

Celiac Disease 2016

Grand Rounds
Regions Hospital

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I have nothing to disclose



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Case Introduction

- 35 year old female referred for IBS. H/O 1-3 episodes of diarrhea. Excessive gas and nocturnal symptoms.
- Glossitis and angular stomatitis
- Patient had H/O diarrhea when baby and in teen age years.
- H/O Iron deficiency, hypothyroidism.
- On supplements and MVI. H/O iron supplements
- H/O miscarriage and irregular menstrual cycle.



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Educational Objectives

- Identify the signs and symptoms of celiac disease for clinicians.
- Understand the Testing and utilization of blood work and Pathology.
- Management plan and long term follow up.
- Appreciate conditions associated with CD.
- Conditions similar to celiac disease

- Non Gluten wheat allergies
- Gluten Intolerance



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INTRODUCTION

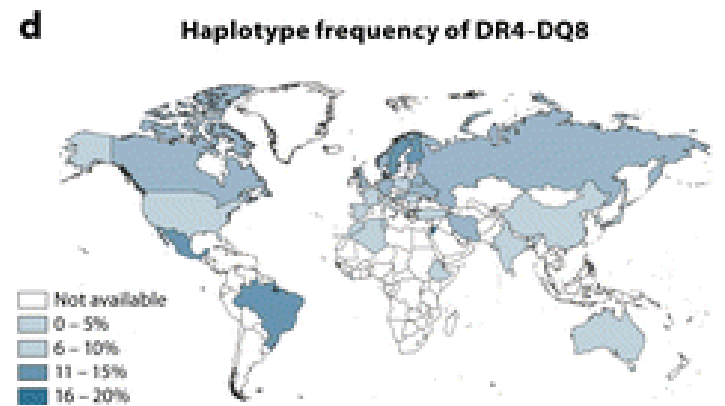
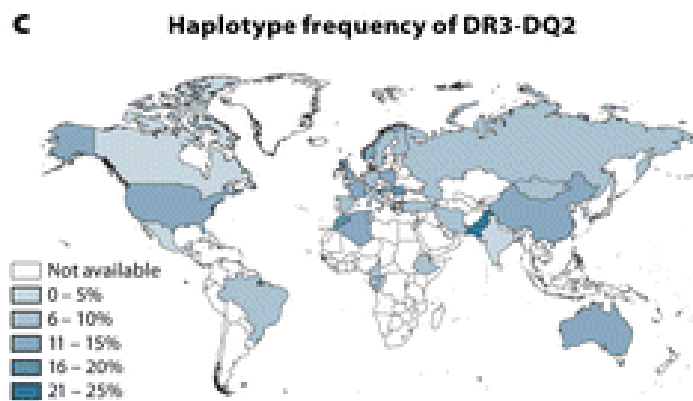
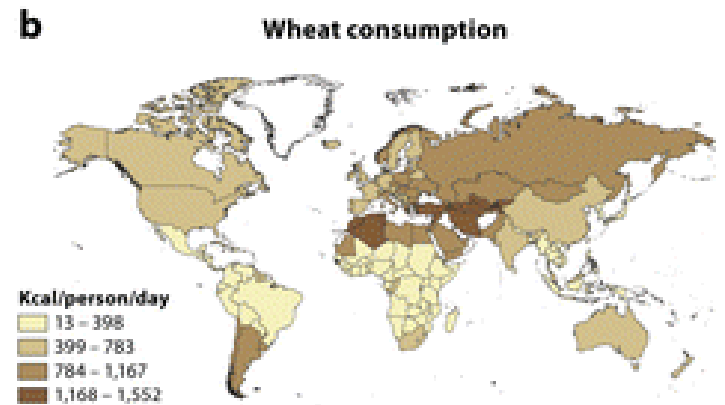
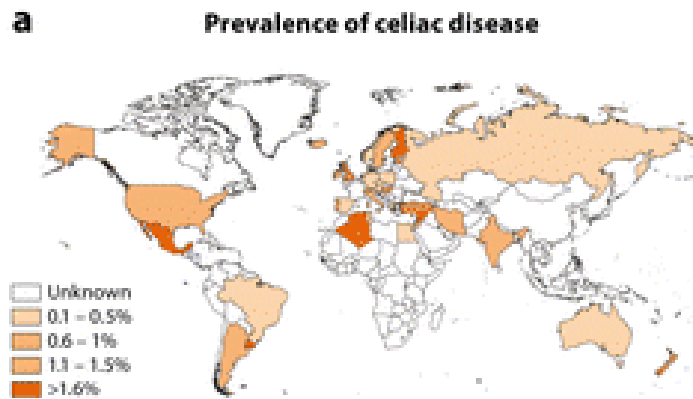
- A small bowel disorder characterized by mucosal inflammation, villous atrophy, and crypt hyperplasia, which occur upon exposure to dietary gluten and which demonstrate improvement after withdrawal of gluten from the diet.
- Celiac disease (also called gluten-sensitive enteropathy and non-tropical sprue) was first described by Samuel Gee in 1888



