THE CHANGING FACE OF CELIAC DISEASE AND THE ROLE OF GENETIC TESTING
Final Project

Introduction: Celiac disease (CD) (OMIM Entry #212750[1]) "is a chronic small intestinal immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed people."[2] Over the past fifty years, there has been a marked increase in both the incidence and prevalence of the disease throughout the world.[3] Moreover, the clinical presentation of CD has become more varied.[4] This report discusses the bases for these changes and the evolving role of genetic testing for CD. In order to provide the necessary background for that discussion, the history, symptoms, genetics, pathogenesis, diagnosis and treatment of CD are first reviewed.

Celiac Disease – Its History and Symptoms: While a dietary trigger for CD had already been suspected, it was the pioneering work of the Dutch pediatrician, Willem-Karel Dicke, that first identified a component of wheat as the offending agent in the disease.[5] As early as 1934-1936, Dicke was using a wheat-free diet to treat CD, having been informed by the mother of a patient that her child's symptoms improved if the patient avoided eating bread. Dicke's suspicions were heightened when he noticed that his CD patients improved during the forced starvation of the Dutch population at the end of World War II, when cereals such as wheat were in limited supply.[6] These observations led Dicke to undertake his classic dietary fat absorption experiments which showed that fat absorption went down and the fat content of wet feces went up when patients were fed wheat flour.[7] Dicke's work was the basis for the recommendation that gluten, the main storage protein of wheat, be eliminated from the diet of CD patients. The gluten-free diet remains the only proven therapy for CD.

CD was originally considered a disease of children, who presented with malabsorption, as evidenced by the classic CD symptoms of diarrhea, steatorrhea, abdominal distention and weight loss or a failure to thrive.[8] It was subsequently recognized that CD often first presents in adulthood and with a wide range of gastrointestinal and nongastrointestinal symptoms.[9] The classic form of CD in children usually begins between 6 and 24 months of age, following the introduction of gluten-containing wheat, rye and/barley into the diet.[10] On rare occasions, an infant experiences celiac crisis, a medical emergency characterized by explosive watery diarrhea, dehydration, hypotension, lethargy, and severe electrolyte abnormalities.[11] Older children can present with a

range of gastrointestinal complaints that includes the classic symptoms, as well as abdominal pain, constipation, nausea and vomiting.[12] Nongastrointestinal manifestations can include osteoporosis, iron deficient-anemia, short stature, delayed puberty, dental enamel defects, and dermatitis herpetiformis (DH), a pruritic skin rash on the elbows, buttocks and knees.[13] In adults, the average age of presentation of CD is in the fifth decade.[14] Diarrhea is a frequent complaint, but there are other presentations such as recurrent abdominal pain, bloating, glossitis, dyspepsia, esophageal reflux, irritable bowel syndrome, anemia, osteoporosis, chronic fatigue, infertility and DH.[15] Neurological symptoms have been reported in both children and adults with CD, the most frequent being ataxia, peripheral neuropathy, epilepsy, headache and psychiatric manifestations.[16] A number of conditions have been associated with an increased prevalence of CD, such as type 1 diabetes, autoimmune thyroiditis, Down syndrome, Turner syndrome, Williams syndrome, selective IgA deficiency and first degree relatives of celiac patients.[17] Screening of these high-risk individuals for CD has revealed the presence of biopsy-proven active enteropathy in patients without any celiac symptoms, the so-called asymptomatic CD patient.[18] The wide range of clinical presentations of CD is increasingly recognized by healthcare providers and, as will be discussed below, there has been a pronounced shift away from the classical symptoms (indicative of malabsorption) to non-classical symptoms.[19]

Genetics of CD: Almost every patient with CD harbors specific allelic variants in two HLA genes: *HLA-DQA1*[20] and *HLA-DQB1*.[21, 22] Each of these genes, located on chromosome 6p21.32, encodes one of the two polypeptide chains of a heterodimeric major histocompatibility complex class II protein on the surface of antigen presenting cells (APCs) that presents peptides derived from extracellular proteins to $CD4^+$ T-helper cells (see FIGURE 1).[23] The class II protein consists of an α chain (HLA-DQA1[24]) (encoded in the *HLA-DQA1* gene) and a β chain (HLA-DQB1[25]) (encoded in the *HLA-DQB1* gene) (see FIGURE 1). Certain polymorphisms in the encoding genes alter the peptide binding specificity of the class II heterodimer.[26] The HLA-DQ2 heterodimer and the HLA-DQ8 heterodimer have been associated with CD.[27] The HLA-DQ2 heterodimer consists of an α chain encoded in the *HLA-DQA*1*0501 allele and a β chain encoded in the *HLA-DQB1**0201 allele (see FIGURE 1).[28] Both of these alleles are on the same parental chromosome (i.e. in a *cis* configuration). There is also an HLA-DQ2 heterodimer composed of an α and a β chain where the encoding alleles (*HLA-DQA*1*0505 and *HLA-DQB1**0202) are on separate parental chromosomes (i.e. in a *trans* configuration) (see

