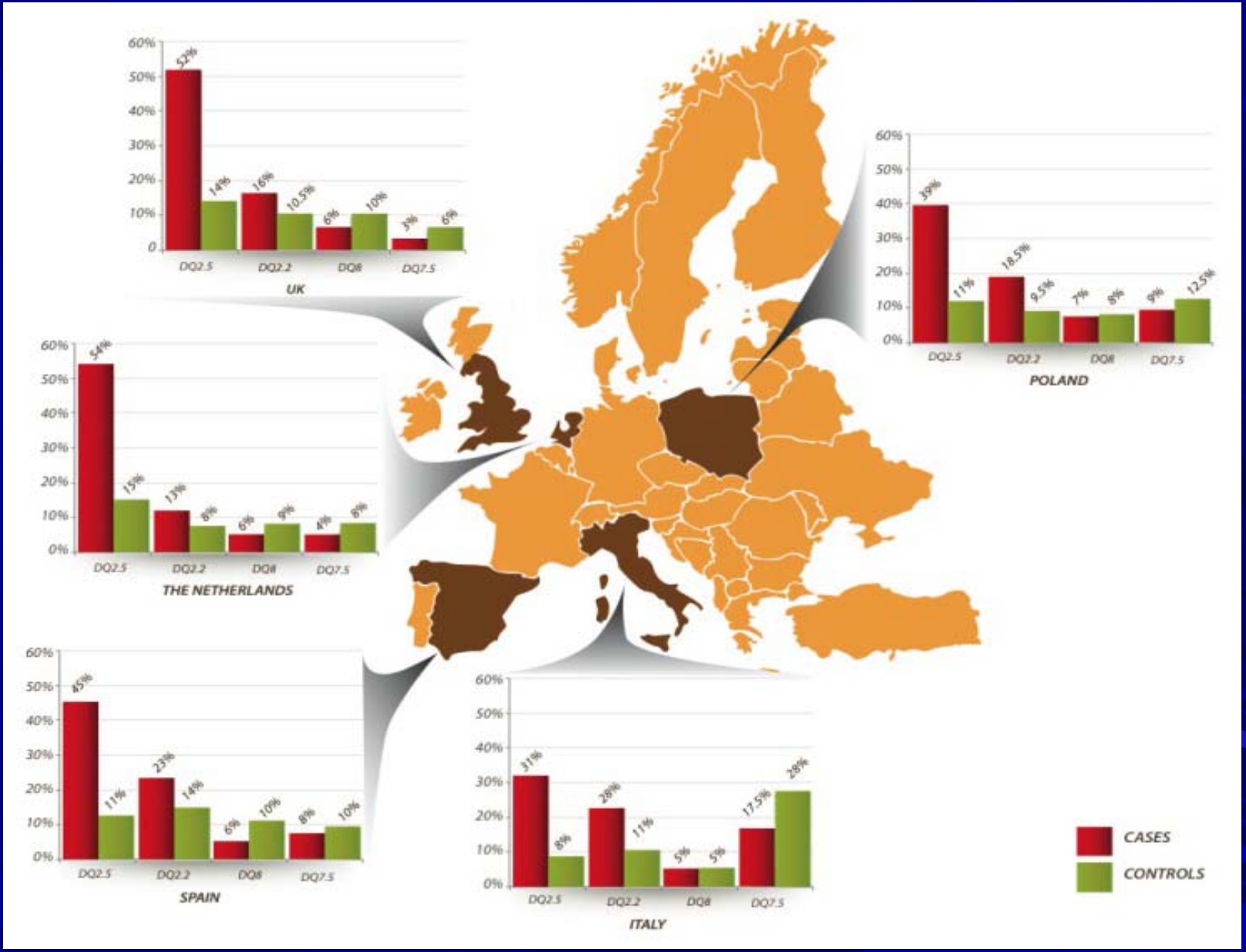
Málo frekventní HLA haplotypy u pacientů s celiakií



Kovářová P., Malušková A.
Krevní centrum Fakultní nemocnice Ostrava

Megiorni and Pizzuti Journal of Biomedical Science 2012, 19:88

Frekvence DQ2.5, DQ2.2, DQ8 a DQ7.5 heterodimerů u CD pacientů.



