Coeliac disease (CD), also called gluten-sensitive enteropathy or coeliac sprue, is a chronic inflammatory disorder of the small intestine triggered by ingesting gluten or related proteins found in wheat, barley and rye. It is one of the most common diseases affecting Caucasians with a prevalence of 1:110 to 1:500 in Europe and North America based on serological screening data (1). However, it often remains undiagnosed since a considerable proportion of the patients have atypical or no symptoms at all (2, 3). CD has a wide spectrum of gastrointestinal and extraintestinal manifestations. Classically, the onset of the symptoms occurs between 4 and 24 months of age, following the introduction of cereals into the diet. It is characterised by impaired growth, diarrhoea, and abdominal distension. However, CD can also develop in adults who then commonly present with iron-deficiency anaemia, fatigue, weight loss and diarrhoea. Extraintestinal manifestations include osteoporosis, infertility, neurological and psychiartical syndromes. There are several pathological conditions known to be associated with CD such as dermatitis herpetiformis, type 1 diabetes mellitus and autoimmune thyroiditis (1, 4).

CD is an acquired disease which is caused by interactions between genetic and environmental factors. Certain HLA-molecules (most notably, HLA-DQ2 and -DQ8) have been identified as risk factors which confer predisposition to the disease. An environmental factor that precipitates the disease is gluten (5). Wheat gluten is a mixture of glutenin and gliadin polypeptides, of which the latter are considered to be the principal toxic component of wheat gluten (6). It has recently been shown that proteolytic degradation of α-gliadin by gastric and pancreatic enzymes generates a stable 33-mer peptide which reacts with tissue transglutaminase and elicits vigorous response of gut-derived human T cell lines from CD patients (7). This finding leads to the following hypothesis of sequential events which play a role in the pathogenesis of CD (8): toxic food grain proteins such as gliadin and related peptides are broken down by digestive enzymes, leaving a 33-mer peptide fragment which arrives intact in the small intestine, where it undergoes deamidation by tissue transglutaminase; the deamidated peptide is endocytosed and processed by antigen-presenting cells to form epitopes that bind to the HLA-DQ2 or -DQ8 molecule and are subsequently recognised by CD4+ T cells; the activated CD4+ T cells generate cytokines, leading to villous atrophy and crypt hyperplasia which are the immunopathological hallmarks of CD.

A high prevalence rate of approx. 10 % among first degree relatives of CD patients indicates a strong genetic influence on susceptibility to develop this disease (9, 10). The HLA region alone is believed to confer 36.2 % of the increased risk of CD to siblings of affected individuals (11).
Table 1 (based on references 5, 6 and 12)

<table>
<thead>
<tr>
<th>CD predisposing HLA-DQ</th>
<th>Serological typing notation</th>
<th>Genotype 1. Haplotype</th>
<th>Genotype 2. Haplotype</th>
<th>Frequency in CD patients</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>DRB1*</td>
<td>DQA1*</td>
<td>DQB1*</td>
</tr>
<tr>
<td>DQ2</td>
<td>DR3 – DQ2 / DR3 – DQ2</td>
<td>03:01</td>
<td>05:01</td>
<td>02:01</td>
</tr>
<tr>
<td></td>
<td>DR3 – DQ2 / DR7 – DQ2</td>
<td>03:01</td>
<td>05:01</td>
<td>02:01</td>
</tr>
<tr>
<td></td>
<td>DR5 – DQ7 / DR7 – DQ2</td>
<td>11/12</td>
<td>05:05</td>
<td>03:01</td>
</tr>
<tr>
<td>DQ8</td>
<td>DR4 – DQ8</td>
<td>04</td>
<td>03:01</td>
<td>03:02</td>
</tr>
</tbody>
</table>

Individuals who are DR3-DQ2 homozygous or DR3-DQ2/DR7-DQ2 heterozygous have a particular risk for CD which might be explained by a gene dosage effect of the DQB1*02 allele (13). A similar gene-dosage effect of DQ8 was also observed (14). Few CD patients have DQB1*02 without DQA1*05:01 or DQA1*05:01 without DQB1*02 (14, 15). CD patients who carry neither the DQ2 or DQ8 heterodimers nor one half of the DQ2 heterodimer are exceedingly rare (0.4 to 0.7 %) (14, 15). Remarkably, the closely related DQA1*05-DQB1*03:01 and DQA1*02:01-DQB1*02 heterodimers alone do not confer susceptibility to CD (6, 16).

The diagnosis of CD is based on a combination of history and clinical presentation, serological tests (tissue transglutaminase or endomysial antibody) and small bowel biopsy (1, 17). Screening for HLA-DQ2 and -DQ8 has a low specificity and positive predictive value as approx. 30 % and 20 % of healthy people are positive for DQA1*05:01-DQB1*02 (DQ2) and the DQA1*03-DQB1*03:02 (DQ8) haplotype, respectively (18). However, in difficult cases in which the diagnosis has not been confirmed due to equivocal small bowel histological finding, HLA-DQ2 and -DQ8 determination can be useful in exclusion, probably lifelong, of CD because absence of the relevant alleles makes the disease unlikely. In addition, HLA-DQ typing is less expensive and distressing to the patient than repeated small bowel biopsies (17, 19). Alternatively, HLA typing may be performed in CD relatives as a pre-screening test to restrict the number of subjects that must undergo further investigations. Unlike the serological markers, the presence of which is strictly dependent on dietary exposure to gluten, HLA alleles are always detectable even during symptom-free intervals of the disease (11).
References