FIGURE 1).[29] Approximately 90% of CD patients carry the alleles encoding the HLA-DQ2 heterodimer.[30] Almost all of the HLA-DQ2-negative CD patients carry the alleles encoding the HLA-DQ8 heterodimer: *HLA-DQA*1*03 and *HLA-DQB1**0302 in a *cis* configuration (see FIGURE 1).[31] As will be discussed below, the HLA-DQ2 and the HLA-DQ8 heterodimers on APCs have a high affinity for certain of the degradation-resistant fragments of gluten proteins and are particularly effective in inducing gluten reactivity in $CD4^+$ T cells, which activate the inflammatory immune response that causes the gastrointestinal manifestations of CD.[32]

While the vast majority of CD patients harbor the HLA class II *DQ* alleles that encode either the HLA-DQ2 or the HLA-DQ8 heterodimer, these alleles are also found in 20 to 30% of individuals in the general population, the majority of whom will never have CD.[33] This observation has lead to the often-repeated statement that harboring the predisposing *HLA-DQ* alleles is necessary but not sufficient to contract CD.[34] Clearly, environmental factors have an essential role in the development of CD. The most significant of these is exposure to dietary gluten, but other environmental factors have been suggested, such as a recent viral infection altering intestinal permeability or an individual's gut microbiota.[35] There is also evidence that there are genetic factors, other than the *HLA-DQ* risk alleles, that contribute to the development of CD. Studies have indicated that the concordance rate of CD in monozygotic twin pairs is approximately 70%, while the concordance rate in HLA-identical siblings is only 30%.[36] This indicates that non-HLA linked genes have a role in the genetic predisposition to CD.[37] In fact, it has been estimated that the predisposing *HLA-DQ* alleles are responsible for only 40% of the heritability of CD.[38] In an effort to identify the genetic variations that account for the remaining 60% of the heritability of CD, researchers have turned to genome-wide association studies (GWASs). The first such study of CD was undertaken in 2007 by van Heel et al.[39] and the results obtained are representative of the findings in subsequent similar studies. The GWAS by van Heel et al. was a case/control study of UK individuals in which 310,605 SNPs were genotyped in 778 patients with CD and 1,422 controls.[40] Two regions of the genome harboring SNPs that are associated with CD susceptibility were identified. Not surprisingly, there was a highly significant association around the HLA-DQ locus. SNP rs2187668, which maps to the first intron of the gene *HLA-DQA1* on chromosome 6, showed the strongest association, with a $P < 10^{-19}$ and an OR = 7.04.[41] The other region of association was in a ~480-kb linkage disequilibrium block on chromosome 4q27 that contains the genes *IL2* and *IL21* that encode the immune response proteins IL-2 and IL-21, respectively. The

SNPs in this region that were associated with susceptibility for CD showed a less robust association than that found for the HLA SNP and, in contrast to the associated HLA SNP, these non-HLA SNPs had only a modest effect on the risk of contracting CD.[42] Since the GWAS by van Heel et al., close to 40 CD susceptibility variants outside of the HLA region have been identified in GWASs, replication studies and linkage analyses.[43] Many of these non-HLA variants have been identified in more than one study and are in or near immune response genes that could have a role in the pathogenesis of CD.[44] However, each of these associated non-HLA variants makes only a small contribution to the risk of developing CD and, despite studies that suggest that testing for non-HLA risk genotypes can aid in the identification of individuals at high risk for CD,[45] current diagnostic testing algorithms for CD do not include non-HLA genotyping[46] (see discussion on the diagnosis of CD below).

Pathogenesis of CD: Since the identification of gluten as the offending agent in CD, a great deal has been learned regarding the pathogenesis of the disease (see FIGURE 2).[47] As noted above, CD is a multifactorial disorder in which genetic and environmental factors contribute to the development of the disease.[48] The role of dietary gluten in the pathogenesis of CD has been the subject of extensive study.[49] Following ingestion, gluten proteins are degraded by proteolytic enzymes in the small intestine into proline-rich peptides that are resistant to further degradation and are transported across the epithelial barrier (see FIGURE 2).[50] These peptides are then deamidated by tissue transglutaminase (TG2 or TTG), resulting in peptides in which positively charged glutamine residues are transformed into negatively charged glutamic acid residues by deamidation.[51] In individuals harboring predisposing *HLA-DQ* alleles, and therefore susceptible to developing CD, these negatively charged peptides are preferentially bound by HLA-DQ2 or HLA-DQ8 heterodimers on the surface of APCs that have positively charged binding pockets.[52] The bound deamidated peptides are then presented to $CD4^+$ T cells in the lamina propria, resulting in the activation of the T cells (see FIGURE 2).[53] It is not clear why only certain of the individuals harboring the predisposing *HLA-DQ* alleles go on to develop CD upon gluten exposure.[54] Contributions from non-HLA susceptibility variants and environmental factors (e.g., a recent gastrointestinal infection) almost certainly influence who will contract CD. There is compelling evidence, however, that for those individuals who develop the disease, the gluten-activated $CD4^+$ T cells have a key role in initiating the effector mechanisms that result in the chronic inflammation of the mucosa of the small