Javier Gutierrez-Achury, et al. Fine mapping in the MHC region accounts for 18% additional genetic risk for celiac disease Nature Genetics (2015) 47: 577–578

Málo frekventní haplotypy u CD

CD+ pacient s genotypem: DRB1*12:01, **DQA1*05:03,** DQB1*03:01 DQ7.5 (DRB1*01:01, DQA1*01:01, DQB1*05:01)

… CD pacienti, kteří nejsou DQ2.5, DQ2.2, nebo DQ8, jsou skoro vždy DQ7.5 (DQA1*05, DQB1*03:01) pozitivní - 6% (57/61 celkem z 1008)
(Karell *et al*. Hum Immunol. 1998 Mar;59(3):169-75).

… the binding motif of DQ7.5, which does not include the involvement of charged residues, suggests that DQ7.5 restricted gluten epitopes (if they exist) are qualitatively different — likely without the key role of glutamate residues resulting from transglutaminase 2-mediated deamidation as seen for the gluten epitopes characterized to date.
Elin Bergseng, Siri Dørum, Magnus Ø. Arntzen *et al.:* Different binding motifs of the celiac disease-associated HLA molecules DQ2.5, DQ2.2, and DQ7.5 revealed by relative quantitative proteomics of endogenous peptide repertoires. *Immunogenetics* (2015) 67: 73–84

HLA genotyp a riziko CD

FAKULTNÍ NEMOCNICE OSTRAVA

Table 1 | HLA determined risk of coeliac disease ranked highest to lowest[4,7,90]

Genotype	Serotype	General population frequency (%)	Frequency in celiac disease (%)	Relative level of risk‡
DQA1*05xx/DQB1*02xx DQA1*05xx/DQB1*05xx or DQA1*05xx/DQB1*02xx DQA1*0201/DQB1*02xx	DQ2.5/DQ2.5 DQ2.5/DQ2.2	2	25	10-13% (very high)
DQA1*05xx/DQB1*02xx DQA1*03xx/DQB1*0302	DQ2.5/DQ8	1	10	Higher
DQA1*05xx/DQB1*02xx DQA1*§____/DQB1*¶____	DQ2.5/DQx	20	60	Increased
DQA1*0301/DQB1*0302 DQA1*§____/DQB1*¶____	DQ8/DQx	20	3–5	Coeliac disease possible
DQA1*0201/DQB1*0202 DQA1*§____/DQB1*¶____	DQ2.2	10	1	Unlikely
DQA1*05xx/DQB1*¶____ DQA1*§____/DQB1*¶____ or DQA1*§____/DQB1*0201 DQA1*§____/DQB1*¶____	1/2g DQ2.5‖	10	1	Very unlikely
All others	DQx/DQx	35	<1	Extremely unlikely

Husby, S. & Murray, J. A. *Nat. Rev. Gastroenterol. Hepatol.* 2014

Murray, J. A. *et al.* HLA DQ gene dosage and risk and severity of celiac disease. *Clin. Gastroenterol. Hepatol.* **5**, 1406–1412 (2007).

Karell, K. *et al.* HLA types in celiac disease patients not carrying the DQA1*05-DQB1*02 (DQ2) heterodimer: results from the European Genetics Cluster on Celiac Disease. *Hum. Immunol.* **64**, 469–477 (2003).

Pietzak, M. M., Schofield, T. C., McGinniss, M. J. & Nakamura, R. M. Stratifying risk for celiac disease in a large at-risk United States population by using HLA alleles. *Clin. Gastroenterol. Hepatol.* **7**, 966–971 (2009).

