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Celiac Disease

[*Coeliac Disease, Celiac Sprue, Nontropical Sprue, Gluten-Sensitive Enteropathy*]

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Summary

Disease characteristics. Celiac disease is a systemic immune disease that can be associated with gastrointestinal findings (diarrhea, weight loss, abdominal pain, anorexia, lactose intolerance, abdominal distention, and irritability) and/or highly variable non-gastrointestinal findings (iron-deficiency anemia, dermatitis herpetiformis, chronic fatigue, joint pain/ inflammation, migraines, depression, attention-deficit disorder, epilepsy, osteoporosis/ osteopenia, infertility and/or recurrent fetal loss, vitamin deficiencies, short stature, failure to thrive, delayed puberty, dental enamel defects, and autoimmune disorders). Classic celiac disease, characterized by mild to severe gastrointestinal symptoms, is less common than nonclassic celiac disease, characterized by absence of gastrointestinal symptoms.

Diagnosis/testing. The diagnosis of celiac disease relies on characteristic histologic findings on small-bowel biopsy and clinical and/or histologic improvement on a gluten-free diet. Most individuals with celiac disease have celiac disease-associated antibodies and specific pairs of allelic variants in two HLA genes, *HLA-DQA1* and *HLA-DQB1*. Because 30% of the general population has one of the celiac disease-associated HLA alleles and only 3% of individuals with one or both of these alleles develop celiac disease, presence of celiac disease-associated HLA alleles is not diagnostic of celiac disease; however, their absence essentially excludes a diagnosis of celiac disease.

Management. *Treatment of manifestations:* lifelong adherence to a strict gluten-free diet (avoidance of wheat, rye, and barley); treatment of nutritional deficiencies (iron, zinc, calcium,

fat-soluble vitamins, folic acid); standard treatment of osteoporosis. *Prevention of primary manifestations:* lifelong gluten-free diet. *Surveillance:* for symptomatic individuals responsive to a gluten-free diet, periodic physical examination and assessment of growth, nutritional status, and non-gastrointestinal disease manifestations; repeat small-bowel biopsy one to three years following diagnosis. For symptomatic individuals unresponsive to a gluten-free diet, periodic evaluation for refractory sprue, ulcerative enteritis, T-cell lymphoma, and other gastrointestinal cancers. *Agents/circumstances to avoid:* dietary gluten. *Testing of relatives at risk:* when the celiac disease-associated HLA alleles in the family are known, molecular genetic testing of first-degree relatives (including young children) to monitor those with known celiac disease-susceptibility alleles for early evidence of celiac disease in order to institute gluten-free diet early in the disease course.

Genetic counseling. Celiac disease is a multifactorial disorder resulting from the interaction of *HLA-DQA1* and *HLA-DQB1* gene variants known to be associated with celiac disease susceptibility, less well-recognized variants in non-HLA genes, gliadin (a subcomponent of gluten), and other environmental factors. Some empiric risk data are available for at-risk relatives.

Diagnosis

Clinical Diagnosis

The diagnosis of celiac disease is made through the combination of the following [Hill et al 2005, NIH Consensus Committee 2005, Green & Cellier 2007]:

- Small-bowel biopsy that shows characteristic histologic abnormalities
- Subsequent improvement (clinical and/or histologic) on a gluten-free diet

Additional findings in most affected individuals:

- Clinical findings or abnormal laboratory findings (although some individuals are asymptomatic and lack laboratory abnormalities)
- Celiac disease-associated antibodies

  Note: Although positive specific antibody testing is highly associated with celiac disease and greatly facilitates its diagnosis [Fasano 2001, Farrell et al 2002], small-bowel biopsy remains the gold standard in confirming the diagnosis of celiac disease.
- Celiac disease-associated human leukocyte antigen (HLA) alleles

Testing

Celiac-associated antibody testing

Note:

(1) It is important for the individual being tested to remain on a gluten-containing diet before celiac disease-associated antibody testing and small-bowel biopsy are performed because antibody levels and histologic abnormalities gradually revert to normal on a gluten-free diet.

(2) For individuals on a gluten-free diet, diagnostic celiac disease-associated antibody testing and small-bowel biopsy should follow a gluten challenge (i.e., eating gluten-containing foods [the equivalent of one to three slices of bread per day] for one to three months and sometimes longer if no symptoms are observed). However, the gluten challenge can make some individuals very ill.

- **Tissue transglutaminase (tTG) IgA.** Measurement of serum concentration of tissue transglutaminase (tTG) immunoglobulin A (IgA) is often recommended for initial testing because of its high sensitivity and specificity for celiac disease, relatively low cost, and ease of test performance and reliability. However, the sensitivity and specificity differ among laboratories [Abrams et al 2006]. False positive test results may occur in persons with acute coronary syndromes and in individuals with cirrhosis and chronic liver disease.
- **Endomysial antibody (EMA) IgA.** Serum concentration of endomysial antibody (EMA) IgA has the highest specificity (~99%), but is more expensive and more time-consuming to perform and is potentially more prone to false negative results than serum concentration of tTG IgA. Because it is determined by indirect immunofluorescence, serum concentration of EMA IgA is subject to observer variability, which affects its sensitivity (Murray 2004). When performed in an experienced laboratory, this test has a higher specificity (approaching 100%) than tTG antibody testing and is useful in individuals with cirrhosis.
- **Anti-deamidated gliadin-related peptide (a-DGP) antibodies IgA and IgG.** This new test detects antibodies binding synthetic deamidated gliadin-related peptides (DGPs). In preliminary studies examining groups with a high prevalence of celiac disease, both isotypes (IgA and IgG) were shown to be highly sensitive and specific for active celiac disease. Specificity is greater than in antigliadin (AGA) testing and similar to that for tTG testing. An increase in DGP antibody levels may precede an increase in serum concentration of tTG-IgA in young children [Liu et al 2007, Niveloni et al 2007]. However, as in all antibody tests, a minority of individuals have false negative results.
- **Measurement of serum concentration of total IgA to evaluate for selective IgA deficiency**. The prevalence of selective IgA deficiency, a condition of unknown cause, is 1:700 in the general population. For unknown reasons the prevalence of selective IgA deficiency is higher (1:50) in individuals with celiac disease than in the general population [Wong el al 2003, Alaedini & Green 2005].

  Note: Because individuals with selective IgA deficiency do not produce IgA antibodies, the celiac-associated IgA antibodies tTG IgA and EMA IgA are not present in these individuals. Therefore, in these individuals, testing for celiac-associated IgG antibodies (tTG IgG) or DGP-IGG should be performed instead.
- **Antigliadin antibody (AGA) IgA and IgG.** The NIH Consensus Development Conference on Celiac Disease recommended against the use of AGA in the diagnosis of celiac disease because of the low specificity of this assay and the availability of more specific and sensitive tests, including tTG and EMA IgA [Hill et al 2005].

Note: (1) The overall sensitivity of celiac disease-associated antibody testing may be slightly increased when all four tests (serum concentrations of tTG IgA, EMA IgA, total IgA, and AGA IgA and IgG) are performed. However, the use of panels that incorporate AGA markedly increase the false positive rate as a result of a lone positive AGA antibody and drop the positive predictive value to low levels except in the case of a very high pre-test prevalence. (2) Although a positive result on celiac disease-associated antibody testing is likely to be diagnostic of celiac disease, false positive results occur. (3) Conversely, normal celiac-associated antibody test results do not exclude the diagnosis of celiac disease, especially in the presence of lesser degrees of villous atrophy or in persons on a gluten-free diet prior to testing.

Small-bowel biopsy generally refers to multiple (four or more) biopsies taken endoscopically from the post-bulbar duodenum.

Characteristic histologic findings that are the gold standard for the diagnosis of celiac disease include partial or complete villous atrophy, crypt hyperplasia, and increased intraepithelial lymphocytes (IELs). Based on the dynamic development of the pattern of the intestinal lesions and the frequency of mild lesions in celiac disease, Marsh [1992] proposed a four-stage grading classification to establish the diagnosis and to assess improvement in response to a gluten-free diet (Table 1). Although these changes are not unique to celiac disease, reversion of intestinal damage after gluten withdrawal is unique to celiac disease. The positive predictive nature of the biopsies depends on the relative prevalence of celiac disease as compared to other causes of enteropathy in the population.

Table 1. Classification of Intestinal Lesions in Celiac Disease

Type	Mucosal Findings
Stage 0. Preinfiltrative stage	Normal
Stage 1. Infiltrative lesion [1]	Increased intraepithelial lymphocytes
Stage 2. Hyperplastic lesion	Stage 1 changes plus hyperplastic crypts
Stage 3. Destructive lesion [2]	Stage 2 changes plus: Partial villous atrophy (termed 3a) Subtotal villous atrophy (3b) Total villous atrophy (3c)
Stage 4. Hypoplastic lesion [3]	Total villous atrophy with crypt hypoplasia

[Hill et al 2005]

1. Stage 1 can also be the result of other disease processes such as inflammatory bowel disease (IBD), use of nonsteroidal anti-inflammatory drugs (NSAIDs), Sjögren syndrome, *helicobacter pylori* gastritis, and possibly other food intolerances.

2. Stage 3, the classic lesion of celiac disease and the most common biopsy finding, can be seen with other conditions including tropical sprue, small-bowel bacterial overgrowth, use of NSAIDS, acute gastroenteritis, and self-limited enteritis.

3. Stage 4 is occasionally seen in elderly individuals.

Small-bowel biopsy can fail to detect histologic changes of celiac disease in the following circumstances:

- Gluten-free diet
- Early stages of the disease
- Patchy mucosal lesions
- Masking of celiac effect by peptic changes
- Insufficient number of samples taken
- Incorrect orientation of the slide during microscopic analysis
- Latent celiac disease (defined as a positive celiac-associated antibody screen but no villous atrophy on small-bowel biopsy) [Alaedini & Green 2005, Hill et al 2005]

False-positive interpretations of celiac disease also occur as a result of over-interpretation of poorly oriented biopsies.

Note: The diagnosis of celiac disease can be complicated by the highly variable age at which symptoms first appear and the lack of symptoms in many individuals (i.e., silent celiac disease, defined as the lack of symptoms in the presence of a positive celiac-associated antibody screen and villous atrophy on small-bowel biopsy) [Farrell & Kelly 2002, Alaedini & Green 2005].

Other endoscopic methods such as water immersion, high-resolution imaging, and chromoendoscopy may be used to improve tissue sampling or poor sensitivity resulting from partial atrophy.

Capsule endoscopy, a noninvasive method for investigation of the small bowel involving ingestion of a small camera, provides serial detailed images of the small-bowel mucosa. It may be used to evaluate the extent of disease, monitor response to treatment, and assess individuals who do not respond to the gluten-free diet. For individuals not willing to undergo a small-bowel biopsy, capsule endoscopy offers an alternative approach for gaining information about possible damage to the small bowel [Green & Rubin 2006, Murray et al 2008]. Nonetheless, the role of capsule endoscopy in the diagnosis of celiac disease remains to be defined.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Genes. Specific pairs of allelic variants in two HLA genes, *HLA-DQA1* and *HLA-DQB1*, are associated with celiac disease:

- *HLA-DQA1* encodes the alpha chain of the celiac disease-associated HLA heterodimers.
- *HLA-DQB1* encodes the beta chain of the celiac disease-associated HLA heterodimers.