intestine that leads to the typical gastrointestinal pathology found in CD. While less is known about these effector mechanisms, it is believed that the release of pro-inflammatory cytokines by $CD4^+$ T cells and intraepithelial $CD8^+$ T cells and the production of autoantibodies to TG2 lead to the gastrointestinal pathology seen in the disease (see FIGURE 2).[55] It has also been suggested that the autoantibodies contribute to the nongastrointestinal manifestations of CD.[56]

The question of whether CD is truly an autoimmune disease has been debated.[57] On the one hand, the disease is categorized as a food hypersensitivity.[58] The manifestations of CD are triggered by the ingestion of gluten and the disease is "cured" by the removal of gluten from the diet. On the other hand, CD has several autoimmune features. For example, patients with CD generate a disease-specific autoantibody, i.e., the anti-TG2 antibody. Moreover, as noted above, a number of the conditions that are associated with an increased prevalence of CD are autoimmune diseases, e.g., type 1 diabetes, and autoimmune thyroiditis. In this regard, it is noteworthy that a region on chromosome 4q27 that contains non-HLA variants that have been associated with susceptibility to CD (see above) is also associated with susceptibility to type 1 diabetes and rheumatoid arthritis, suggesting that it may be a general autoimmune susceptibility locus.[59] Finally, as has been observed with a number of autoimmune diseases, CD can be transmitted from a donor to a recipient following an allogeneic bone marrow transplantation which is undertaken to treat leukemia.[60] Irrespective of the outcome of the debate regarding its classification, CD is considered "a unique human disease model to study tissue autoimmunity."[61]

Diagnosis of CD: Untreated CD is characterized by recurring morbidity and an increased mortality.[62] In patients with CD, regular exposure to dietary gluten not only triggers the gastrointestinal and nongastrointestinal manifestations of the disease, but is associated with an increased risk of developing infertility, certain autoimmune diseases and/or malignancies, including T cell lymphoma of the small intestine.[63] The fact that the likelihood of developing these disorders can be reduced by the elimination of gluten from the diet[64] makes it particularly troublesome that a large percentage of CD patients go undetected.[65] Accordingly, researchers have focused on the development of optimized diagnostic testing algorithms for CD.[66] One such algorithm, which closely tracks what is known about the pathogenesis of the disease, is presented in FIGURE 3. Serological testing is the initial step in evaluating a patient suspected of having CD.[67] As discussed above, patients with CD who are regularly ingesting dietary gluten develop autoantibodies to tissue transglutaminase

(TG2 or TTG). An elevated serum level of immunoglobulin A (IgA) directed against TG2 is highly sensitive and specific for active CD,[68] and the low cost of measuring the concentration of this autoantibody, which can be done with ease and reliability, has made this test the first of the CD-specific antibody screens to be used in an effort to diagnose the disease.[69] In cases where the results of anti-TG2 antibody testing are equivocal, testing for the presence of another IgA autoantibody, anti-endomysial antibody (EMA), is recommended.[70] The endomysium is a structure of smooth muscle connective tissue and the antigenic target of anti-EMA is known to be TG2.[71] Anti-EMA is highly specific for active CD,[72] although the test for anti-EMA is more expensive and more time-consuming than the one for anti-TG2.[73] It has recently been shown that IgA antibodies directed against deamidated gliadin-related peptide (a-DGP), a gluten breakdown product, are also highly specific for active CD and are often screened for in conjunction with anti-EMA testing.[74] Testing for IgA antibodies is the preferred approach when screening for CD because of "[t]he high sensitivity and specificity for celiac disease of [the] IgA class … antibodies …[,which] is most plausibly explained by the prominent production of IgA by mucous membranes, especially those of the intestinal tract."[75] However, as noted above, CD is associated with IgA deficiency and in the presence of such deficiency elevations of IgA antibodies may not be seen in CD, despite active disease. Accordingly, serological testing for CD includes the concomitant screening for IgA deficiency,[76] and if the latter is found, CD-specific IgG antibodies (as opposed to IgA antibodies) will be screened for.[77] Since the presence of CD-related antibodies is a measure of active disease, serological testing should only be performed on individuals who have continued to ingest gluten.[78] Those individuals who have positive CD serology, or for whom there is a strong suspicion of disease based on other evidence, are subjected to small bowel biopsy, which remains the gold standard for making a diagnosis of CD.[79] The characteristic findings of villous atrophy, crypt hyperplasia and increased intraepithelial lymphocytes are indicative of the small bowel pathology found in CD and are required for a definitive diagnosis of the disease.[80]