Celiac Disease

- CD is an immune response to Gliadins in the diet in susceptible patients that lead to inflammatory response and damage in the small bowel.
- Highest prevalence in European. (Finland 2.4%)
- Female to male ratio is 2:1
- Disease of all ages (>20% older than 60)
- North American Prevalence
 - General 1:100
 - Symptomatic 1:50
 - FDR 1:10





 Abadie V, et al. 2011.
 Annu. Rev. Immunol. 29:493–525



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The Changing Face of Celiac

PAST

Rare

More in kids

High mortality

Classic features:

- + Diarrhea
- + Weight loss
- + Failure to thrive

PRESENT

Much more common

All ages

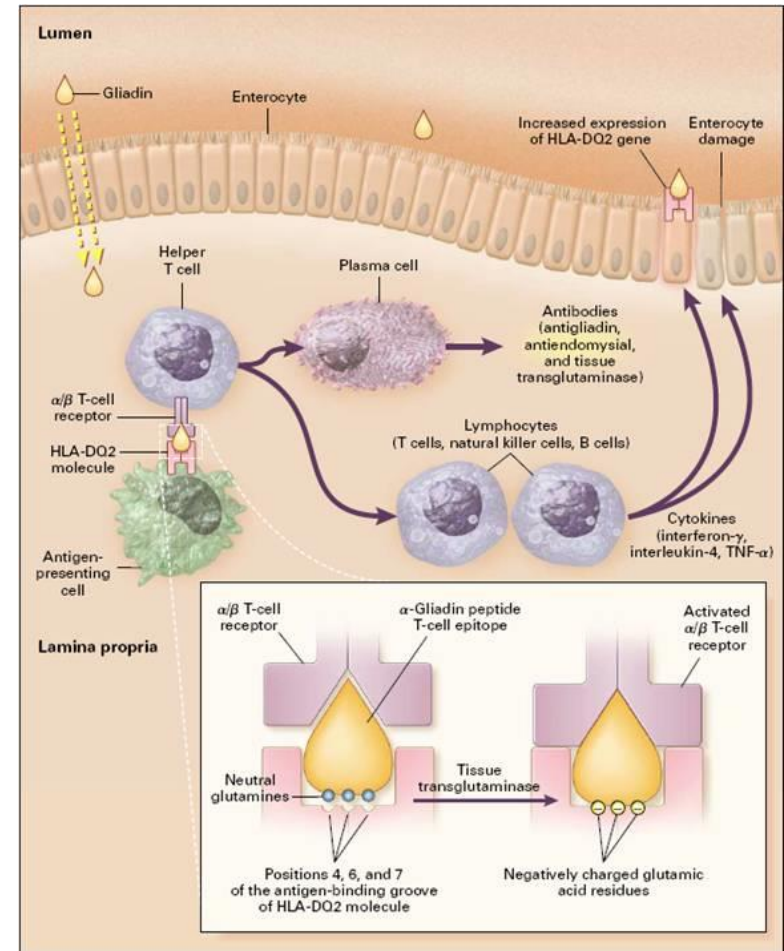
Low mortality

Protean features:

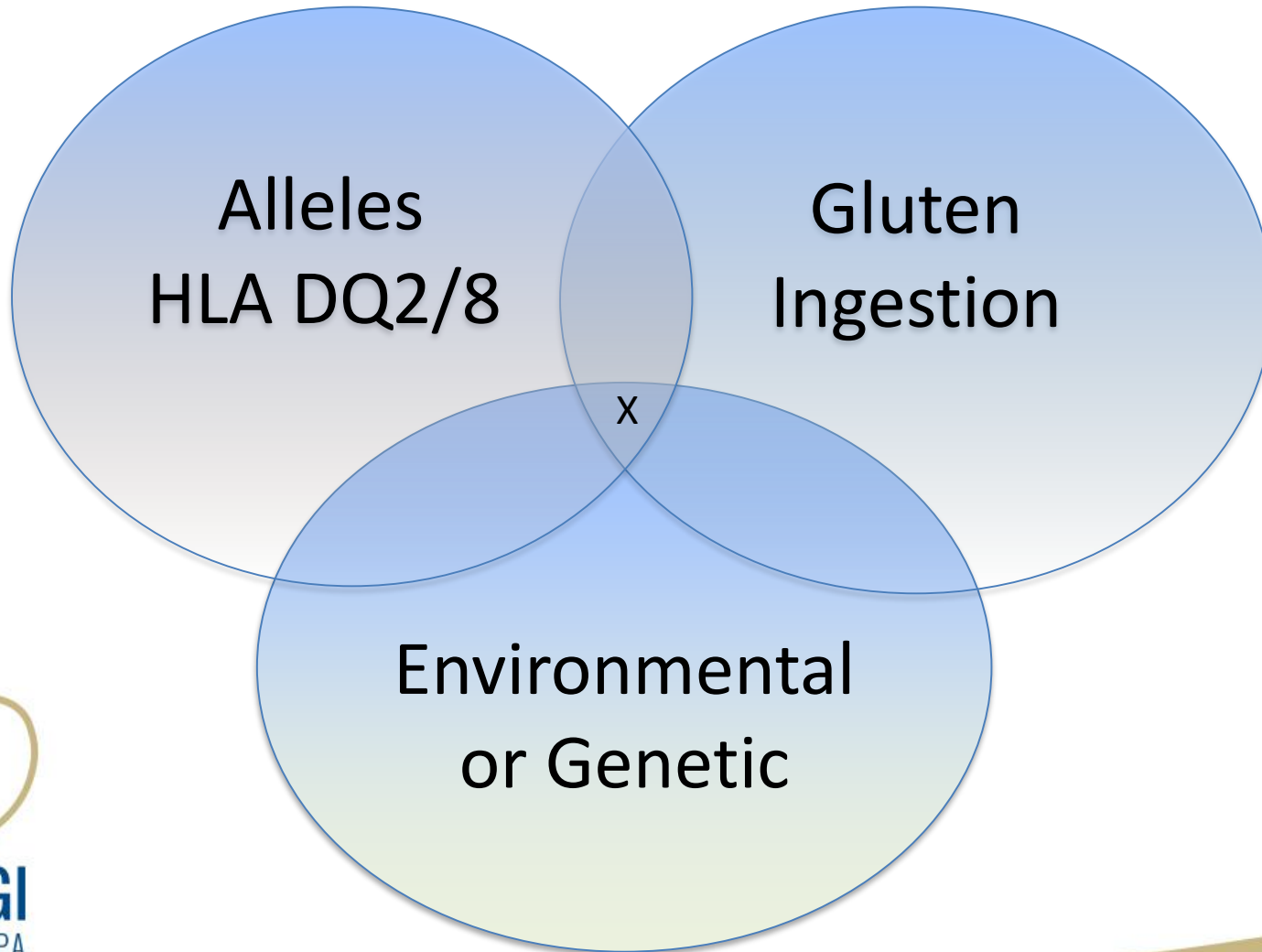
- + GI features
- + Extra-intestinal features

Pathogenesis

- CD patients ingest glutens which are resistant to proteases
- Antigen presenting cell (HLA DQ2/8) present gliadin to T cells.
- T cells recruit other immune cells, cytokines are released.
- tTG is released which make residue of gliadin more antigenic
- tTG targeted by humoral response creates antibodies



