HLA and Autoimmune Disease Diagnosis

~ the coeliac disease story

- Coeliac disease (CD) has strong HLA association. Non-HLA loci and environmental association.
- Coeliac disease is caused by an abnormal intestinal T-cell response to glutamine- and proline - rich gluten proteins of wheat, barley and rye.
- CD4+ T cells of CD patients, but not healthy subjects, recognize gluten peptides

NZBLOOD Te Ratonga Toto O Aotearoa

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Coeliac Disease (background)

- Disease of the duodenum caused by peptides found in gluten
- Gluten found in wheat, barley and rye. Confers elasticity to dough
- Affects ~1% of 'Western World': 2-3 % Sweden/Finland; 0.2% Germany
- Only 1 in 7 patients properly diagnosed
- Symptoms vary from mild discomfort to severe e.g. anaemia, fatigue, failure to thrive.
- Hundreds of different gluten proteins (gliadins, glutenins) found in wheat
- Gliadins and glutenins are glutamine- and proline -rich peptides
- Gluten does not contain aspartic acid or glutamic acid
- Tissue transglutaminase deamidates glutamine to glutamic acid.

Coeliac Disease, continued….

- In small intestine vili create large surface area for absorption.
  In CD, gluten diet →disruption of vili.

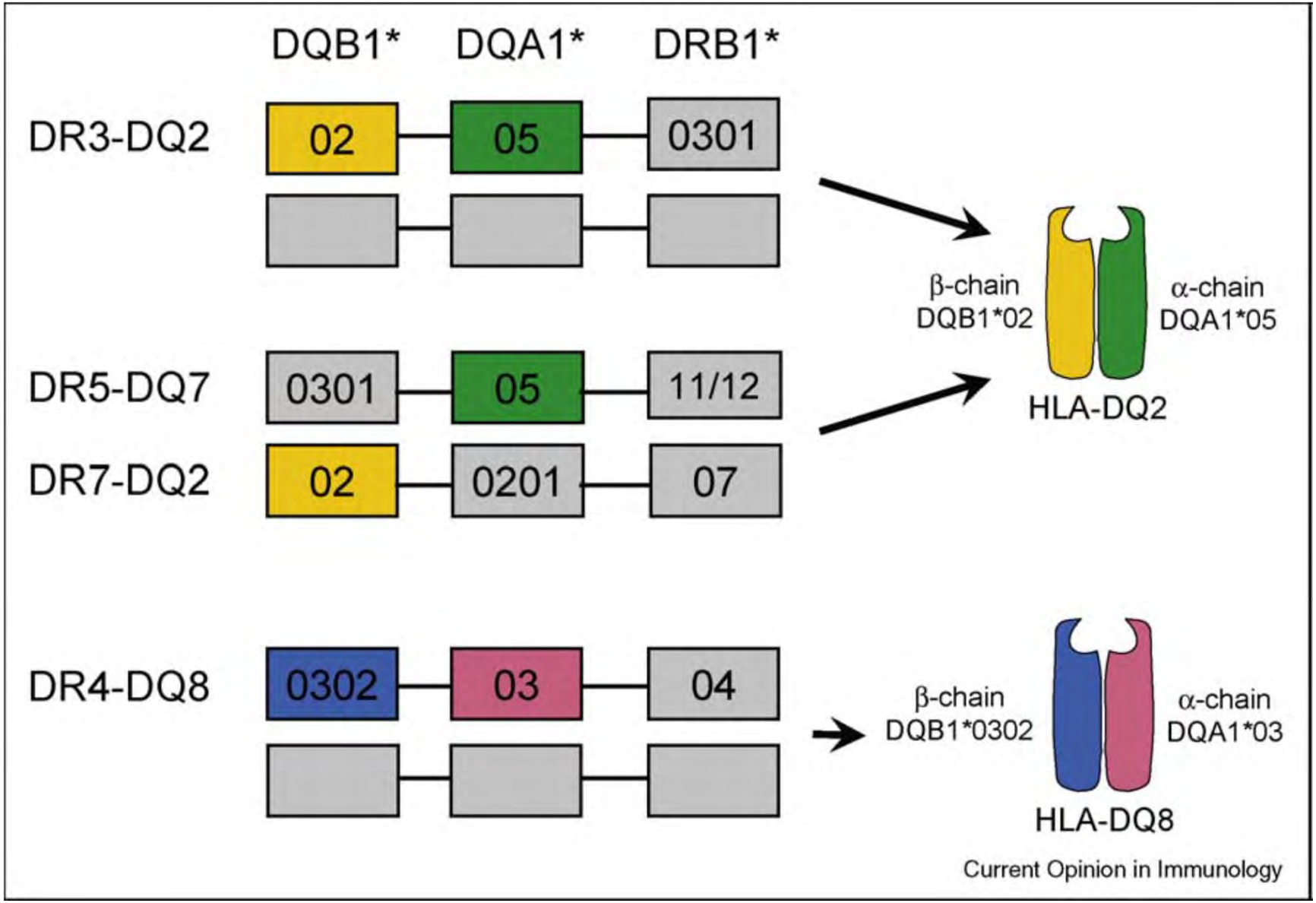
- Multifactorial disease including genetics (HLA-DQ, non-HLA) and environment (gluten). Effector CD4+ T cells recognising Q-rich peptide