As indicated in FIGURE 3, genetic testing has only an ancillary role in making a diagnosis of CD in an individual suspected of having the disease.[81] Since the presence of predisposing *HLA-DQ* alleles is necessary, but not sufficient, for the development of CD (see above), *HLA-DQ* genotyping is most useful in excluding the diagnosis. However, *HLA-DQ* genotyping is used in certain circumstances (e.g., equivocal or negative antibody test results in an individual who is strongly suspected of having CD on other grounds), where a positive result

can tip the balance in favor of a diagnostic small bowel biopsy. The role of *HLA-DQ* genotyping for CD is discussed in greater detail in a subsequent section. As noted above, screening for non-*HLA* genetic variants has not, as yet, been recommended for routine diagnostic testing for CD.[82]

Treatment of CD: The only proven treatment for CD is a strict adherence to a gluten-free diet (GFD).[83] However, maintenance of such a diet requires a significant commitment on the part of the patient and it remains difficult to avoid unintentional exposure to gluten in food, despite the increasing awareness of the disease within the food industry. This has prompted ongoing research efforts to find alternative approaches to the treatment of CD, based on an understanding of the pathogenesis of the disease.[84] For example, it has been suggested that endoproteolytic enzymes that can degrade proline-rich peptides be administered orally to patients with CD to counter the deleterious effect of dietary gluten.[85] Tissue transglutaminase inhibitors are also being considered as treatment in order to block the gluten-peptide deamidation that is required for the high affinity binding of these peptides by HLA-DQ2 or HLA-DQ8 heterodimers on the surface of APCs in CD patients, although there are concerns regarding the side effects of inhibiting this enzyme which has multiple functions and substrates.[86] Other therapeutic approaches, such as blocking the binding sites of HLA-DQ2 or HLA-DQ8 heterodimers, the selective elimination of gluten-reactive T cells or interfering with the effector mechanisms that cause the tissue damage in CD, are also being investigated as possible treatments for CD patients.[87] Some of these alternative approaches to the treatment of CD are currently being evaluated in clinical trials.[88]

The Increase in the Incidence and Prevalence of CD and the Changing Clinical Presentation of the Disease: One of the most interesting observations regarding CD is that, over time, the incidence and prevalence of the disease appear to have increased substantially and the clinical presentation of CD has shifted from the classical symptoms of malabsorption to so-called atypical symptoms.[89] A number of reports have documented the increasing frequency of CD worldwide.[90] In a study of the occurrence of CD over the period from 1950 to 2001 in Olmsted County, Minnesota (a medically well-defined population in the upper Midwest), it was found that there was a dramatic increase in the incidence of the disease.[91] Between 1950 and 1989, the annual incidence of CD was 0.9 per 100,000 person-years, whereas the rate increased to 3.3 in the 1990s and to 9.1 in the last two years of the study.[92] All of the patients identified were of white European ancestry and in the majority of cases CD was diagnosed in adulthood. While the incidence rate was greater for women than for men

(as is typically found), the increase in the incidence of the disease was seen for both genders.[93] The prevalence of CD also increased dramatically from 18.3 per 100,000 person-years in 1991 to 44.1 at the end of the study in 2001.[94] In a follow-up study of the same population from 2000-2011, it was reported that the incidence of CD continued to increase, rising from 11.1 per 100,000 person-years in 2000-2001 to 17.3 in 2008-2010.[95] The increase in the incidence and prevalence of CD has been documented in other populations throughout the world.[96]

Various explanations have been provided for the observed increase in the frequency of CD, with a focus on whether there is a true increase in new cases or simply better detection of existing disease in CD patients whose disease had previously gone undiagnosed. The authors of the Olmsted County studies suggested that the observed increase in the frequency of CD may reflect a true increase in the occurrence of the disease in adults.[97]

> Although the high (and increasing) incidence [of CD] may partly be explained by high physician awareness and large-scale efforts to screen at-risk groups (increasing detection rate), we believe that other factors have a substantial role since the rising incidence in the 1990s, when serological screening tools (e.g., endomysial and tissue transglutaminase antibodies) became readily available, was not followed by a drop in incidence after 2000, as would be expected if the Olmsted County population had merely been swept of unrecognized prevalent CD cases…. Considering the predominance of a Caucasian population in Olmsted County now, as in the 1950s, the rise of CD cannot be explained by a change in the underlying genetic makeup of the community. Instead an environmental factor(s) is likely. As we … and others … have found an association between infectious disease (especially gastroenteritis) and CD, a changing pattern in infections may have contributed to the rise in CD in Olmsted County. Another explanation concerns amount, timing and frequency of gluten consumption. For instance … [it has been] reported that high amounts of gluten increased the risk of CD. Unfortunately, we have no data on gluten consumption in individuals from Olmsted County, although gluten enriched foods (e.g., pizza, bagels, and high-protein and high-fiber bread) are increasingly ingested in the United States.[98]