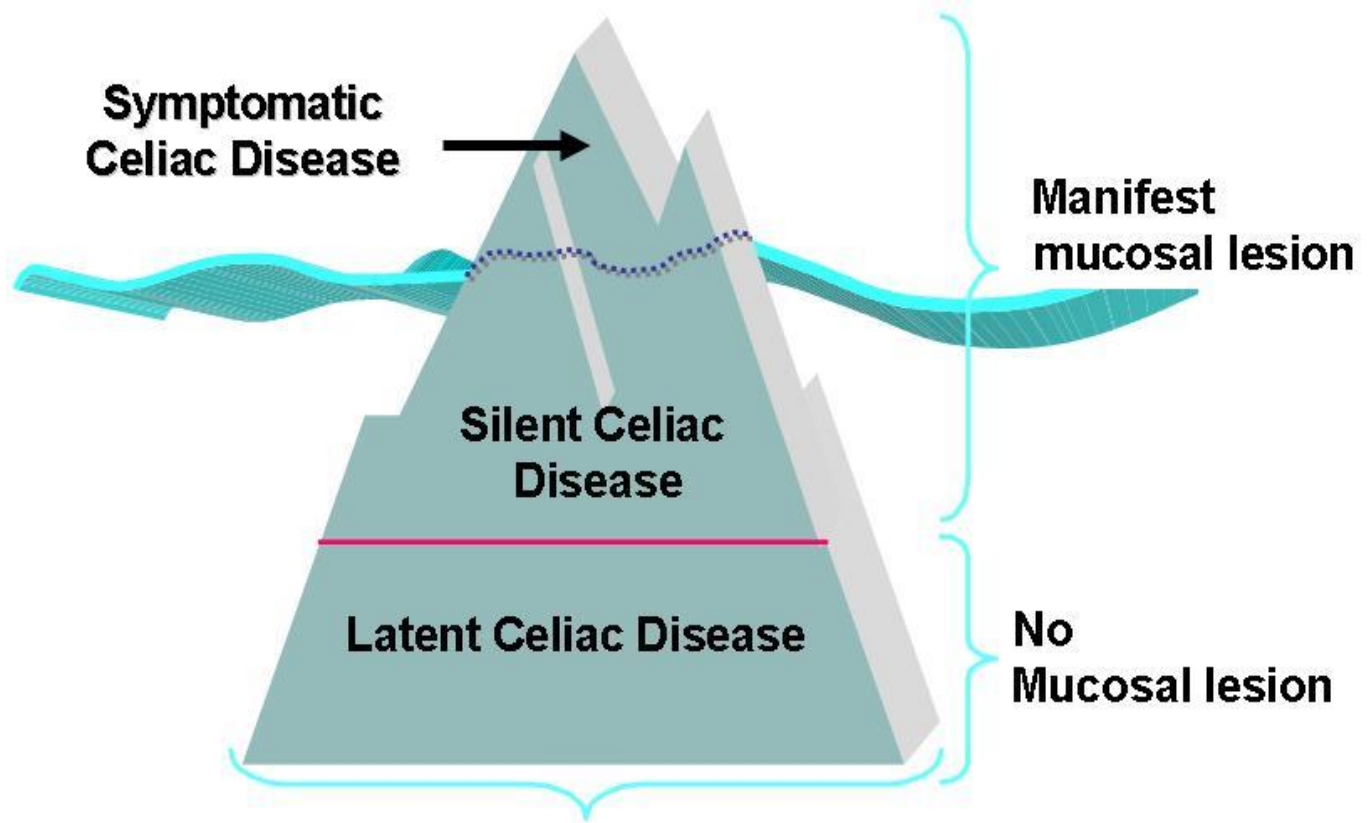
Pathogenesis



Change in Awareness

- Patients with symptoms of diarrhea
 - Before 1981: 91.3%
 - In 1990's: 58.3%
 - After 2000: 37.0%
- Average # of visit to pediatrician before diagnosis is 8.
- Average duration of symptoms (except diarrhea) is 4 year.

The Celiac Iceberg



Genetic susceptibility: HLA-DQ2, DQ8
Positive serology (TTG)



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Genetics OF celiac disease

- HLA DQ2 or DQ8 required. (prevalence about 30-40%)
- Family risk of CD
 - Monozygotic twins 80%
 - Siblings 10%
 - Kids 5-10%



• Syndromes associated with CD

- Down's, Turner's, William's

Diagnosis

- History and supportive clinical features
- Supportive Serologies
- Small bowel Biopsies characteristics.
 - Gold standard for Dx.
- Clinical response to Gluten free diet.