Table 2. HLA Terminology

Term	Meaning	Example
HLA-DQ#	Gene symbol	*HLA-DQA1*
DQ#	Specific heterodimer	DQ2
*##	Family of alleles	*03
*####	Specific sequence variation [1]	*HLA-DQB1**0302 [2]

Terminology is unique to the HLA system of indicating sequence variants.

1. Two digits are appended to an allele family number to indicate an allele with a specific sequence variation.

2. Indicates *HLA-DQB1,* allele family *03, allelic variant 02

Celiac disease results from the presence of the following:

- The major histocompatibility complex (MHC) class II antigens (necessary but not sufficient):
  - DQ2 heterodimer (encoded by specific *HLA-DQA1**05 alleles and specific *HLA-DQB1**02 alleles)

    and/or
  - DQ8 heterodimer (encoded by specific *HLA-DQA1**03 and *HLA-DQB1**0302 alleles)
- Dietary gluten
- Other as-yet-undetermined factors that promote manifestation of the disorder in some genetically susceptible individuals

The HLA-DQ2 **heterodimer** (see Figure 1) comprises the specific products of the following two gene variants:

- *HLA-DQA1* (designated *HLA-DQA1**0501 or *0505)

- *HLA-DQB1* (designated *HLA-DQB1**0201 or *0202)

DQ2 is found in more than 90% of individuals with celiac disease and in 20%-30% of the general population [Sollid & Lie 2005, Liu 2006].

A small percentage of individuals with celiac disease have **either** an *HLA-DQA1* sequence variant (*0501 or *0505) **or** an *HLA-DQB1* sequence variant (*0201 or *0202), but not both (i.e., only half of the DQ2 heterodimer) [Sollid 2002, Margaritte-Jeannin et al 2004, Sollid & Lie 2005].

The HLA-DQ8 heterodimer (see Figure 1) comprises the specific products of the *HLA-DQB1* sequence variant *HLA-DQB1**0302. This sequence variant is always inherited with the *HLA-DQA1**03 variant because of linkage disequilibrium (i.e., a nonrandom association of alleles).

DQ8 is found in 5%-10% of individuals with celiac disease and approximately 10% of the general population (see Figure 1) [Sollid & Lie 2005,Liu 2006].

Other loci. Non-HLA celiac disease-susceptibility genes must contribute to the risk of developing celiac disease in individuals who are predisposed based on the 70% concordance rate between identical twins, which is much higher than that between HLA-identical sibs (30%) [Greco et al 2002]. Several loci and candidate susceptibility genes have been identified. Further research is needed to confirm the significance of these candidate genes [Sollid & Lie 2005].

Candidate celiac disease-susceptibility genes include the following:

- ***MICA* and *MICB*.** MHC class I chain-related genes (MIC) express non-conventional HLA class I molecules involved in the hypersensitive innate immune response in individuals with celiac disease (see Molecular Genetic Pathogenesis). MICA and MICB are stress molecules encoded by *MICA* and *MICB* (respectively) that are overexpressed on villous enterocytes (epithelial cells) in celiac disease in response to IL-15, a cytokine induced by exposure to certain gliadin peptides. MICA binds to and upregulates NKG2D receptors on IELs and leads to direct killing of enterocytes. Different isoforms of MICA have differing binding affinities for NKG2D that could affect T-cell responses [Hue et al 2004]. Genetic variations in *MICA* and *MICB* may contribute to the increased risk of celiac disease in individuals with either of the HLA heterodimers (DQ2 or DQ8) that predispose to celiac disease. In one study, specific allelic variants in the MIC gene region, including *MICA*-A5.1, appeared to confer a fivefold increase in risk for celiac disease [Bolognesi et al 2003]; however, another study showed no HLA-class II-independent contribution of the MICA genotype to celiac disease risk [Bilbao et al 2002].
- ***IL10*.** An allelic variant in the *IL10* gene promoter that decreases the production of this anti-inflammatory cytokine is associated with early-onset celiac disease and a severe intestinal lesion (Stage 3c) (see Table 1) [Barisani et al 2006].
- **Myosin IXB *(MY09B)*.** A common sequence variant in *MYO9B* that encodes a myosin molecule involved in actin remodeling of the cytoskeleton and tight junction assembly leads to enhanced epithelial paracellular permeability. In one report, individuals in the Dutch population homozygous for this variant had a 2.3 times greater risk for celiac disease than those without the variant [Monsuur et al 2005]. However, the potential role of *MY09B* in celiac disease has not been fully elucidated. Wolters et al [2007] found a strong association of a single nucleotide variant of *MY09B* (rs7259292) with refractory celiac disease type II (RCDII) and enteropathy-associated T-cell lymphoma (EATL), complications of celiac disease with poor prognoses.

Despite these discoveries, a genome-wide association study for celiac disease did not associate the *MYO9B* gene region with this disease [van Heel et al 2007]. Further studies are needed.

- **IL-2 and IL-21.** IL-2, a cytokine involved in T-cell activation and proliferation, is secreted by antigen-stimulated T cells. IL-21, a T-cell-derived cytokine, enhances B, T, and NK (natural killer) cell proliferation and interferon-γ production. Both IL-2 and IL-21 are involved in mechanisms of other intestinal inflammatory diseases. A recent genome-wide association study identified sequence variants of the *IL2* and *IL21* genes as risk factors for celiac disease [van Heel et al 2007].
- ***CTLA4, ICOS,* and *CD28* (chromosomal region 2q33)** are genes involved in regulation of T-cell activity and were previously associated with other autoimmune diseases. *CTLA4* functions as a negative regulator of T-cell activation and competes for receptors used by *CD28*. The evidence for association between markers in or around *CTLA4* and celiac disease has been controversial [Brophy et al 2006]. *ICOS* and *CD28* influence T-cell activation.
- ***CCR3*, *IL12A*, *IL18RAP*, *RGS1*, *SH2B3*** (rs3184504**), and *TAGAP*** are additional genes involved in immune response of celiac disease [Hunt et al 2007].

Additional candidate susceptibility loci (genes unknown) have been mapped to chromosomal regions 5q31-q33 and 11q [Nalaui et al 2001].

Clinical testing

- **Targeted mutation analysis.** *HLA-DQA1* and *HLA-DQB1* genotypes are determined to detect the presence or absence of the celiac disease-associated alleles, *HLA-DQA1**0501, *HLA-DQA1**0505, *HLA-DQB1**0201, *HLA-DQB1**0202, and *HLA-DQB1**0302.

  A variety of methods may be used to detect specific sequence variants in a gene (e.g., sequencing, allele-specific hybridization). Allele-specific polymerase chain reaction (PCR) amplification and an internal control followed by gel electrophoresis have been utilized.

Table 3 summarizes molecular genetic testing for this disorder.

Table 3. Molecular Genetic Testing Used in Celiac Disease

Gene Symbol	Test Method	Alleles Detected [1]	Allele Detection Frequency by Test Method	Test Availability
HLA-DQA1	Targeted mutation analyses [2]	*HLA-DQA1**0501 *HLA-DQA1**0505	>99.9%	Clinical Testing
HLA-DQB1		*HLA-DQB1**0201 *HLA-DQB1**0202 *HLA-DQB1**0302		

1. This terminology is unique to the HLA system of indicating sequence variants (see Table 2). Alleles detected may vary among testing laboratories.

2. A variety of methods may be used to detect specific sequence variants in a gene (e.g., sequencing, allele-specific hybridization).

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Because 30% of the general population has one of the celiac disease-associated HLA alleles (encoding the heterodimers DQ2 and/or DQ8), and only 3% of individuals with one or both of these heterodimers develop celiac disease, identification of celiac disease-associated HLA alleles is not diagnostic of celiac disease. However, absence of any celiac disease-associated HLA alleles (see Table 3) essentially **excludes** a diagnosis of celiac disease [Zubillaga et al 2002,Sollid & Lie 2005]. Absence of the DQ2 celiac disease-susceptibility haplotype and the

DQ8 celiac disease-susceptibility haplotype reduces the lifetime risk of developing celiac disease to well below 1%, independent of diet.

Unlike antibody testing and small-bowel biopsy, for which test reliability depends on the presence of gluten in the diet, the results of molecular genetic testing for celiac disease-associated HLA alleles can be interpreted accurately independent of diet [Farrell & Kelly 2002, Alaedini & Green 2005, Green & Jabri 2006].

Testing Strategy

Circumstances in which molecular genetic testing to identify celiac disease-associated HLA alleles are most useful include the following:

- Symptomatic individuals with borderline or ambiguous celiac-associated antibody results or small-bowel biopsy results
- Previously symptomatic individuals who are asymptomatic on a gluten-free diet and do not want to undergo a gluten challenge
- Symptomatic individuals who have not responded to a gluten-free diet
- Differential diagnosis of an individual with celiac disease-like symptoms
- Family members at risk for celiac disease
- Evaluation of an individual with a disorder known to be associated with celiac disease (e.g., Down syndrome, Turner syndrome, selective IgA deficiency, autoimmune disorders [insulin-dependent diabetes mellitus, Sjögren syndrome, thyroiditis])

Differences of opinion exist among health care professionals regarding the testing strategies for individuals with a clinical suspicion of celiac disease and those at increased risk based on family history. The testing strategies below are recommendations based on clinical practice of celiac disease centers and a review of the literature.

Testing strategy to establish the diagnosis of celiac disease in a symptomatic individual **prior to beginning a gluten-free diet** (for a description of symptoms see Clinical Description):

- Specific celiac disease-associated antibody testing (except AGA). Positive or equivocal results should be followed up by small-bowel biopsy.
- If the clinical suspicion for celiac disease is strong or frank malabsorption is present, a small-bowel biopsy should be performed irrespective of the results of specific celiac disease-associated antibody testing.
- When celiac disease-associated antibodies are absent, molecular genetic testing for celiac disease-associated HLA alleles can assist in excluding or determining susceptibility to celiac disease if suspicion for celiac disease remains.
- A definitive diagnosis of celiac disease is made in the presence of a small-bowel biopsy showing characteristic histologic changes and clinical and/or histologic improvement on a gluten-free diet; however, exceptions include individuals with self-limited enteritis and tropical sprue who improve on a gluten-free diet.
- For individuals with no detectable celiac disease-associated HLA alleles on molecular genetic testing, examination for alternative causes of symptoms is necessary.

Testing strategy to establish the diagnosis of celiac disease in a symptomatic individual who is on a **gluten-free diet** includes molecular genetic testing for celiac disease-associated HLA alleles to exclude or determine susceptibility to celiac disease:

- Individuals who continue to have symptoms despite adherence to a gluten-free diet are unlikely to have celiac disease; molecular genetic testing for celiac disease-associated HLA alleles may allow for exclusion of celiac disease in a substantial proportion of such individuals. In these individuals, examination for alternative causes of symptoms is necessary.
- If molecular genetic testing detects celiac disease-associated HLA alleles and the degree of clinical suspicion is high, the patient can undergo a gluten challenge (consisting of a gluten-containing diet for at least one month or until symptomatic) prior to small-bowel biopsy to confirm the diagnosis.
- If the individual does not wish to pursue a gluten challenge because of the risk of illness and intestinal damage, a definitive diagnosis of celiac disease is not possible. The individual foregoes establishing the diagnosis with certainty and continues the gluten-free diet if it is alleviating symptoms.