- Majority of coeliacs are DQ2.5 (DQB1*02-DQA1*05), remainder DQ8.1 (DQB1*03:02 – DQA1*03).

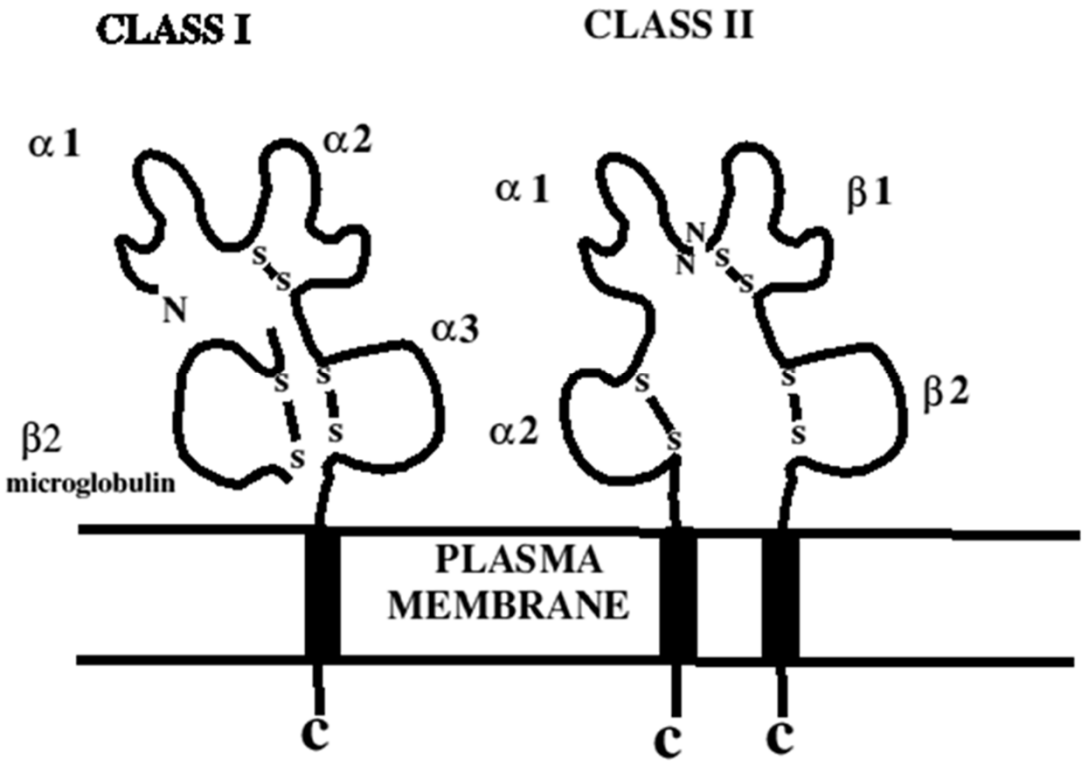
- DQ2.5 is common in healthy inviduals

- Digestive symptoms can be triggered – e.g. gastroenteritis or other infection

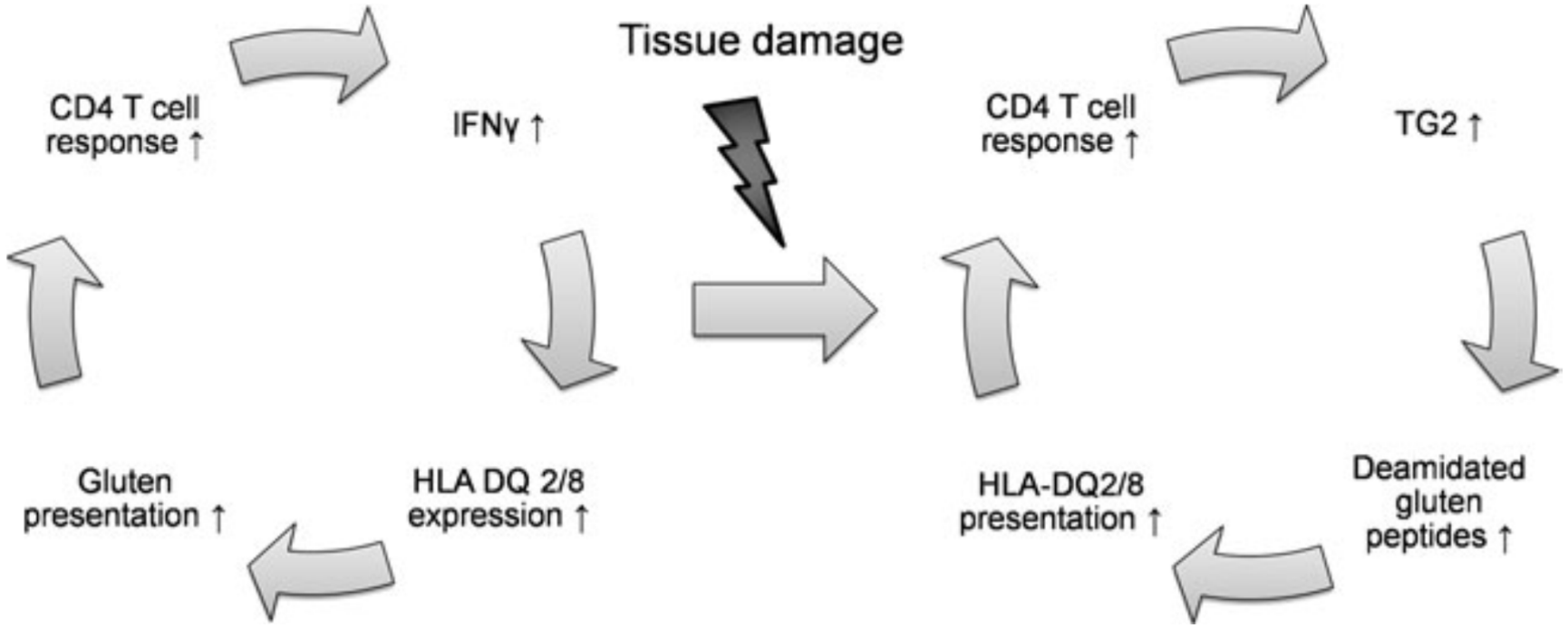
- Co-morbidities e.g. T1D, osteoporosis



HLA association in celiac disease. A vast majority of celiac patients express the HLA-DQ2 heterodimer encoded by the DQA1*05 and DQB1*02 genes.
These two genes are carried either in cis on the DR3-DQ2 haplotype, or in trans in individuals who are DR5-DQ7 and DR7-DQ2 heterozygous. Most DQ2-negative patients express DQ8 encoded on the DR4-DQ8 haplotype. [Qiao et al (2009) Curr Opin Imm 21, 111]



Gliadin: SGQGSFQPSQQN.
Deamidation by transglutaminase, converts Q to E: SGEGSFEPSEEN
DQ2 and DQ8 heterodimers present peptides with negative charges at anchor residues – much stronger recognition by T cells
Isolate T cells from patients, response to peptides varies, patient to patient.
The extent of CD is determined by the type of T cell you develop.