Celiac Disease

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graph TD; A[Celiac Disease] --> B[Classic Disease]; A --> C[Atypical Celiac Disease]; A --> D[Asymptomatic (silent) Celiac Disease]; A --> E[Latent Celiac Disease];
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Classic
Disease

Atypical
Celiac
Disease

Asymptomatic
(silent)
Celiac Disease

Latent
Celiac
Disease

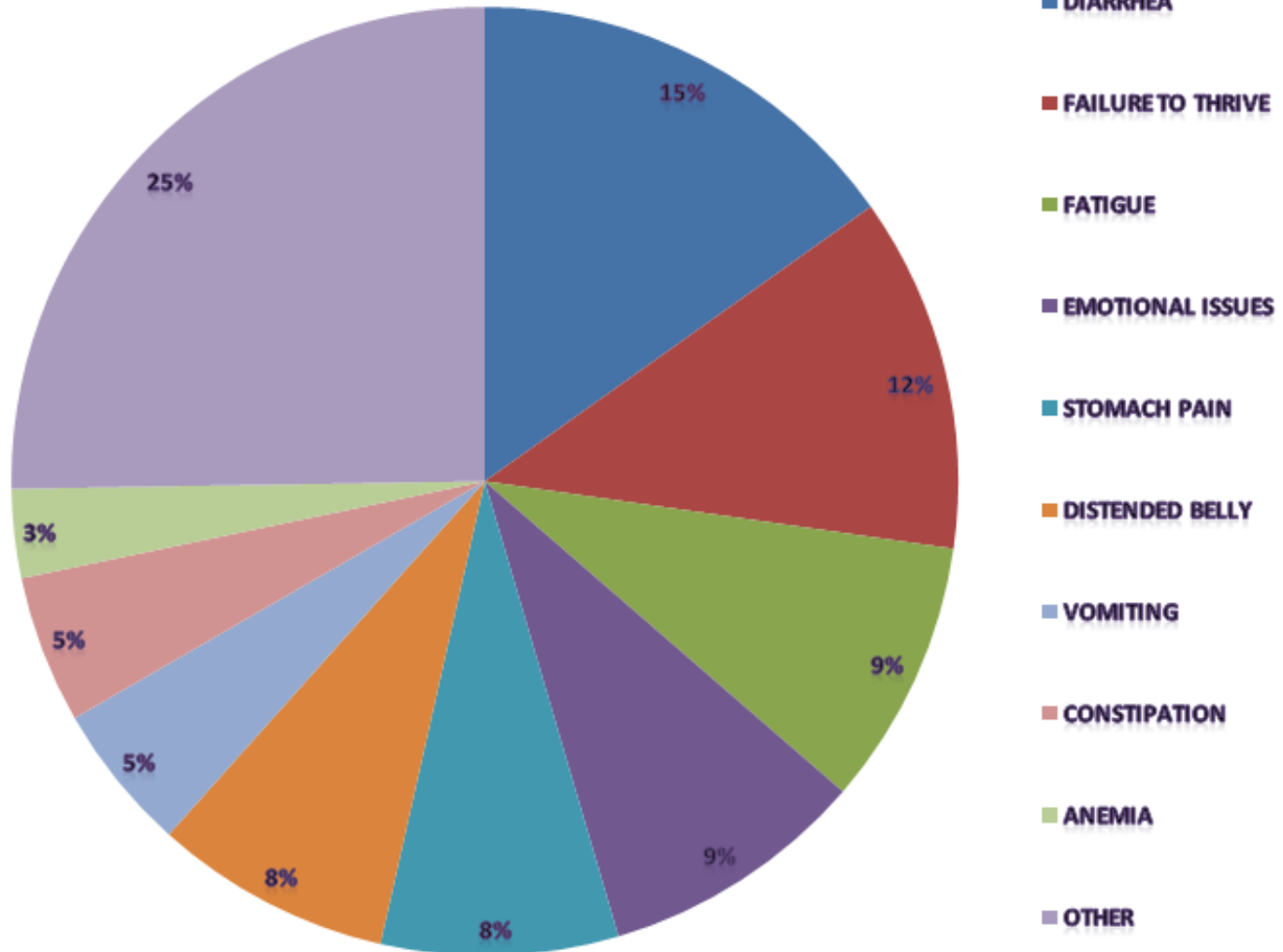
Manifestations of Celiac Disease

General	Gastrointestinal
Short Stature	Diarrhea, steatorrhea
Weight loss*	Flatulence, distension
Failure to thrive	Abdominal discomfort
Lethargy	Anorexia, nausea, vomiting
Delayed puberty	Constipation**
Edema	Aphthous stomatitis