Testing strategy to establish the diagnosis of celiac disease in a symptomatic individual with **borderline or ambiguous celiac-associated antibody testing** includes testing for the combination of tTG, EMA, DGPs IgA and IgG, and total IgA, if not done previously:

- For individuals who continue to have borderline or ambiguous results on celiac disease-associated antibody testing, molecular genetic testing for celiac disease-associated HLA alleles is recommended to exclude or determine HLA susceptibility to celiac disease.
- Small-bowel biopsy is recommended for individuals with celiac disease-associated HLA alleles and a high degree of clinical suspicion who are well established on a gluten-containing diet (the equivalent of one to three slices of bread/day for three months or until symptomatic).
- A definitive diagnosis of celiac disease is made in a person with a positive small-bowel biopsy and clinical and/or histologic improvement on a gluten-free diet.

Testing strategy to establish the diagnosis of celiac disease in a symptomatic individual with **borderline or ambiguous small-bowel biopsy results** includes a review of the pathologic slides with an expert gastrointestinal pathologist. Molecular genetic testing for celiac disease-associated HLA alleles is also of value:

- For individuals with celiac disease-associated HLA alleles, repeat celiac disease-associated antibody testing (EMA, TTG, and/or DGPs) and perform small-bowel biopsy if indicated.
- For individuals with negative celiac disease-associated antibody testing (i.e., EMA, TTG, or DGPs) with or without celiac disease-associated HLA alleles, investigation into other causes of symptoms is indicated.

Testing strategy to establish the diagnosis of celiac disease in a symptomatic individual who has **not responded to a gluten-free diet** includes review of the results of the original celiac disease-associated antibody testing (if completed) prior to initiation of the gluten-free diet and a review of the original biopsy (if completed) by an expert in gastrointestinal pathology to confirm a diagnosis of celiac disease. If results are negative or inconclusive, the following are recommended:

- Molecular genetic testing for celiac disease-associated HLA alleles to determine HLA susceptibility to celiac disease.
- Investigation into other causes for symptoms other than celiac disease.

- Consultation with an expert dietician to analyze the diet for hidden sources of gluten and to evaluate for lactose or fructose intolerance, which can contribute to poor clinical response to a gluten-free diet.

If **refractory sprue** is suspected, the following are recommended:

- Immunohistochemical studies to assess for abnormal IELs
- Studies for clonal T-cell receptor (TCR) gene rearrangements
- Assessment for T-cell lymphoma, if indicated (see also Types of Celiac Disease, **Refractory sprue/celiac disease**)
- Imaging studies for both benign and malignant complications

Testing strategy to establish the diagnosis of celiac disease in **asymptomatic relatives** of an individual with celiac disease includes molecular genetic testing to determine the presence or absence of celiac disease-susceptibility HLA haplotypes:

- Molecular genetic test results that reveal celiac disease-associated HLA alleles are followed by celiac disease-associated antibody testing at three- to five-year intervals.
  - Small-bowel biopsy is recommended when celiac disease-associated antibody testing is positive.
  - A definitive diagnosis of celiac disease is made for a person with a positive small-bowel biopsy and clinical and/or histologic improvement on a gluten-free diet.
- Molecular genetic test results that do not detect celiac disease-associated HLA alleles essentially exclude a diagnosis of celiac disease. Approximately one-third of family members are expected to be in this category [Bonamico et al 2006]. No additional clinical follow-up is recommended.

Genetically Related (Allelic) Disorders

No phenotypes other than the broad and variable presentation of celiac disease, associated disorders, and secondary autoimmune conditions have been described in association with these celiac disease-associated HLA alleles (see Prevalence).

Clinical Description

Natural History

While previously considered to be primarily a gastrointestinal disorder of malabsorption, celiac disease is now known to be a systemic autoimmune disease with gastrointestinal symptoms and multiple, highly variable non-gastrointestinal symptoms (see Figure 2). It is induced by dietary gluten in genetically susceptible individuals.

The onset of celiac disease may occur at any age after weaning; for adults, the peak age of diagnosis is between ages 30 and 50 years.

The average time between the onset of symptoms and diagnosis is 11 years because of the wide range of non-specific symptoms shared by other disorders, the highly variable age of onset of symptoms, and the lack of symptoms in certain individuals (i.e., silent celiac disease) [Green et al 2001]. However, the range in time between the onset of symptoms and diagnosis can depend on the degree of awareness of the disease and the patient's clinical presentation.

The female-to-male ratio of diagnosed celiac disease is reported to be 3:1. However, population-based studies have suggested that it is equally common in females and males.

Affected females more often have an HLA-DQ2 haplotype of paternal origin than affected males, suggesting a possible parental imprinting effect of the HLA region (see Figure 2) [Megiorni et al 2007].

Manifestations of Celiac Disease—Phenotypic features of celiac disease include but are not limited to the following:

- **Gastrointestinal manifestations.** Chronic or recurrent diarrhea, malabsorption, abdominal pain and distention, bloating, vomiting, and weight loss. Patients often receive the diagnostic label of irritable bowel syndrome (IBS) [Hill et al 2005]. As many as 50% of individuals with celiac disease do not have daily diarrhea at the time of diagnosis. Additionally, many are overweight, even obese [Murray et al 2004].
- **Non-gastrointestinal manifestations.** Dermatitis herpetiformis, chronic fatigue, joint pain/inflammation, iron-deficiency anemia, migraines, depression, attention-deficit disorder, epilepsy, osteoporosis/osteopenia, infertility and/or recurrent fetal loss, vitamin deficiencies, short stature, failure to thrive, delayed puberty, dental enamel defects, and various secondary autoimmune disorders (see **Autoimmune disorders associated with celiac disease**) [Green & Jabri 2003, Hill et al 2005, NIH Consensus Committee 2005].

Types of Celiac Disease—Classic celiac disease refers to the presence of mild to severe intestinal symptoms such as diarrhea, failure to thrive, weight loss, abdominal pain, anorexia, lactose intolerance, abdominal distention, and irritability [Hill et al 2005]. Children with classic celiac disease typically present with symptoms between ages six and 24 months [Catassi & Fabiani 1997, Fasano & Catassi 2005].

Nonclassic celiac disease refers to celiac disease without prominent gastrointestinal symptoms (see Figure 2); however, individuals with atypical celiac disease can also have gastrointestinal symptoms such as reflux, bloating, vomiting, constipation, and dyspepsia, which are often mislabeled as IBS. Approximately 70% of patients are diagnosed based on extraintestinal manifestations associated with celiac disease [Telega et al 2008].

Iron-deficiency anemia is the most common presentation of nonclassic celiac disease, and may be the only finding.

Dermatitis herpetiformis, an intensely pruritic rash on the extensor surfaces of the extremities, is a common non-gastrointestinal manifestation.

Other extraintestinal presentations include osteoporosis/osteopenia, dental enamel hypoplasia, infertility and/or recurrent fetal loss, vitamin deficiencies, elevated transaminases, fatigue, psychiatric syndromes, and various neurologic conditions, including peripheral neuropathy, ataxia, seizures, migraines, attention-deficit hyperactivity disorder (ADHD), and poor school performance [Zelnik et al 2004, Hill et al 2005, NIH Consensus Committee 2005, Niederhofer & Pittschieler 2006].

Nonclassic celiac disease usually presents in later childhood or adulthood. Children with nonclassic celiac disease can present with unexplained short stature, neurologic symptoms, and delayed puberty.

Nonclassic celiac disease is more common than classic celiac disease.

Silent celiac disease. Silent celiac disease is defined as the lack of symptoms in the presence of a positive celiac-associated antibody screen and villous atrophy on small-bowel biopsy. Individuals with silent celiac disease are most often identified through an affected family

member or through screening programs. (see Figure 3) [Hed et al 1986,Fasano & Catassi 2001].

Latent celiac disease. Latent celiac disease is defined as a normal small-bowel biopsy in:

- An individual who is currently ingesting gluten, but previously had a small-bowel biopsy consistent with celiac disease
- An individual positive for EMA

Note: Not all authorities include individuals with the described findings in this classification. However, with the advent of capsule endoscopy, which may reveal villous atrophy more distal to the duodenum, latent celiac disease remains difficult to diagnose (see Figure 3). Individuals not suspected of having celiac disease or those whose symptoms are not investigated make up an even larger base of the "celiac iceberg" (see Figure 3).

Refractory sprue/celiac disease. Refractory sprue or RCD refers to persistence of symptoms of frank malabsorption with persistent intestinal inflammation and villous atrophy despite a strict gluten-free diet for at least six to 12 months. All individuals with refractory sprue are over age 20 years. Few studies of persons with well-characterized refractory sprue have been reported in the literature. The prognosis is uncertain, although some persons respond to corticosteroids and immunosuppressive agents:

- **Primary refractory sprue** describes the condition in which individuals have never responded to a gluten-free diet. Molecular genetic testing is important in this group because the individuals lack a response to the gluten-free diet, which is one of the major diagnostic criteria.
- **Secondary refractory sprue** refers to the condition in which individuals have a full recovery, followed later by a relapse, despite adherence to the gluten-free diet.

An alternate classification involves the determination of the IELs in persons with RCD:

- In active, uncomplicated celiac disease the IELs have surface expression of CD3 and CD8, a normal occurrence. In addition, these lymphocytes are not clonally restricted (i.e., polyclonal).
- In RCDI, the IELs are normal.
- In RCDII, the IELs are abnormal in the following ways:
  - They have lost surface expression of CD3, CD8, and the TCR.
  - CD3 is detectable within the cell.
  - They have generally become clonal.

RCDII has a worse outcome than RCDI because of high mortality resulting from the poor response to immunosuppression and a high rate of progression to enteropathy-associated EATL. The risk for EATL in persons with refractory sprue may exceed 50% [Green & Jabri 2003, Krauss & Schuppan 2006].

Morbidity and mortality. The clinical spectrum of celiac disease is wide, from a lack of symptoms to severe malabsorption syndromes. The manifestations of untreated celiac disease can include vitamin and mineral deficiencies, anemia, osteoporosis, infertility, neuropsychiatric conditions, secondary autoimmune disorders, and certain malignancies including non-Hodgkin's lymphoma, adenocarcinoma of the small intestine, and esophageal and oropharyngeal squamous carcinoma.

Overall, persons with untreated or unresponsive celiac disease have increased early mortality compared to the general population, mainly because of the higher rate of malignancies. This risk is highest in the year after initial diagnosis, likely because of a prolonged period of unrecognized symptoms associated with celiac disease. Malignancy and mortality rates are high in individuals with refractory sprue [Corrao et al 2001].