HLA a riziko CD

FAKULTNÍ NEMOCNICE OSTRAVA

HLA status	Disease risk
DQ2.5 and **DQ8**	**Very high**
DQ2.5 (double dose of DQB1*02)	**Very high**
DQ8	High
DQ2.5 (single dose of DQB1*02)	**High**
DQ2.x (double dose of DQB1*02)	**High**
DQ2.x (single dose of DQB1*02)	**Low**
DQX.5	**Extremely low**
DQX.x	**Extremely low**

Megiorni and Pizzuti
Journal of Biomedical Science 2012, 19:88

437 celiac children and 551 healthy controls
91.1% patients and 29.0% controls carried DQ2 and/or DQ8 heterodimers

Disease risk

	Patients%	Controls%	Risk	F	M
DQ2 and DQ8	2.5	0.2	1:7	1:7	1:8
DQ2, *B1*02/*02*	23.1	2.4	1:10	1:8	1:13
DQ8, *B1*02* pos.	3.0	0.7	1:24	1:16	1:52
β2, *B1*02/*02*	1.4	0.4	1:26	1:27	1:26
DQ2, *B1*02/X*	55.1	19.2	1:35	1:26	1:54
DQ8, *B1*02* neg.	7.3	6.5	1:89	1:62	1:157
β2, *B1*02/X*	4.6	9.7	1:210	1:211	1:208
α5	2.1	37.9	1:1842	1:8327	1:1027
Other	0.9	23.0	1:2518	1:2530	1:2497

F. Megiorni et al. / Human Immunology 70 (2009) 55-59

HLA haplotypy a riziko CD

Risk category	HLA genotypes Absolute	HLA risk (%)
Low risk	DQ7/DQ7	0.0000
	DQX/DQX	0.0433
	DQ7/DQX	0.0470
Intermediate risk	DQ2.2/DQX	0.1661
	DQ8/DQ7	0.2765
	DQ8/DQX	0.5326
	DQ2.5/DQ8	1.5769
	DQ2.2/DQ2.2	1.6366
	DQ8/DQ8	1.6366
	DQ2.5/DQ7	2.2587
	DQ2.5/DQX	2.6194
	DQ8/DQ2.2	2.9600
	DQ2.2/DQ7	3.7232
High risk	DQ2.5/DQ2.2	7.7079
	DQ2.5/DQ2.5	12.8137

Celkový počet pacientů s CD 530, kontrolní skupina 582

Jihane Romanos & Cisca Wijmenga: Predicting susceptibility to celiac disease by genetic risk Profiling. *Annals of Gastroenterology and Hepatology*. 2010;1(1):11-18.

HLA genotyp u pacientů s CD

Table 1. Frequencies of HLA-DQ genotypes (A) and haplotypes (B) detected in 666 CD patients from south Italy.

A)

HLA-DQ GENOTYPES[a]	M	F	TOT
	n (%)	n (%)	n (%)
DQ2 and/or DQ8 (+)	**220 (33.0)**	**418 (62.8)**	**638 (95.8)**
Double dose of DQ2 and/or DQ8			
DQ2/DQ2	58 (25)[b]	82 (18.9)	140 (21.0)
DQ8/DQ8	2 (0.9)	0	2 (0.3)
DQ2/DQ8	16 (6.9)	26 (6.0)	42 (6.0)
Single dose of DQ2 and/or DQ8			
DQ2/DQX[c]	123 (53.1)	285 (65.6)[b]	408 (61.5)
DQ8/DQX[c]	21 (9.0)	25 (5.8)	46 (7.0)
DQ2 and DQ8 (-)	**12 (5.1)**	**16 (3.7)**	**28 (4.2)**

B)