*10%+ obese

** 20% constipated

PREVALENCE OF SYMPTOMS



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Non Classical CD

Category	Examples
Hematologic	Anemia (Iron,B12,folate), Functional Asplenia (H-J bodies)
Other Labs	Vit. Deficiencies, Abnormal Liver Function tests
Musculoskeletal	Osteopenia, osteoporosis, osteomalacia, arthropathies
Neuro	Seizures, ataxia, neuropathy
Reproductive	Infertility, Miscarriages
Skin	Dermatitis Herpetiformis

Autoimmune Diseases

- Type 1 Diabetes, Addison's disease, Thyroiditis
- IBD, Microscopic colitis (70 times more likely)
- IgA deficiency
- Autoimmune Hepatitis, PBC,PSC
- RA, Sjogren's
- IgA mesangial nephropathy.



Iron Deficiency Anemia

- CD prevalence in patients with IDA
 - (3-9% with no sx)
 - (10-15% with sx)
- 33% of patient with CD also had other source of IDA on EGD.
- Most overlooked in Menstruating women
- During EGD Small bowel Biopsies should be done on patient with IDA



Abnormal LFT and CD

- ALT and AST
 - Autoimmune hepatitis, NAFLD, Reactive hepatitis
- Alkaline Phosphatase
 - PBC,PSC, Osteomalacia (vit D deficiency)



Autoimmune Liver Disease in CD

30 patients with CD and liver biopsy

19 with autoimmune cause, (26% with CD sx)

Autoimmune hepatitis (9)

PSC (7)

PBC (3)

11 with other causes, (82% with CD sx)

Cryptogenic, hep C, fat, sarcoid, lymphoma

Dermatitis Herpetiformis (DH)

- DH represents intestinal sensitivity to gluten – not from skin contact
- Pruritic papulovesicular
- Extensor surfaces
- Symmetrical
- 80-90% no GI symptoms, but 75% with villous atrophy



Dermatitis Herpetiformis (DH)

- When a person with celiac disease consumes gluten, the mucosal immune system in the intestine responds by producing a type of antibody called immunoglobulin A (IgA)
- As IgA enters the bloodstream, it can collect in small blood vessels under the skin, triggering further immune reactions that result in the blistering rash of DH.
- Biopsies for diagnosis are taken from the affected area AND normal skin adjacent to the affected area



CLINICAL MANIFESTATIONS

- Gastrointestinal manifestations
- Non-gastrointestinal manifestations
 - Neuropsychiatric disease
 - Arthritis
 - Iron deficiency
 - Metabolic bone disease
 - Hyposplenism
 - Kidney disease
 - Idiopathic pulmonary hemosiderosis

WHO SHOULD BE TESTED?

- Those with gastrointestinal symptoms including
 - Chronic or recurrent diarrhea,
 - Malabsorption, weight loss,
 - Abdominal distension or bloating.
 - Irritable bowel syndrome or severe lactose intolerance.



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WHO SHOULD BE TESTED?

- Individuals without other explanations for signs and symptoms such as iron deficiency anemia, folate or vitamin B12 deficiency, persistent elevation in serum ALT, short stature, delayed puberty, recurrent fetal loss, low birthweight infants, reduced fertility, persistent aphthous stomatitis, dental enamel hypoplasia, idiopathic peripheral neuropathy, nonhereditary cerebellar ataxia, or recurrent migraine headaches.
- Patients with type 1 diabetes mellitus, and first-degree relatives of individuals with celiac disease if they have signs, symptoms, or laboratory evidence of possible celiac disease

CELIAC DISEASE DIAGNOSIS

- Blood tests
- Small intestine biopsy
- Genetic testing



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When to test for celiac Disease

- Before testing Patient should be on Gluten containing diet. Sensitivity of serologies drop significantly on gluten free diet.
- Gluten challenge
 - 2 slices of wheat bread/day for 2 weeks
 - If poor tolerance, test than
 - If tolerable, than 6 more weeks, than test



SERUM ANTIBODY ASSAYS

- **AGA**
 - Anti gliadin antibody (IgA/IgG)
- **EMA**
 - IgA endomysial antibody (IgA EMA)
- **Tissue Transglutaminase:**
 - IgA tissue transglutaminase antibody (IgA tTG)
 - IgG tissue transglutaminase antibody (IgG tTG)
- **Deaminated Gliadin Peptide:**
 - IgA deaminated gliadin peptide (IgA DGP)
 - IgG deaminated gliadin peptide (IgG DGP)