Self amplifying loops in development of CD in DQ2+ or DQ8+ individuals

Tjon, Bergen & Koning (2010) Immunogenetics 62 614

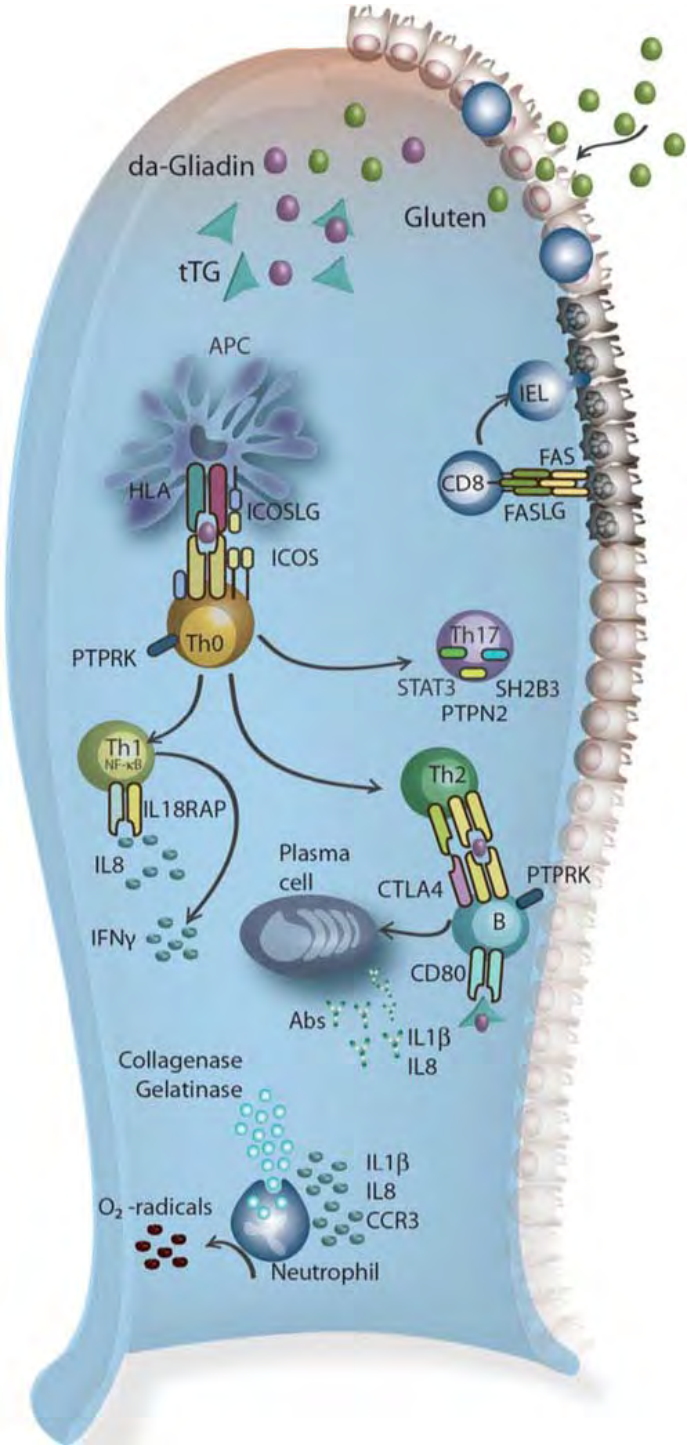
GWAS & Pathway Analysis

Immune cell types implied to be involved in celiac disease by pathway analyses.