HLA-DQ HAPLOTYPES	Entire CD cohort	DQ2/DQ8 (+) CD patients	DQ2/DQ8 (-) CD patients
	n (%)	n (%)	n (%)
DQ2.5	371 (28.0)	371 (29.0)	-
DQ2.2	356 (27.0)	356 (28.0)	-
DQ7	324 (24.0)	303 (24.0)	21 (38.0)[d]
DQ5	108 (8.0)	95 (7.4)	13 (23.0)[d]
DQ8	92 (7.0)	92 (7.2)	-
DQ6	61 (4.6)	48 (3.7)	13 (23.0)[d]
DQ9	12 (0.9)	5 (0.4)	7 (13.0)[d]
DQ4	4 (0.3)	2 (0.1)	2 (3.0)
DQ2.3	3 (0.2)	3 (0.2)	-
Chromosomes	1332	1276	56

Tinto N, Cola A, Piscopo C, Capuano M, Galatola M, Greco L, et al. (2015) High Frequency of Haplotype HLA-DQ7 in Celiac Disease Patients from South Italy: Retrospective Evaluation of 5,535 Subjects at Risk of Celiac Disease. PLoS ONE 10(9): 7 pp

HLA genotyp a riziko CD

HLA-DQA1 alleles	HLA-DQB1 alleles	HLA-DQ heterodimers	Predisposition for CD+
*05:01, *05:01	*02:01, *02:01	DQ2.5 (homozygous)	Very high
*05:01, *03	*02:01, *03:02	DQ2.5/DQ8/DQ2.3/DQ8.5	Very high
*05:01, *02:01	*02:01, *02:02	DQ2.5/DQ2.2 (encoded in cis and trans)	Very high
*05:01, x	*02:01,*02	DQ2.5 (encoded in cis and trans)	Very high
*05:01, x	*02:01, x	DQ2.5 (heterozygous)	High
*05:05, *02:01	*03:01, *02:02	DQ2.5 (encoded in trans)/DQ2.2	High
*03, *03	*03:02, *03:02	DQ8 (homozygous)	High
*03, *02:01	*03:02, *02:02	DQ8/DQ2.2/DQ2.3	High
*03, x	*03:02, *02	DQ8/DQ2.3	High
*03, x	*03:02, x	DQ8 (heterozygous)	Intermediate
*02:01, *02:01	*02:02, *02:02	DQ2.2 (homozygous)	Intermediate
*02:01, x	*02:02, *02	DQ2.2 (encoded in cis and trans)	Intermediate
x, x	*02:01, *02:01	Half DQ2.5	Intermediate
*02:01, x	*02:02, x	DQ2.2 (heterozygous)	Low
x, x	*02:01	Half DQ2.5	Low
*05:01 x,	x	Half DQ2.5	Low
*03:01, x	*02:01, x	DQ2.3/x	ND++, #
*05, x	*03:02, x	DQ8.5/x	ND
*03, x	*03:03, x	DQ9/x	ND

N. Ontiveros, M. Y. Hardy, and F. Cabrera-Chavez. Assessing of Celiac Disease and Nonceliac Gluten Sensitivity. Gastroenterology Research and Practice Volume 2015, Article ID 723954, 13 pp.

Málo frekventní haplotypy u CD

Haplotyp (DR9) DQA1*03 – DQB1*03:03 (DQ9)

Bodd M, Tollefsen S, Bergseng E, *et al.* Evidence that HLA-DQ9 confers risk to celiac disease by presence of DQ9-restricted gluten-specific T cells. Hum Immunol (2012) 73:376-381.

*DRB1*03 , DQA1*05 , DQB1*02*

➡ *DRB1*11, **DQA1*05 , DQB1*03:02***

F. Megiorni et al. / Human Immunology 70 (2009) 55-59

➡ CD+ pacient: **DQA1*05:05**, **DQB1*03:02**
DQA1* 04:01, DQB1* 04:02

Kooy-Winkelaar Y. *et al*. The Journal of Immunology, 2011, 187: 5123–5129.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Děkuji za pozornost