West et al [2004] found no significant difference in mortality rates between affected individuals on a gluten-free diet and controls [Farrell & Kelly 2002, Green & Jabri 2003, Treem 2004, West et al 2004, Alaedini & Green 2005, Catassi et al 2005, Green 2005, Hill et al 2005, NIH Consensus Committee 2005].

Infertility. Celiac disease has been shown to be associated with both infertility and recurrent pregnancy loss. Untreated celiac disease is estimated to be responsible for approximately 3%-6% of all cases of infertility of unknown cause and is a risk factor for low birth weight, intrauterine growth retardation (IUGR), spontaneous abortion, and preterm labor. Appropriate treatment with a gluten-free diet appears to eliminate the increased risk for both infertility and adverse pregnancy outcome [Meloni et al 1999, Wong et al 2000, Bradley & Rosen 2004, Ludvigsson et al 2005].

Autoimmune disorders associated with celiac disease. Autoimmune disorders occur three to ten times more frequently in individuals with celiac disease than in the general population. These include type 1 diabetes mellitus, thyroiditis, Sjögren syndrome, Addison disease, autoimmune liver disease, and neurologic disorders such as peripheral neuropathy.

The relationship between the increased frequency of second autoimmune diseases and celiac disease is attributed to a shared genetic and immunologic mechanism, although cause and effect is difficult to prove directly. There may be an etiologic effect of the celiac disease itself. One study suggested that the risk of developing these autoimmune conditions is proportional to the duration of gluten exposure [Ventura et al 1999]; however, this was not supported in other studies [Sategna Guidetti et al 2001a, Duggan 2004, Viljamaa et al 2005, Green & Jabri 2006].

Although studies suggest that a gluten-free diet does not prevent the development of autoimmune disease [Sategna Guidetti et al 2001a], initiation of a gluten-free diet may confer a benefit to individuals with celiac disease with various autoimmune diseases:

- Diabetes- and thyroid-specific autoantibodies tend to disappear following treatment by a gluten-free diet [Ventura et al 1999].
- Improved linear growth and glycemic control in diet-compliant children with celiac disease and type 1 diabetes mellitus has been recognized in one study [Sanchez-Albisua et al 2005], although Nóvoa Medina et al [2008] recently reported that a gluten-free diet had no impact on metabolic control of diabetes.
- A gluten-free diet may normalize thyroid function in individuals with thyroid disease [Sategna-Guidetti et al 2001b].

Pathophysiology. Celiac disease is caused by an immune-mediated response to gluten in genetically susceptible individuals leading to inflammation of the small bowel, villous damage, and resultant malabsorption. The etiology of many of the extraintestinal manifestations has not been fully elucidated.

Genotype-Phenotype Correlations

Individuals with the HLA-DQ8 genotype only are much less likely to have celiac disease than those with HLA-DQ2 genotype only.

Among affected individuals, no difference in clinical severity of celiac disease is observed between those with the HLA-DQ2 genotype only and those with the HLA-DQ8 genotype only.

Individuals with both the HLA-DQ2 genotype and the HLA-DQ8 genotype do not appear to be at greater risk for celiac disease than those who have the HLA-DQ2 genotype only [Green 2005].

Individuals who have both the HLA-DQ2 and HLA-DQ8 genotypes are more likely to have celiac disease than those with the HLA-DQ8 genotype only.

Homozygosity for the *HLA-DQB1**02 allele in individuals with DQ2 only who have celiac disease has been reported to be associated with an approximately fivefold greater risk for celiac disease [Murray et al 2007].

Homozygosity for the *HLA-DQB1**02 allele is reportedly found more frequently in individuals with classic celiac disease than in individuals with nonclassic celiac disease and in complicated cases including refractory sprue and EATL [Al-Toma et al 2006, Karinen et al 2006].

It is possible for individuals who have half of the DQ2 molecule (only the *HLA-DQA1* sequence variant [*0501 or *0505] **or** the *HLA-DQB1* sequence variant [*0201 or *0202]) to develop celiac disease, but the risk is much lower than for individuals who have the full HLA-DQ2 genotype (i.e., both the *HLA-DQA1* sequence variant [*0501 or *0505] and the *HLA-DQB1* sequence variant [*0201 or *0202]) [Zubillaga et al 2002, Margaritte-Jeannin et al 2004, Qiao et al 2005].

Penetrance

An individual:

- With celiac disease-associated HLA alleles has an approximately 3% overall risk of developing celiac disease (~30% of the general population has DQ2 and/or DQ8 and ~1% of the general population is affected with celiac disease).
- Whose HLA status is unknown and who has an affected first-degree relative with celiac disease has a risk in the range of 5%-10% for developing celiac disease [Bonamico et al 2006, Fasano et al 2003].
- Who has an affected first-degree relative and the same celiac disease-associated HLA allele as the affected individual has up to a 40% risk of developing celiac disease [Treem 2004]
- Who has half of the DQ2 heterodimer (i.e., only the *HLA-DQA1* sequence variant (*0501 or *0505) OR the *HLA-DQB1* sequence variant (*0201 or *0202) but not both) has a less than 1% risk for developing celiac disease.
- With DQ2 who is homozygous for an *HLA-DQB1**02 allele may have a fivefold greater risk for developing celiac disease than a DQ2-positive individual without *HLA-DQB1**02 homozygosity [Vader et al 2003, Treem 2004, Koning 2005, Qiao et al 2005, Murray et al 2007].
- With DQ8 is much less likely to develop celiac disease in the absence of DQ2 than in the presence of DQ2. The absolute risk of celiac disease occurring in those circumstances is very low.

Genetic influences on penetrance of celiac disease in HLA-DQ2- or HLA-DQ8-genotype-positive individuals clearly exist, as evidenced by clustering of celiac disease in families. The

following differences are theorized to affect penetrance (see **Molecular Genetics**, Innate immune response):

- **Intestinal permeability**. Increased intestinal permeability has been observed in individuals with celiac disease compared to individuals without the disorder, possibly allowing entry of more gliadin peptides into the submucosa. Zonulin, a protein involved in tight junction regulation, is upregulated by gliadin in a sustained fashion in individuals with celiac disease, leading to increased paracellular permeability, whereas this effect is limited and transient in individuals without the disorder [Drago et al 2006]. The *MY09B* gene variant may increase intestinal permeability.
- **Innate immune response to gliadin**. Genetic differences in the innate immune response to gliadin separate from the HLA-associated immune response appear to contribute to development of celiac disease and villous atrophy in some individuals.

For a description of other genes involved in the immune response that are implicated in penetrance, see Molecular Genetic Testing, **Other loci**.

Prevalence

Celiac disease, once thought to be a rare condition, now appears to affect approximately 1% of individuals in the US; however, at this time only 3%-5% of individuals with celiac disease are diagnosed [Collin et al 2007]. Physician education about the variable clinical presentation and the use of celiac disease-associated antibody testing in diagnosis can increase the rate of diagnosis, as demonstrated in Ireland and Finland [Dickey & McMillan 2005, Collin et al 2007]. In some regions of Finland, up to 70% of the 1% of the general population predicted to have celiac disease has been diagnosed [Collin et al 2007].

Celiac disease is considered to be common in Europe, the US, Australia, Mexico, and some South American countries. Celiac disease is also found in parts of northwest India [Hung et al 1995].

In the most comprehensive US study to date, the overall prevalence of celiac disease in a group with no known risk factors was one in 133 (0.8%), compared to one in 22 in first-degree relatives of an index case, one in 39 in second-degree relatives, and one in 56 in individuals with either gastrointestinal symptoms or an extra-gastrointestinal disorder associated with celiac disease [Fasano et al 2003].

Gudjónsdóttir et al [2004] found that the risk for celiac disease in families with at least two affected children is approximately three times higher than in families with only one affected child.

Using tTG IgA testing, Hoffenberg et al [2003] found that the prevalence of celiac disease in children age five years is one in 104 in the general population in Denver, Colorado.

The highest reported prevalence of celiac disease is 5.6%, found in a refugee population in North Africa [Catassi et al 1999]. The authors speculate that in this population celiac disease gives a selective advantage to affected individuals by “protecting” them from intestinal infections and parasites.

Celiac disease is rarely diagnosed in individuals of sub-Saharan African descent, although African-Caribbean and African-American individuals with celiac disease have been reported [Brar et al 2006]. The rate of underdiagnosis in these and other minority groups may be high.

The prevalence of celiac disease is increased in the following disorders [Giannotti et al 2001, Fasano et al 2003, Hoffenberg et al 2003, Treem 2004, Troncone et al 2004, Green 2005, NIH Consensus Committee 2005]:

- Down syndrome (prevalence of celiac disease: 5%-12%)
- Turner syndrome ~3%)
- Williams syndrome (3%-10%)
- Selective IgA deficiency (~2%-10%)
- Autoimmune disorders including:
  - Insulin-dependent diabetes mellitus (~6%)
  - Sjögren syndrome (~5%)
  - Thyroiditis (~2%-4%)

The prevalence of refractory sprue is not known; it is probably quite rare.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Celiac disease is underdiagnosed because of its variable, often subtle presentations and clinical overlap with several other conditions.

Conditions that tend to mask or divert a diagnosis of celiac disease include dyspepsia, IBS, inflammatory bowel disease (IBD), tropical sprue, constipation, chronic fatigue, and various neurologic syndromes [Alaedini & Green 2005, NIH Consensus Committee 2005]. Some of these conditions can occur in conjunction with celiac disease.

It is estimated that 36% of individuals diagnosed with celiac disease initially had the diagnosis of IBS [Green et al 2001]. Approximately 5% of individuals with IBS and 2% of persons with IBD also have celiac disease [Sanders et al 2001, Yang et al 2005].

Non-celiac gluten sensitivity is a condition distinct from celiac disease and is present in some individuals who do not have celiac disease but have gluten sensitivity that improves on a gluten-free diet. The pathogenic mechanism for this condition is not currently known. One study revealed that those diagnosed with IBS responded to gluten withdrawal if they were DQ2 positive [Wahnschaffe et al 2001]. Individuals with neurologic or gastrointestinal symptoms in the absence of celiac disease who report improvement with a gluten-free diet are difficult to evaluate and may receive a diagnostic label of gluten sensitivity or intolerance.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with celiac disease, the following evaluations are recommended:

- Small-bowel biopsy in those who are well established on a gluten-containing diet to assess the degree of villous atrophy (Table 1). However, the degree of villous atrophy does not correlate with the severity of the clinical findings [Brar et al 2007].

- Baseline bone-density test in adults to evaluate for osteoporosis/osteopenia. In those with osteoporosis, vitamin D and parathyroid hormone concentrations should be evaluated [Green & Jabri 2003].
- Screening tests for anemia, abnormal liver function, and nutrient deficiencies (iron, zinc, calcium, fat-soluble vitamins, folic acid)
- Evaluation for a coexisting malignancy or autoimmune disease in symptomatic and/or elderly individuals [Alaedini & Green 2005, Pietzak 2005]

Treatment of Manifestations

Celiac disease. Ideally, the care of a newly diagnosed individual should be provided by a team including a gastroenterologist, primary care physician, and experienced nutritionist (see Figure 4). Local branches of national support groups can be helpful as additional resources [NIH Consensus Committee 2005,Green & Jabri 2006] (see Figure 4).