Whatever the basis for the observed increase in the frequency of CD over the years, the disease is now considered one of the most common genetically-based diseases,[99] occurring in about 1% of the population worldwide.[100] What was once considered a rare childhood disorder is now recognized as one of the most common lifelong diseases.[101]

Perhaps even more intriguing than the increased incidence and prevalence of CD is the observation that the clinical presentation of the disease has been changing over time.[102] In a comparison of the clinical features and modes of presentation of CD patients at a medical center in New York before and after 1993 (the year when CD serological testing was first widely used), it was found that there was a shift away from the classical

symptoms of malabsorption to other presentations.[103] There was a significant decrease in the percentage of patients presenting with diarrhea (from 73% prior to 1993 to 43% after 1993). Moreover, there was a trend toward an older age at diagnosis. As anticipated, a significant percentage (17%) of the CD patients diagnosed after 1993 were identified as a result of serological screening of high-risk first degree relatives of CD patients. The majority of these affected relatives were asymptomatic. The authors of the study concluded that the observed change in the presentations of their patients over time resulted from the advent of serological screening for CD. However, in a subsequent and more detailed study from the same medical center it was suggested that factors, other than the widespread use of serological testing, may have contributed to the observed change in the presentation of CD patients.[104] The authors of this study noted that the decrease in the percentage of CD patients presenting with diarrhea began in the 1980s, well before the onset of serological testing and that, in addition to asymptomatic patients identified through screening, there was a growing number of patients who presented with atypical CD (i.e., without diarrhea or malabsorption).[105] The atypical CD patients, who presented with bone disease, anemia, gastric reflux-type symptoms, constipation and/or neurological symptoms, comprised up to 19% of all patients over the last 14 years of a 52 year study.[106] The reasons for this observed shift in the clinical presentation of CD in this patient population were not identified. Other studies have also noted the change in the clinical presentation of CD over time without providing a comprehensive explanation for the change.[107] What is significant, however, is the growing recognition that CD can be diagnosed in patients with non-classical symptoms or with no symptoms at all. Considering that a large percentage of patients with CD are currently undiagnosed,[108] there is a need for the medical community to heighten its awareness of the varied presentations of the disease and to make effective use of the serological and genetic testing methods that are (or will become) available in order to increase success in diagnosing this common and potentially serious disease.

The Evolving Role of Genetic Testing for CD: The basis for, and the role of, genetic testing in the diagnosis of CD has been discussed above. To reiterate, only *HLA-DQ* genotyping is routinely performed, and then only as an adjunct to serological testing and a diagnostic biopsy of the small intestine.[109] *HLA-DQ* genotyping is currently recommended to determine whether a diagnostic biopsy should be undertaken or repeated in the case of a patient suspected of having CD on other grounds who (i) has not yet had a biopsy and

whose serological test results are negative or equivocal, (ii) has not yet had a biopsy and is already on a GFD, (iii) has had a biopsy where the results were equivocal, or (iv) has had a biopsy showing changes typical of CD but continues to experience gastrointestinal symptoms despite a GFD.[110] *HLA-DQ* genotyping is also recommended to exclude the diagnosis of CD in high-risk individuals, such as a first degree relative of a patient with CD or a patient with a disease associated with an increased prevalence of CD (see above).[111] Negative results on *HLA-DQ* genotyping virtually rules out the possibility that the tested individual has CD or will contract the disease in the future, and obviates the need for any further CD-related follow-up. The fact that the absence of predisposing *HLA-DQ* alleles eliminates the risk of developing CD has lead to the suggestion that *HLA-DQ* genotyping be considered as part of a population-wide screening effort.[112] The approximately 70% of the population without the predisposing *HLA-DQ* alleles[113] will be spared of any additional CD-related testing, while those who harbor the predisposing alleles can be the object of a more focused, cost-effective medical surveillance program. This suggestion, however, has not as yet been adopted. As noted above, the predisposing *HLA-DQ* alleles are responsible for only 40% of the heritability of CD. The remaining 60% of the genetic susceptibility to CD is shared between a number of non-HLA variants, only a few of which have been identified.[114] It is anticipated that as the remaining predisposing genetic variants become known, screening for non-HLA alleles will be included in the routine diagnostic testing algorithm for CD.[115]

Despite the secondary role that genetic testing currently has in the diagnosis and management of CD, the potential value of such testing has been recognized. As Megiorni and her colleagues stated:

> Celiac disease is a rare example of [a] multifactorial disorder in which a genetic test is of great importance in clinical practice. From this point of view, the peculiarity of CD is due to several issues: the gluten ingestion is known to be the environmental triggering factor, and a gluten-free diet represents a valid therapy that leads to complete remission of the clinical signs; the disease is largely underdiagnosed, because most patients have silent or atypical forms; untreated CD significantly increases risk of developing long-term complications such as lymphomas or autoimmune disorders; thus an early diagnosis is important so as to start a therapeutic diet as soon as possible and to avoid severe consequences. The primary genetic susceptibility component has been well defined, and the disease rarely develops in the absence of specific HLA class II alleles.[116]

As knowledge of the genetic basis for CD increases, the cost of genetic testing decreases, and the use of genomic information in the provision of personalized health care becomes routine, the role of genetic testing for CD will almost certainly expand.