Assay sensitivity and specificity

- IgA endomysial antibodies – sensitivity 90 to 98 % ; specificity 97 to 100 %
- IgA tissue transglutaminase antibodies – sensitivity 90 to 98 %; specificity 95 to 97 %
- IgA deaminated gliadin peptide (DAP)– sensitivity 74-84 %; specificity 99 %
- IgG deaminated gliadin peptide(DAP) – sensitivity 92 %; specificity 100 %




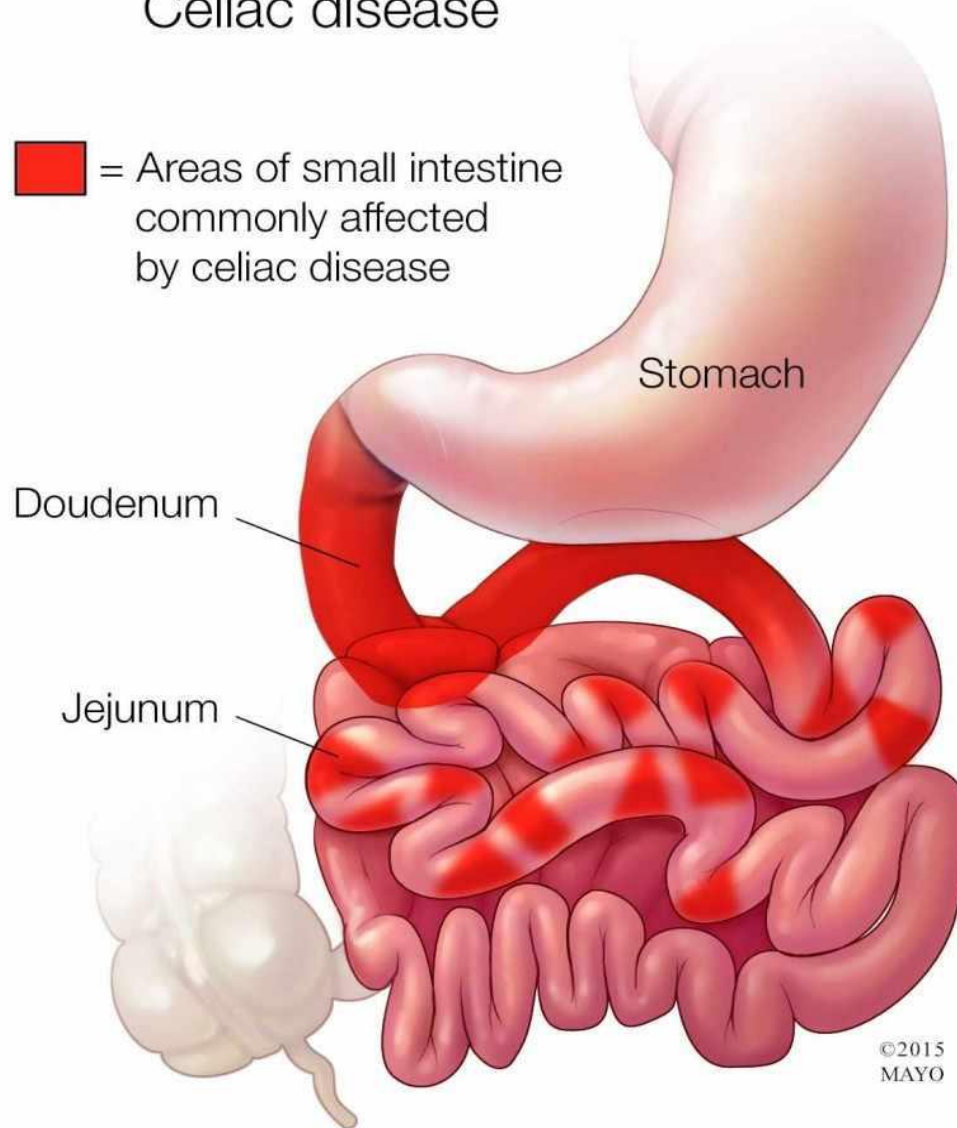
When To do EGD and Biopsy

- All patients with celiac disease should have biopsy before GFD.
 - Allows to confirm diagnosis.
 - Allows baseline for future progression.
- Should be done in those with:
 - Positive serologies.
 - Strong symptoms
 - Iron deficiency anemia