The only treatment for individuals with celiac disease is strict adherence to a gluten-free diet that requires lifelong avoidance of wheat, rye, and barley:

- Treatment with a gluten-free diet should be started only after the diagnosis has been established by intestinal biopsy.
- A dietitian experienced in treating celiac disease should be involved.
- In approximately 70% of affected individuals, symptoms improve within two weeks after starting a gluten-free diet.
- For some patients, even a small amount of gluten (i.e., 100 milligrams) can damage the small intestine. Note that a slice of bread contains approximately 2.5 grams of gluten.
- It can be difficult to adhere to the gluten-free diet, as gluten is found in many foods and other ingested products. Some hidden sources of gluten:
  - Non-starchy foods such as soy sauce and beer
  - Non-food items such as some medications, postage stamp glue, and cosmetics (e.g., lipstick)

Any deficiencies of iron, zinc, calcium, fat-soluble vitamins, and folic acid should be treated.

Osteoporosis should be treated in the usual manner.

'Unresponsive celiac disease' refers to patients with celiac disease who show no improvement on a gluten-free diet:

- The most common reason for unresponsive celiac disease is the presence of small amounts of gluten in the diet. This gluten ingestion may be intentional, such as "cheating" at social events or using communion wafers, or unintentional, including ingestion of gluten in medications and gluten-containing foods in restaurants. Advice from a nutritionist experienced in management of the gluten-free diet is recommended to achieve the best results.
- Assessment for lactose or fructose intolerance is important because these conditions can be responsible for lack of response to the gluten-free diet [Green & Jabri 2003].
- Assessment for alternative or additional diagnoses such as microscopic colitis, pancreatic exocrine insufficiency, IBS, and eating disorders is necessary in those in whom gluten contamination is not the explanation.

For persons who are not responding to a gluten-free diet, identification of a celiac disease-susceptibility HLA haplotype can provide motivation to continue the diet, to examine the diet for hidden sources of gluten, or to address the possibility of refractory sprue.

Refractory sprue or celiac disease. Individuals with persistent symptoms and intestinal inflammation despite adherence to a gluten-free diet may need to be treated with systemic corticosteroids (e.g., local-active budesonide) and immunosuppressants or anti-TNF-alpha antibodies [Green & Jabri 2003, Alaedini & Green 2005, NIH Consensus Committee 2005, Krauss & Schuppan 2006, Brar et al 2006].

Prevention of Primary Manifestations

See Treatment of Manifestations.

Breast-feeding has a protective effect against the development of celiac disease in early childhood. Compared to children who were not breast-fed, children who are breast-fed are less likely to develop celiac disease in early childhood and if they do develop celiac disease, they are more likely to have:

- A later age of onset of symptoms
- Fewer classic symptoms such as diarrhea, growth disturbance, vomiting, abdominal pain, or distention [Ivarsson et al 2002]
- A higher rate of "nonclassic" symptoms [D'Amico et al 2005]

In breast-fed genetically predisposed infants, delaying the introduction of small amounts of gluten in the diet until ages four to six months (but not after age nine months) may be beneficial or protective [Norris et al 2005]. This strategy delays the development of celiac disease in early childhood and may prevent the development of celiac disease. Studies are underway to evaluate prevention.

Prevention of Secondary Complications

Treatment with a gluten-free diet can:

- Reverse growth failure and the reduced bone mineralization in children with celiac disease;
- Decrease the rate of spontaneous abortions and frequency of low-birth-weight infants in women with celiac disease;
- Reduce to the general population level the risk for certain types of cancers including small-intestine adenocarcinoma, esophageal cancer, and non-Hodgkin's lymphoma;
- Reduce the excess risk of mortality in symptomatic disease.

Surveillance

For symptomatic individuals with celiac disease, periodic physical examinations and assessments of symptoms, growth, and adherence to a gluten-free diet are recommended.

Note: There is no evidence to support screening for malignancies:

- tTG IgA and EMA IgA normalize in two to six months following the initiation of the gluten-free diet. Testing for these celiac disease-associated antibodies is useful for assessing recovery and adherence to the gluten-free diet. Testing for celiac disease-associated antibodies should be performed one year after initiation of a gluten-free diet. Although most individuals have no detectable tTG IgA and EMA IgA at that

time, it can occasionally take up to three years for celiac disease-associated antibody levels to normalize.

- A repeat small-bowel biopsy one to three years following diagnosis is often recommended to assess response to a gluten-free diet, as histologic findings usually revert to normal after three to 12 months on a gluten-free diet.

Because celiac disease is a chronic multisystem disorder, affected individuals should be:

- Screened for nutritional deficiencies including iron-deficiency anemia and fat-soluble vitamin deficiencies;
- Followed for common complications of untreated celiac disease including osteoporosis, neurologic problems, and the development of secondary autoimmune diseases;
- Evaluated for the presence of refractory sprue, ulcerative enteritis, T-cell lymphoma, and other gastrointestinal cancers if they do not respond to a gluten-free diet [Pietzak 2005].

For asymptomatic relatives who have the HLA-DQ2 or HLA-DQ8 celiac disease-susceptibility haplotype on molecular genetic testing and negative antibody results, tTG IgA testing should be performed at three- to five-year intervals to screen for the development of celiac disease-associated antibodies [Wong et al 2003, Hill et al 2005, NIH Consensus Committee 2005, Pietzak 2005].

Agents/Circumstances to Avoid

Gluten in the diet (see Treatment of Manifestations and Prevention of Primary Manifestations).

Testing of Relatives at Risk

It is advisable to test first-degree relatives of individuals with celiac disease (including young children) for celiac disease-associated HLA alleles:

- In infants with celiac disease-associated HLA alleles, introduction of small amounts of gluten between ages four and six months, while continuing to breast-feed, delays and may reduce symptoms of celiac disease [Ivarsson et al 2002, D'Amico et al 2005, Norris et al 2005].
- Individuals who have a celiac disease-associated HLA allele require celiac disease-associated antibody testing every three to five years (starting at age three years) or if symptoms of celiac disease develop.
- If a diagnosis of celiac disease is made, secondary complications can be prevented through treatment with a gluten-free diet.
- Family members who do not have a celiac disease-associated HLA allele require no further testing [Sollid & Lie 2005].

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Drug therapies that could be used as an alternative for or additive to a gluten-free diet are being investigated [Sollid & Khosla 2005].

An intestinal permeability blocker (AT1001) is currently in a phase IIb clinical study.

Possible drug therapies still being researched:

- Oral administration of bacterial endopeptidases that digest the toxic portion of gliadin
- Inhibitors of the zonulin pathway that act to prevent gliadin from inducing increased intestinal permeability
- Peptides that block the binding groove of DQ2 and DQ8
- Transglutaminase (tTG) blockers
- Cytokine blockers

Other therapeutic alternatives to a gluten-free diet currently under investigation:

- Genetically modified wheat
- A vaccine that could desensitize or induce tolerance in individuals with celiac disease [Green & Jabri 2006]

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

The impact of oat ingestion in celiac disease remains controversial. There is concern that most conventional oat products are contaminated with wheat during growing, milling, or processing. Pure oat products uncontaminated with gluten are available and their use is encouraged, as they add fiber and nutritional value to the diet.

Depending on the age at which the gluten-free diet is begun, some problems such as delayed growth and tooth discoloration do not improve on a gluten-free diet. Also, some associated autoimmune diseases are often well established at the time of diagnosis of celiac disease; therefore, their reversal on a gluten-free diet is unlikely.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

HLA-DQ2 genotype-related celiac disease susceptibility is inherited in an autosomal dominant or autosomal recessive manner depending on the parental celiac disease-susceptibility HLA genotypes (see Figure 5A).

HLA-DQ8 genotype-related celiac disease susceptibility is inherited in an autosomal dominant manner (see Figure 5B).

Risk to Family Members

Parents of a proband

- Empiric data suggest that the risk for celiac disease in parents of a proband is approximately 5%-10% [Fasano et al 2003, Treem 2004].
- The risk to a parent of having celiac disease is increased when the parent is known to have the DQ2 heterodimer and/or the DQ8 heterodimer. The risk is less when only half of the DQ2 heterodimer (i.e., the *HLA-DQA1* sequence variant **or** the *HLA-DQB1* sequence variant, but not both) is present [Qiao et al 2005].
- The estimated risk to a parent of having celiac disease is reported to be 12.9% when multiple family members are affected [Gudjónsdóttir et al 2004].
- At least one parent of an individual with, for example, the DQ2 celiac disease-susceptibility HLA haplotype (see Figure 5A) or the DQ8 celiac disease-susceptibility HLA haplotype (see Figure 5B) has the same HLA haplotype as the proband.
- Each parent of an individual who has DQ2 in the *trans* configuration (see Figure 5A) has at least one of the relevant HLA alleles.
- Different extended HLA haplotypes may confer differing levels of risk.

  Note: Although nearly all individuals diagnosed with DQ2- or DQ8-related celiac disease susceptibility have a parent who is positive for the DQ2 or the DQ8 heterodimer or half of the DQ2 heterodimer (i.e., the *DQA1* sequence variant OR the *DQB1* sequence variant), the family history may appear to be negative because of reduced penetrance, failure to diagnose the disorder in family members, late onset of the disease in the affected parent, or early death of the parent before the onset of symptoms.

Sibs of a proband

- The overall empiric risk for celiac disease in sibs of a proband is 7%-20% if the HLA haplotype is not known [Treem 2004]. If the HLA haplotype of the parents is known, the risk to the sibs can be refined.
- Sibs who share the same celiac disease-susceptibility HLA haplotype with the proband have a risk of developing celiac disease that approaches 40% [Treem 2004].
- The risk to a sib of having celiac disease is estimated at 23.6% when multiple family members are affected [Gudjónsdóttir et al 2004].
- If a parent of the proband has the DQ2 celiac disease-susceptibility haplotype in *cis* configuration (see Figure 5A) or the DQ8 celiac disease-susceptibility HLA haplotype (see Figure 5B), the risk to each sib of inheriting the celiac disease-susceptibility HLA haplotype is 50%.
- If one parent of the proband has half of the DQ2 heterodimer (*HLA-DQA1**0501 or *0505) and the other parent has half of the DQ2 heterodimer (*HLA-DQB1**0201 or *0202), the risks to sibs are as follows:
  - Risk of inheriting both HLA haplotypes and having the full DQ2 heterodimer encoded in *trans* configuration: 25%

- Risk of inheriting half of the DQ2 heterodimer (*HLA-DQA1**0501 or *0505) or (*HLA-DQB1**0201 or *0202): 50%
- Risk of inheriting neither the *HLA-DQA1**0501 or *0505 nor the *HLA-DQB1**0201 or *0202 celiac disease-susceptibility haplotype: 25%

Offspring of a proband

- The overall risk for celiac disease in offspring of a proband is 5%-10% if the celiac disease-susceptibility HLA haplotype is not known. The risk increases when the offspring has the DQ2 celiac disease-susceptibility HLA haplotype and/or the DQ8 celiac disease-susceptibility HLA haplotype [Treem 2004]. The risk is lower when only half of the DQ2 heterodimer (i.e., the *DQA1* sequence variant **or** the *DQB1* sequence variant, but not both) is present [Qiao et al 2005].
- Each child of an individual with the DQ2 celiac disease-susceptibility HLA haplotype (see Figure 5A) or the DQ8 celiac disease-susceptibility HLA haplotype (see Figure 5B) has a 50% chance of inheriting the celiac disease-susceptibility HLA haplotype.
- The child of a proband who has the DQ2 celiac disease-susceptibility HLA haplotype in the *trans* configuration (see Figure 5A) will inherit one of the celiac disease-susceptibility HLA haplotypes from the affected parent. Because the DQ2 or DQ8 heterodimer is found in 30%-40% of the general population, testing the proband's reproductive partner is appropriate.