FIGURE 1

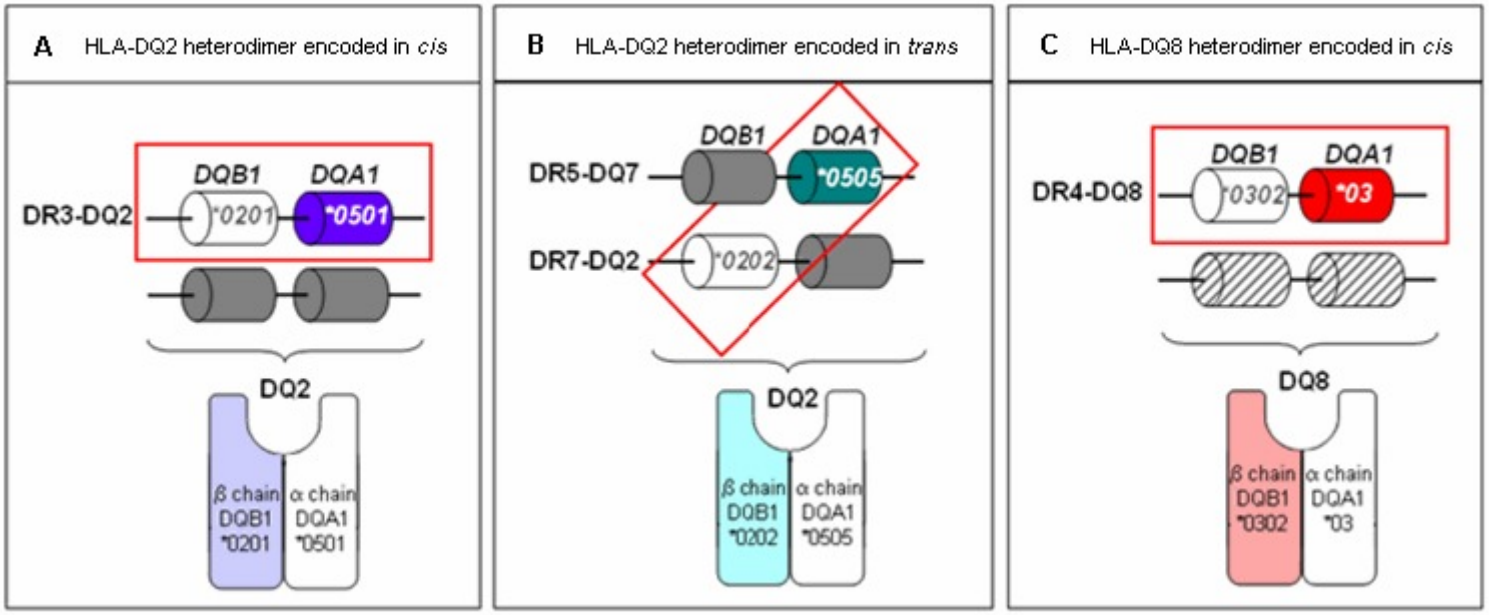
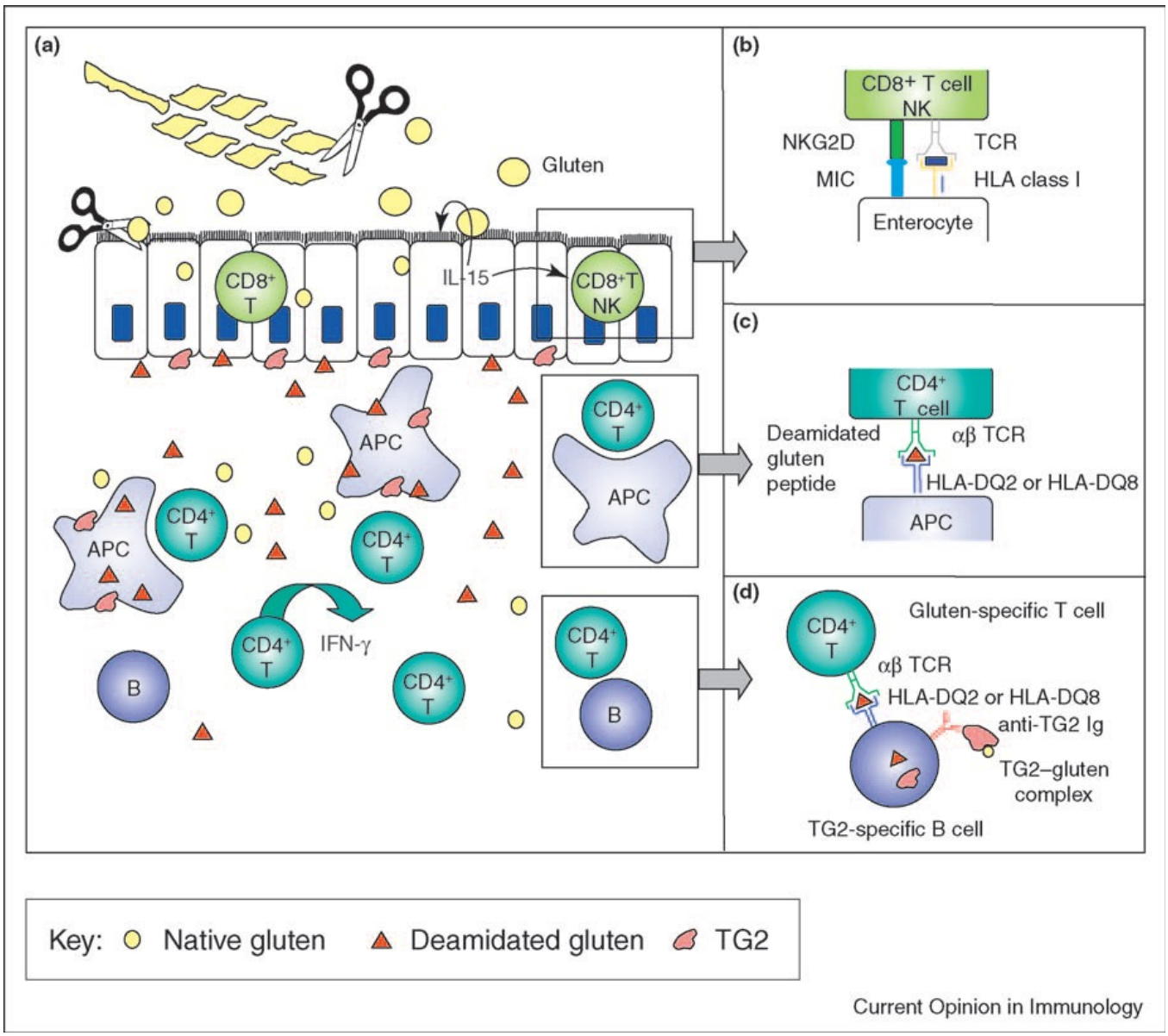


