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

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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 individuals

• 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
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
Increased risk of coeliac disease?

- Regular wheat, rye or barley (gluten) intake:
  - NO: Prepared to eat gluten
    - NO: HLA DQ gene test:
      - DQA1*05 or DQB1*02 or DQB1*0302
        - +gluten:
          - Serology
            - ↓
          - Biopsy
            - ↓
            - HLA DQA/DQB

  - YES: High-risk features:
    - Iron deficiency
    - Anaemia
    - Diarrhoea
    - Age <4 years old

- Serology:
  - NEG: Gastroscopy and biopsies of small intestine
    - NOT coeliac disease
    - YES: Inconsistent test results i.e. serology abnormal and histology not Marsh 3
      - Specialist review & HLA DQ gene test
        - COeliac disease

  - POS: Gluten challenge
    - YES: NOT coeliac disease
    - NO: Normal histology and normal serology
      - Coeliac disease

- Strict gluten free diet; confirm clinical recovery & normalization of pathology. Consider repeat gastroscopy and biopsy ~1 year
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, Australia 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


Comments or enquiries:

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<table>
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<th>HETERODIMER DETECTED</th>
<th>REPORTED ANTIGEN</th>
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