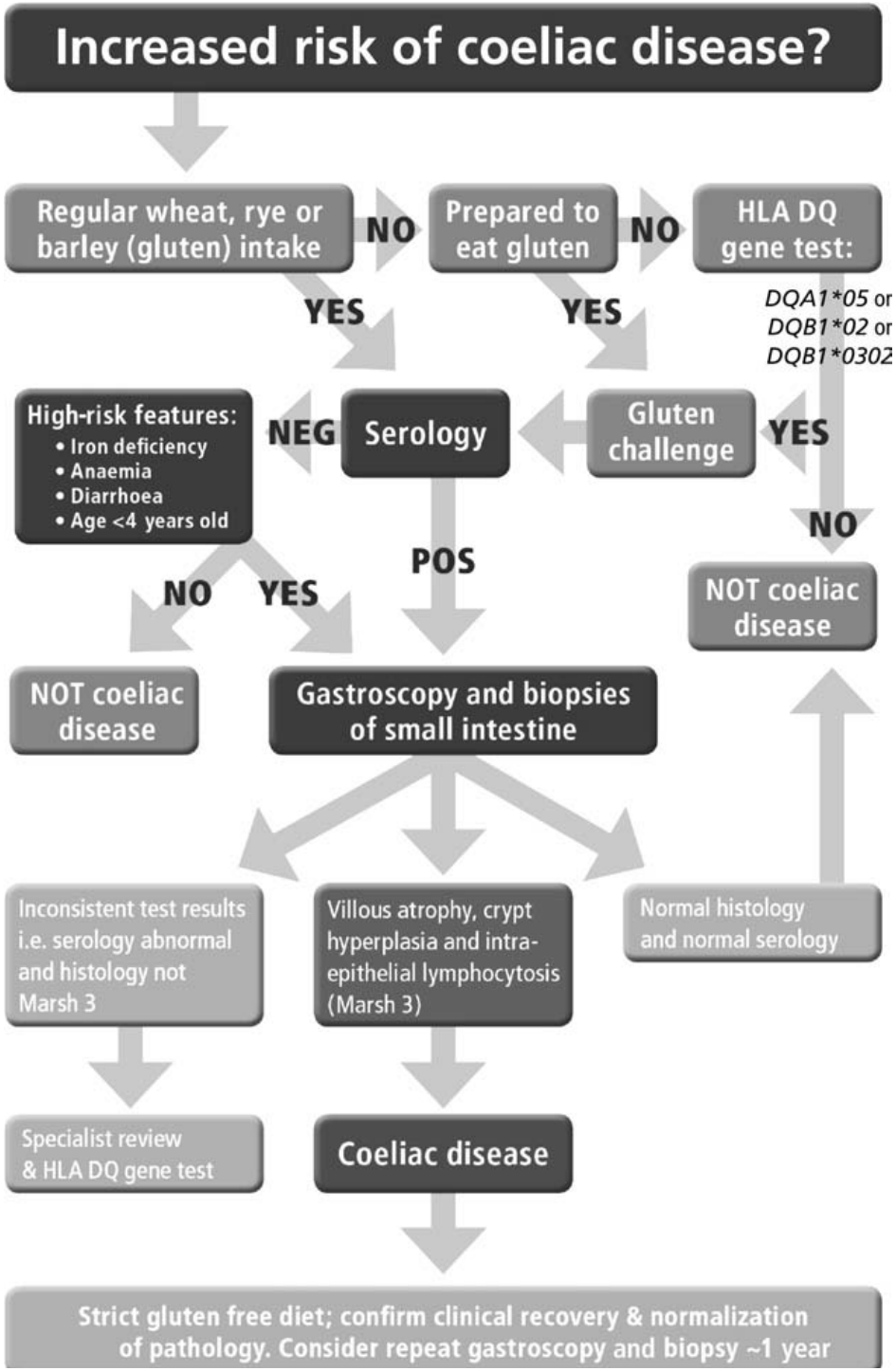
- Gluten molecules, the environmental trigger of CD, are degraded into gliadins which in turn are modified by tissue transglutaminase (tTG) into deamidated gliadin (da-Gliadin).