Figure 1. Formation of DQ2 and DQ8. A. The DQ2 molecule, consisting of the α-chain protein encoded by the *HLA-DQA1**0501 allele and the β-chain protein encoded by the *HLA-DQB1**0201 allele on the same parental chromosome (i.e., in *cis* configuration). B. The DQ2 molecule, consisting of the α-chain 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 [Coeliac Disease: Dissecting a Complex Inflammatory Disorder, Nat. Rev. Immunol. 2, 647-655 (2002) http://www.nature.com/nri/journal/v2/n9/abs/nri885.html] with permission [given to GeneReviews] from LM Sollid

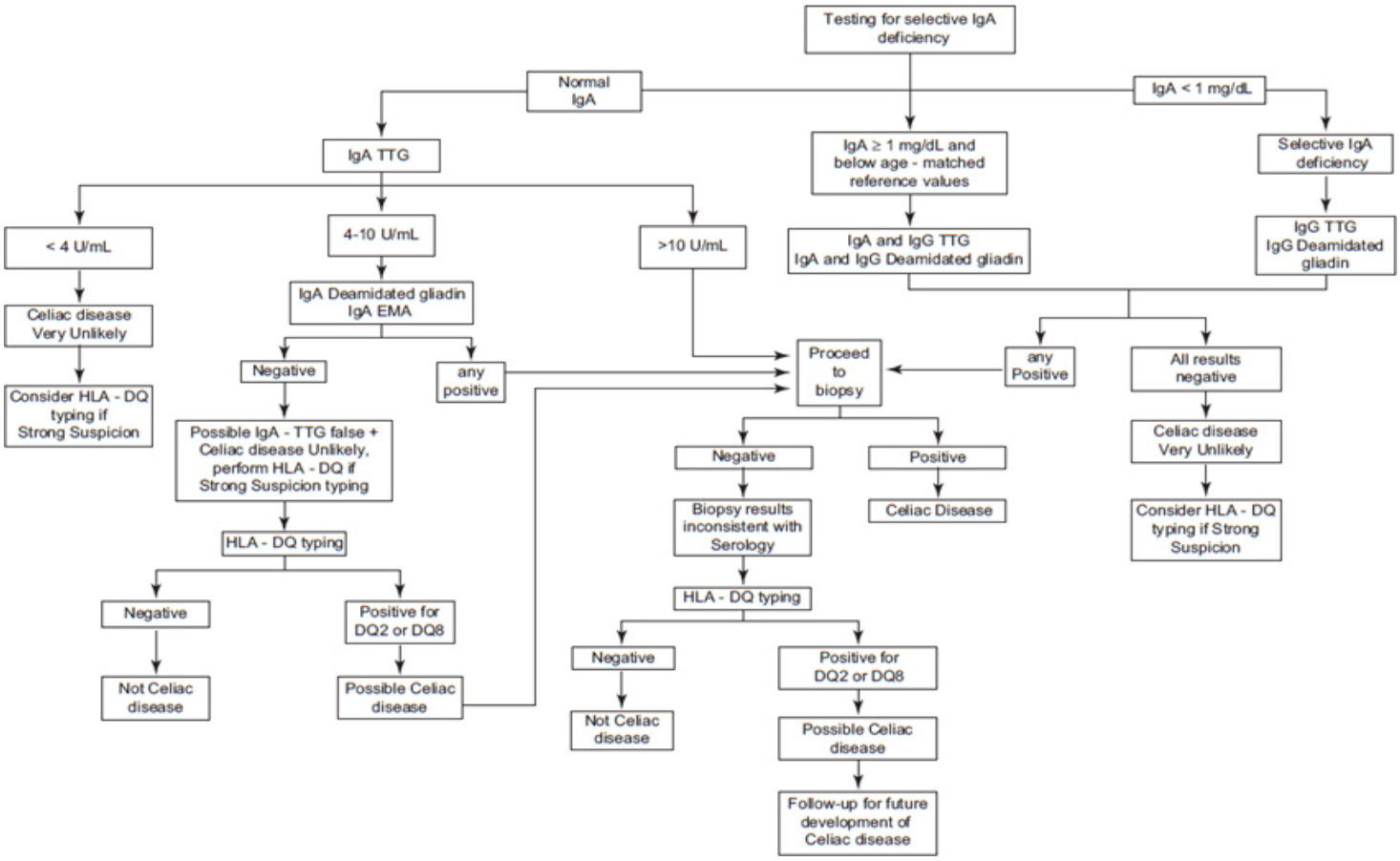
FIGURE taken from: GeneReviews (Celiac Disease)

FIGURE 2



The celiac small intestinal lesion. **(a)** The parts of the gluten proteins that are resistant to processing by luminal and brush border enzymes survive digestion and are transported across the epithelial barrier as polypeptides. Gluten peptides are deamidated by tissue transglutaminase (TG2). $CD4^+$ T cells in the lamina propria recognize predominantly deamidated gluten peptides, presented by HLA-DQ2 or -DQ8 molecules on the cell surface of the APC. In the epithelium there is infiltration of CD8+ T cells that express NK cell receptors, such as NKG2D. In the lamina propria there are B cells specific for gluten and TG2. **(b)** Intraepithelial T cells, by upregulation of NKG2D, can kill enterocytes expressing MIC molecules either by reducing the TCR activation threshold or by mediating direct killing. Gluten can induce NKG2D and MIC expression by stimulating the expression of IL-15. **(c)** HLA-DQ2 and -DQ8 molecules have a preference for binding peptides with negatively charged amino acids and thereby bind gluten peptides deamidated by TG2 with increased affinities. **(d)** A model of how gluten-reactive T cells