Other family members of a proband

- The risk to other family members depends on the DQ2 or DQ8 status of the proband's parents.
- The celiac disease-susceptibility HLA haplotype of the proband's reproductive partner is also important as the DQ2 or DQ8 heterodimer is found in 30%-40% of the general population [Green & Jabri 2006].

Related Genetic Counseling Issues

DNA Banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

While technically possible, prenatal testing of celiac disease-susceptibility HLA haplotypes does not seem relevant in this complex disorder in which (1) the genetic change is common in the general population; (2) the genetic change is predisposing to, but not predictive of, celiac disease; and (3) a highly effective treatment is available.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Celiac Disease

Gene Symbol	Chromosomal Locus	Protein Name
HLA-DQA1	6p21.3	HLA class II histocompatibility antigen, DQ, alpha chain
HLA-DQB1	6p21.3	HLA class II histocompatibility antigen, DQ, beta chain

Data are compiled from the following standard references: gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Celiac Disease

146880	MAJOR HISTOCOMPATIBILITY COMPLEX, CLASS II, DQ ALPHA-1; HLA-DQA1
212750	CELIAC DISEASE; CD
604305	MAJOR HISTOCOMPATIBILITY COMPLEX, CLASS II, DQ BETA-1; HLA-DQB1

Table C. Genomic Databases for Celiac Disease

Gene Symbol	Entrez Gene	HGMD
HLA-DQA1	3117 (MIM No. 146880)	HLA-DQA1
HLA-DQB1	3119 (MIM No. 604305)	

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

Celiac disease is a multifactorial disorder resulting from the interaction of specific well-described variants in HLA genes, less-well-recognized variants in non-HLA genes, gliadin (a subcomponent of gluten), and other environmental factors. The HLA-DQA1 and HLA-DQB1 gene variants known to be associated with celiac disease susceptibility are necessary but not sufficient to cause the disease.

The immunologic mechanisms of celiac disease—When working properly, inflammatory mechanisms and immunologic responses in the digestive system provide protection from bacteria, toxins, and other foreign elements in the food and water supply. IgA, made in abundance by the intestinal immune system, is important in local (mucosal) immunity. In celiac disease, inappropriate immune responses lead to chronic inflammation and damage. The two main categories of immune response involved in celiac disease are: the adaptive immune response (HLA-specific) and the innate immune response (independent of HLA type).

Adaptive immune response (HLA-specific): the role of DQ2 and DQ8—Tissue transglutaminase (tTG), an enzyme found in every tissue of the body, protects the body through wound healing and bone growth. In the intestine, tTG deamidates gliadin, which introduces negative charges to the gluten peptides. Both DQ2 and DQ8, proteins on the surface of antigen-presenting cells (APCs) in the lamina propria, preferentially bind these negatively charged deamidated gluten peptides (see Figures 6 and 7). Gluten-reactive T-helper cells (positive for the surface marker CD4) become activated upon recognition of deamidated gluten peptides bound to DQ2 or DQ8 on APCs and produce cytokines including interferon gamma (IFN-γ). The ensuing inflammatory response results in the release of additional cytokines and chemicals leading to villous damage and atrophy. In response to inflammation, plasma cells in the inflamed intestinal tissue release antibodies, including anti-gliadin and anti-endomysial antibodies, and the autoimmune antibody against tTG (see Figure 7) [Treem 2004, Alaedini & Green 2005, Sollid & Lie 2005].

Celiac disease is strongly associated with the class II HLA protein molecules DQ2 and DQ8, encoded by alleles at the *HLA-DQA1* and *HLA-DQB1* loci. These HLA-DQ sequence variants are the single most important genetic influence in celiac disease susceptibility, with the remainder of disease susceptibility attributed to unknown sequence variants in non-HLA genes. The great majority (>90%) of individuals with celiac disease have the DQ2 celiac disease-susceptibility HLA haplotype, most of the remainder have DQ8 celiac disease-susceptibility HLA haplotype, and a small percentage have half of the DQ2 molecule. DQ2 and DQ8 confer susceptibility to celiac disease by presenting the gliadin subcomponent of gluten to specific CD4+ T-helper cells of the immune system in the intestinal mucosa (see Figures 6 and 7) [Sollid 2002, Sollid & Lie 2005].

Allelic variants involved in making the DQ2 and DQ8 protein molecules—The HLA-DQ2 and -DQ8 proteins are heterodimers found on the surface of APCs. DQ2 and DQ8 proteins are each made up of an α chain and a β chain encoded by specific sequence variants of the *HLA-DQA1* and *HLA-DQB1* genes, respectively.

Individuals with celiac disease who have DQ2:

- Have the DR17-DQ2 celiac disease-susceptibility haplotype [*HLA-DRB1**0301;*HLA-DQA1**0501;*HLA-DQB1**0201]

  or

- Are heterozygous for the celiac disease-susceptibility haplotypes DR11 or DR12-DQ7 [*HLA-DRB1**11/12;*HLA-DQA1**0505;*DQB1**0301] or DR7-DQ2 [*HLA-DRB1**07;*HLA-DQA1**0201;*HLA-DQB1**0202]

Individuals with celiac disease who have DQ8 have the DR4-DQ8 celiac disease-susceptibility haplotype (*HLA-DRB1**04;*HLA-DQA1**03;*HLA-DQB1**0302) [Sollid 2002, Sollid & Lie 2005] (see Figure 1).

Innate immune response—In addition to the adaptive immune mechanism involving $CD4^+$ T-helper cells described in Figure 6, an innate response involving intraepithelial $CD8^+$ cytotoxic T lymphocytes (IELs) plays a role in the pathogenesis of celiac disease. In individuals with celiac disease, gluten independently induces epithelial stress through overproduction of interleukin-15 cytokine (IL-15) from IELs. The stress molecules MIC and HLA-E are also induced; they upregulate the expression of activating NK receptors (e.g., NKG2D) on the surface of $CD8^+$ T cells, conferring NK-like properties to the T cells, which then attack intestinal epithelial cells indiscriminately, leading to intestinal damage [Hüe et al 2004,Jabri et al 2005] (see Figure 7).

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests *for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Celiac Disease Foundation
13251 Ventura Boulevard #1
Studio City CA 91604
Phone: 818-990-2354
Fax: 818-990-2379

Email: cdf@celiac.org
www.celiac.org

Celiac Sprue Association
PO Box 31700
Omaha NE 68131-0700
Phone: 877-CSA-4CSA (877-272-4272)
Fax: 402-558-1347
Email: celiacs@csaceliacs.org
www.csaceliacs.org

Gluten Intolerance Group
31214 124th Avenue Southeast
Auburn WA 98092
Phone: 253-833-6655
Fax: 253-833-6675
Email: info@gluten.net
www.gluten.net

Medline Plus
Celiac disease - sprue

National Foundation for Celiac Awareness (NFCA)
P.O. Box 544
Ambler PA 19002-0544
Phone: 215-325-1306
Email: info@celiacawareness.org
www.celiacawareness.org

NIH Consensus Development Conference Statement 2004
Celiac Disease

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Suggested Reading

Green PH, Jones R (2006) Celiac Disease: A Hidden Epidemic. HarperCollins Publishers

Chapter Notes

Author Notes

www.kimballgenetics.com

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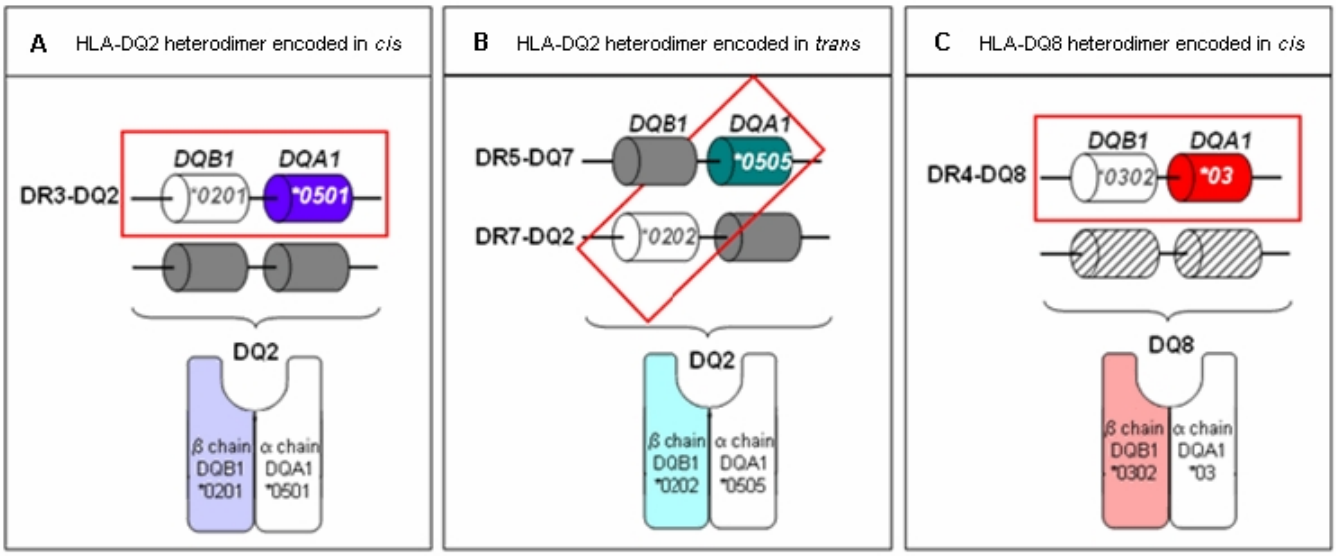

Figure 1. Formation of DQ2 and DQ8. A. The DQ2 molecule, consisting of the α-chain protein encoded by the *HLA-DQA1**0501 allele and the β-chain protein encoded by the *HLA-DQB1**0201 allele on the same parental chromosome (i.e., in *cis* configuration). B. The DQ2 molecule, consisting of the α-chain protein encoded from the *HLA-DQA*1*0505 allele and the β-chain protein encoded by the *HLA-DQB1**0202 allele on separate parental chromosomes (i.e., in *trans* configuration). C. The DQ8 molecule, consisting of the β-chain protein encoded by the *HLA-DQB1**0302 allele and the α-chain protein encoded by the *HLA-DQA1**03 allele on the same parental chromosome (i.e., in *cis* configuration).
Note: The DR alleles are the result of linkage disequilibrium and are included for illustration only.
Modified and expanded from Sollid [2002] with permission from LM Sollid