- da-Gliadin peptides are presented to the immune system, resulting in activation of various immune cell types (according to pathway analyses).

Abs, antibodies; FASLG, FAS ligand; ICOSLG, ICOS ligand; IEL, intraepithelial lymphocytes



Kumar et al (2012) Seminar Immunopathol 34, 567
Abadie et al (2011) Annu Rev Immunol 29, 493.
Trynka et al (2009) Gut 58, 1078.



+gluten:

Serology

↓

Biopsy

↓

HLA DQA/DQB

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Information relating to Coeliac Disease and testing for associated tissue types (HLA)

Coeliac disease is common (0.5-1.0%) in populations from Europe, South America, Australasia and the USA (1,2). The risk of coeliac disease is strongly associated with the DQ2 heterodimer (DQB1*02-DQA1*0501/05) and to a lesser extent with the DQ8 heterodimer (DQB1*0302-DQA1*0301) (3,4). On the rare occasion when a coeliac patient is negative for DQ2 and DQ8, half of the DQ2 heterodimer (e.g. DQB1*02 or DQA1*0501/05) is present (3).
Bearing in mind the importance of the association between DQB1 and DQA1 and coeliac disease the Tissue Typing laboratory now carries out simultaneous typing for HLA-DQB1* and HLA-DQA1* on samples from possible coeliac patients*. Our reports have been altered to include DQA as well as DQB and the comment and information statement will be:

DQB1*02-DQA1*0501/05 (DQ2) = DEMONSTRATED / NOT Demonstrated
DQB1*0302-DQA1*03 (DQ8) = DEMONSTRATED / NOT Demonstrated

"Coeliac disease appears to be linked to the antigen derived from DQB1*02 - DQA1*0501/05 (DQ2) or DQB1*0302-DQA1*03 (DQ8)"

*There is no change in price for the new DQA+DQB test

References

1. Catassi C. The world map of coeliac disease. Acta Gastroenterol Latinoam (2005) **35**: 37-55.
2. van Heel DA, West J. Recent Advances in coeliac disease. Gut (2006) **55**: 1037-46.
3. Karell K *et al.* HLA types in coeliac disease patients not carrying the DQA1*05-DQB1*02 (DQ2) heterodimer: results from the European Genetics Cluster on Coeliac disease. Human Immunol (2003) **64**: 469-77.
4. Monsuur AJ *et al.* Effective detection of human leukocyte antigen risk alleles in coeliac disease using tag SNPs. PLoS (2008) **3**: e2270 (online).

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HLA DQA1/DQB1 testing NZ patients.

HETERODIMER DETECTED	REPORTED ANTIGEN	n	%
DQB1*02-DQA1*0501/05 = DQ2.5	DQ2 PRESENT	499	32.44
None	DQ2 NOT PRESENT DQ8 NOT PRESENT	398	25.88
DQB1*0302-DQAI*03 = DQ8.1	DQ2 NOT PRESENT DQ8 PRESENT	182	11.83
DQA1*0501/05	Half DQ2 heterodimer	147	9.56
DQB1*02	Half DQ2 heterodimer	163	10.60
DQB1*02-DQA1*0501/05 DQB1*0302-DQAI*03 = DQ2+DQ8	DQ2 and DQ8 PRESENT	72	4.68
DQB1*02 DQB1*0302-DQAI*03	DQ2 NOT PRESENT DQ8 PRESENT	40	2.60
DQA1*0501/05 DQB1*0302-DQAI*03	DQ2 NOT PRESENT DQ8 PRESENT	32	3.60
DQB1*02-DQA1*0501/05 DQB1*0302	DQ2 PRESENT : DQ8 NOT PRESENT	3	0.20
DQB1*0302 DQA1*0501/05	DQ2 NOT PRESENT DQ8 NOT PRESENT	1	0.06
DQB1*0302	DQ2 NOT PRESENT DQ8 NOT PRESENT	1	0.06
Total Tested		1538	