control the formation of antibodies to TG2 by intramolecular help. This can happen in the lamina propria or, more likely, in the mesenteric lymph nodes. During the deamidation reaction, gluten peptides and TG2 form enzyme–substrate intermediates that are fairly stable (thiolester linkage). Such complexes of gluten and TG2 bound by surface immunoglobulin on TG2-specific B cells are endocytosed, and deamidated gluten peptides are released for binding to DQ2 or DQ8 molecules. After transport of the HLA molecules and their bound peptides to the cell surface, gluten-reactive T cells can recognize the deamidated gluten peptides and thereby provide T cell help to the TG2-specific B cell. The figure is adapted with permission [given to Curr. Opin. Immunol.] from Sollid, L.M., Molberg, Ø and Lundin, K.E.A, Celiac disease In *The Autoimmune Diseases;* edn. 4. Edited by Mackay, I. and Rose, N., Amsterdam: Elsevier (2006). FIGURE taken from Sollid, L.M. and Jabri, B., Is celiac disease an autoimmune disorder?, Curr. Opin. Immunol. 17, 595-600 (2005) http://www.ncbi.nlm.nih.gov/pubmed/16214317

FIGURE 3



Mayo Clinic Celiac Disease Diagnostic Testing Algorithm. Serology and genetic testing are part of an automated laboratory cascade testing, meaning that a sequence of tests driven by real time results is used to diagnose celiac disease using a single blood draw. This cascade testing is intended for adults on a gluten-containing diet. (Modified and used by permission of Mayo Foundation for Medical Education and Research. All rights reserved). Figure taken from Lebwohl, B. et al., Diagnosis of Celiac Disease, Gastrointest. Endosc. Clin. N. Amer. 22, 661-677 (2012) http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4005880/

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