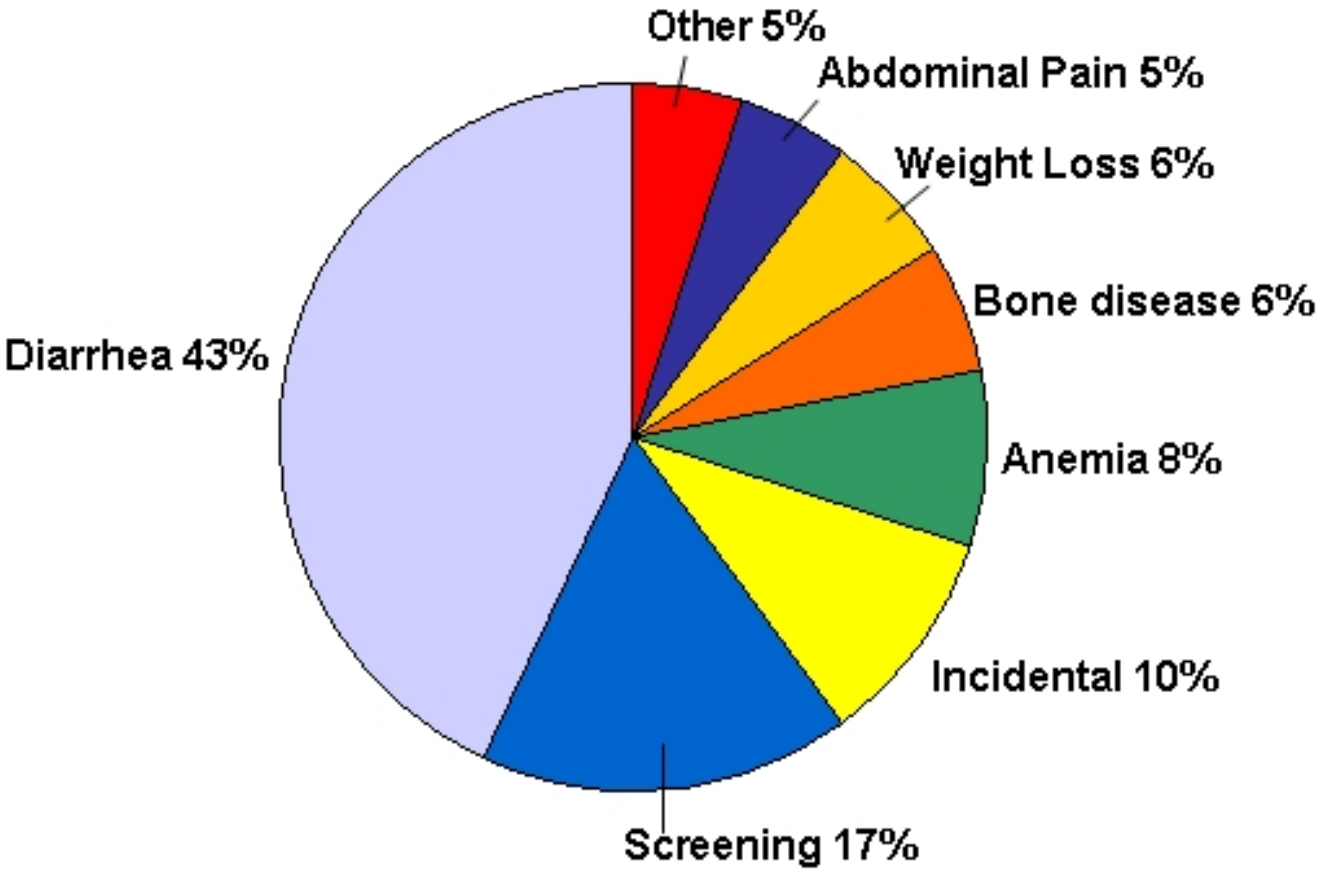

Figure 2. Presenting symptoms in celiac disease. The presenting symptoms are the main symptoms or indications that led to a diagnosis of celiac disease. “Bone disease” refers to evaluation for low bone density. “Incidental” refers to discovery of villous atrophy during endoscopy performed for signs and symptoms not usually associated with celiac disease [Green & Jabri 2003, Lo et al 2003].
With permission from PHR Green, MD

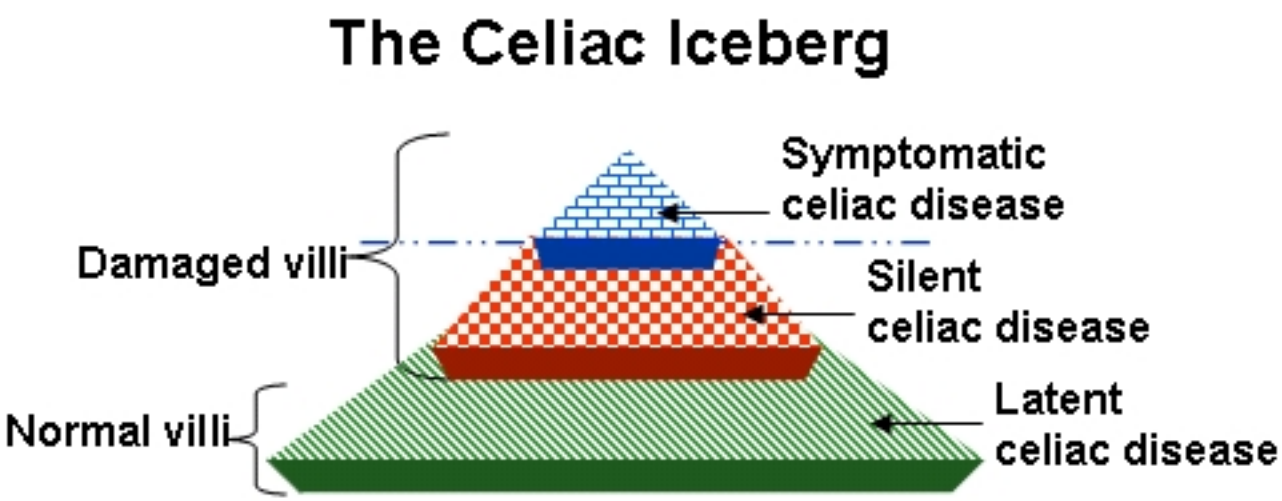

Figure 3. The celiac iceberg represents all persons genetically susceptible to celiac disease because of a positive celiac-associated antibody test. The majority of such persons have latent celiac disease. The “tip of the iceberg” represents the minority of persons who present with classic celiac disease.

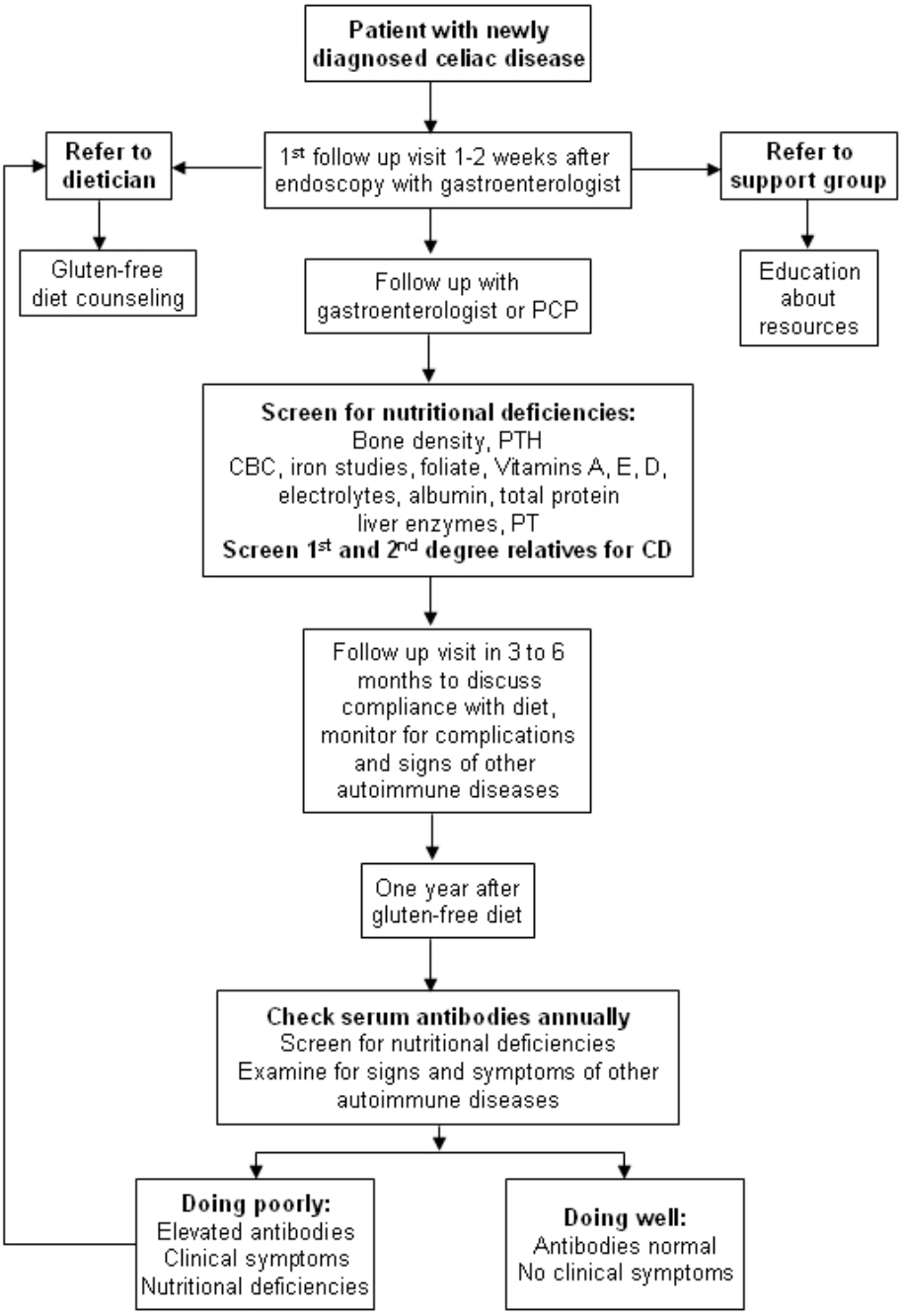

Figure 4. An approach to the management of newly diagnosed celiac disease [Pietzak 2005]
With permission from MM Pietzak, MD

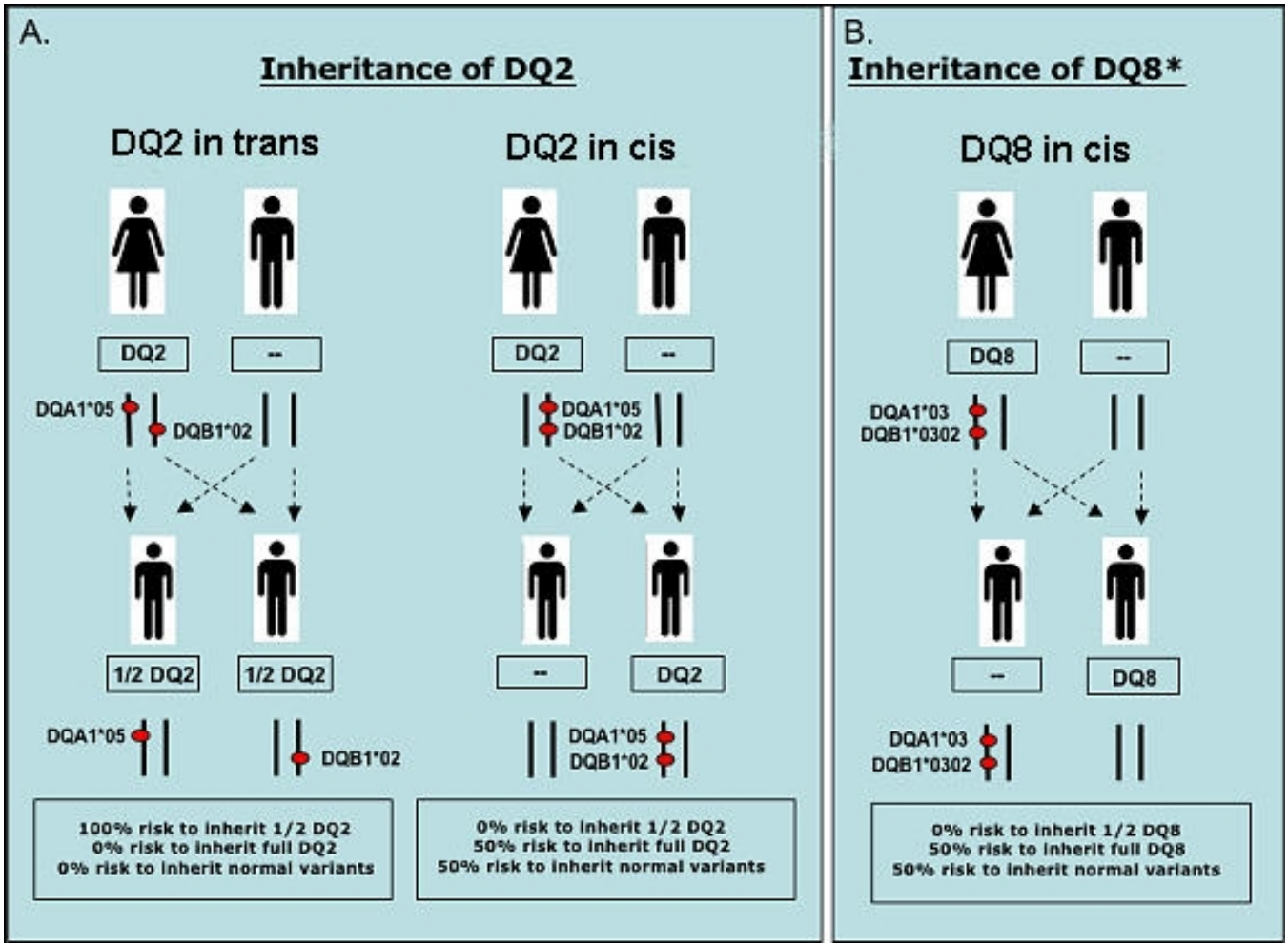

Figure 5. Modes of inheritance of A. DQ2-related celiac disease susceptibility and B. DQ8-related celiac disease susceptibility in families in which one parent has the respective celiac disease-susceptibility HLA haplotype and the other parent does not have the respective celiac disease-susceptibility HLA haplotype. The sequence variant *HLA-DQB1**0302 is always inherited with the sequence variant *HLA-DQA1**03 as a result of linkage disequilibrium. Created by Kimball Genetics, Inc

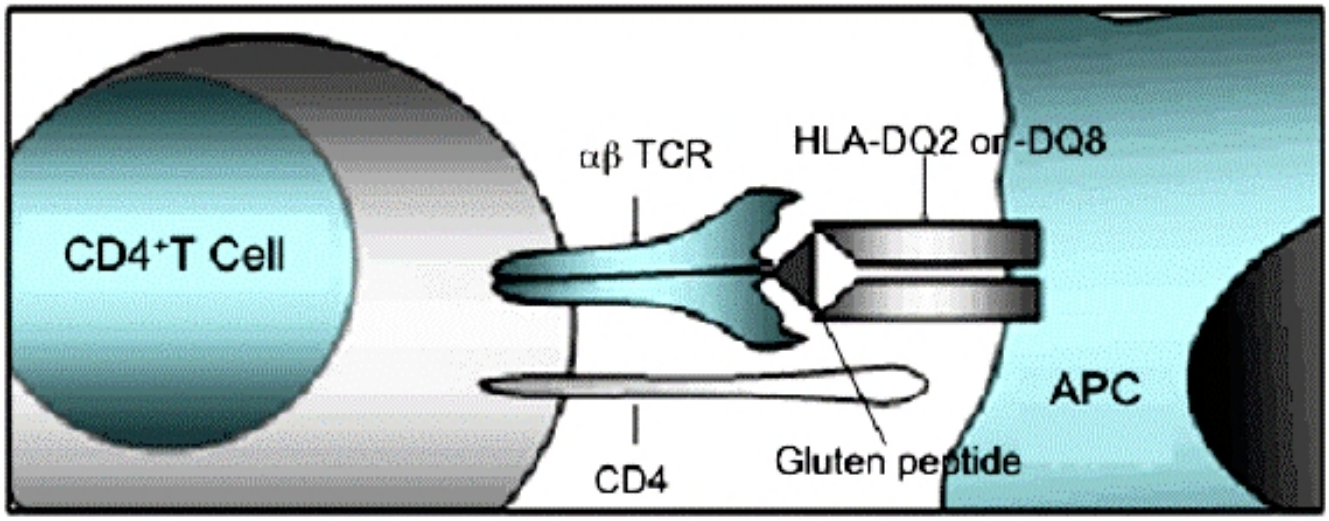

Figure 6. Gluten-reactive CD4+ T-helper cells (with cell-surface CD4 markers) become activated upon recognition by a TCR of gluten peptides presented by HLA-DQ2 or HLA-DQ8 protein molecules on the surface of APCs in the lamina propria.
Modified and expanded from Sollid [2002]. With permission from LM Sollid, MD.

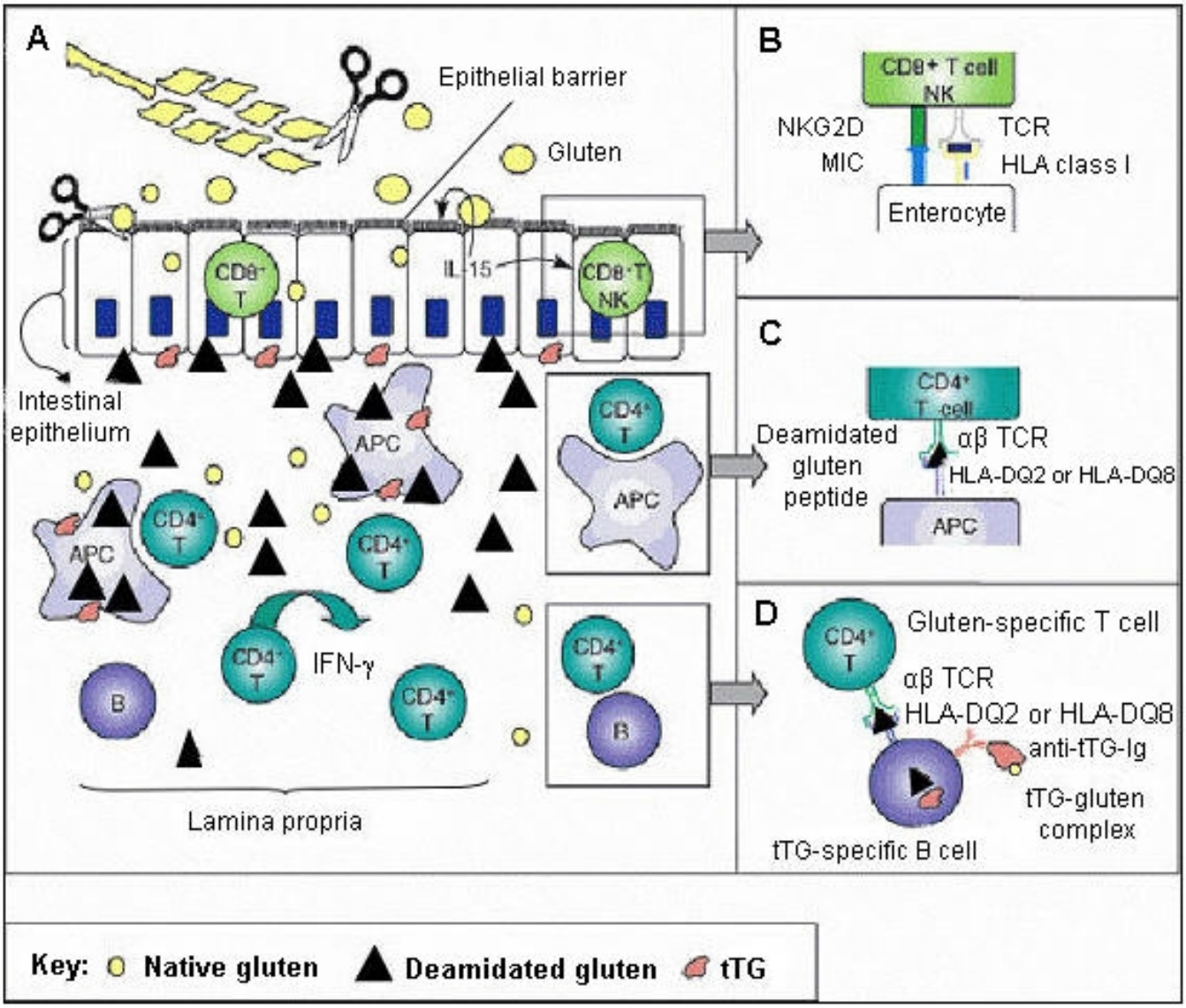

Figure 7. The celiac small intestinal lesion showing both adaptive and innate immune mechanisms. A. Gluten peptides are transported across the epithelial barrier and are deamidated by tissue transglutaminase (tTG). CD4+ T cells in the lamina propria recognize the gluten peptides presented by HLA-DQ2 or HLA-DQ8 molecules on the cell surface of the antigen presenting cells. In the epithelium-infiltrated CD8+ T cells express NK cell receptors, such as NKG2D. B cells specific for gluten and tTG are in the lamina propria. B. Intraepithelial T cells, upregulated by NKG2D, can kill enterocytes expressing MIC molecules directly or by reducing the TCR activation threshold. Gluten can induce NKG2D and MIC expression by stimulating the expression of IL-15. C. HLA-DQ2 and -DQ8 molecules bind with increased affinity gluten peptides deamidated by tTG. D. Gluten-specific T cells control the formation of antibodies to tTG by intramolecular help [Sollid & Jabri 2005].
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