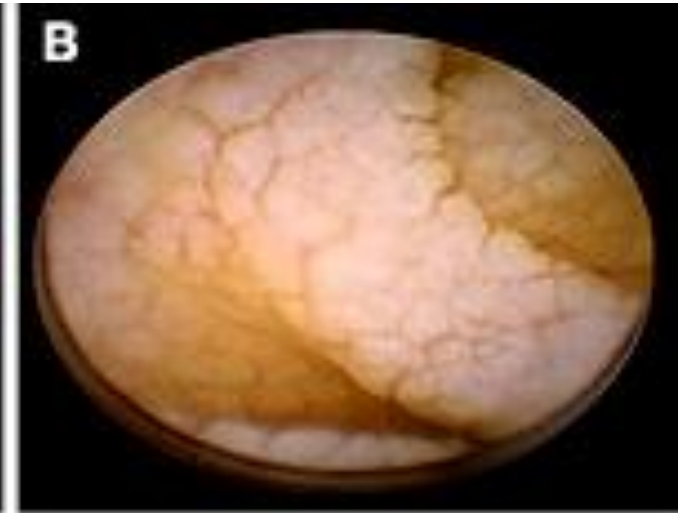


Celiac disease

 = Areas of small intestine commonly affected by celiac disease

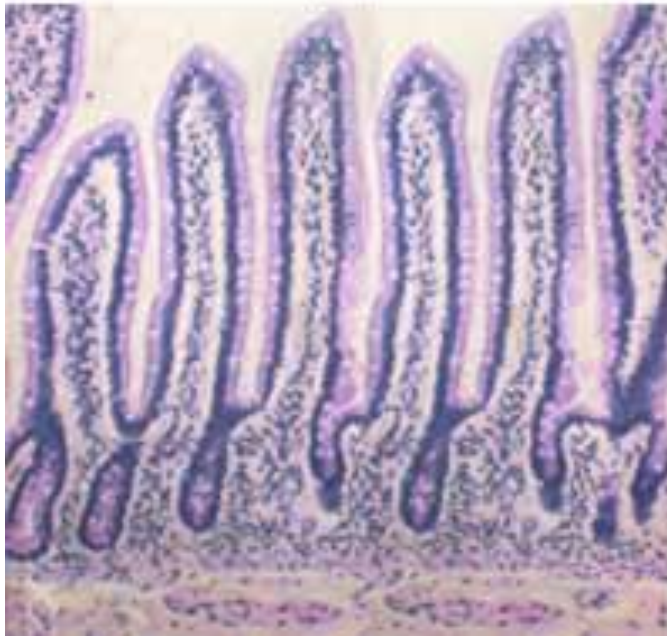


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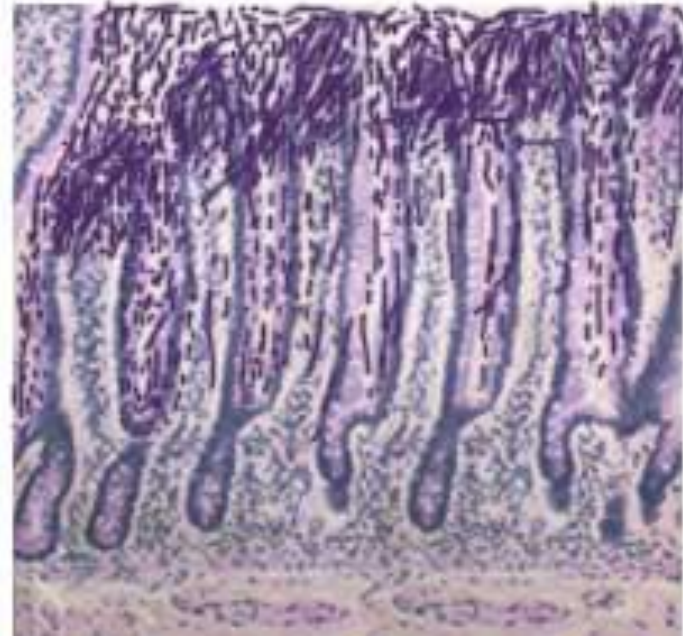


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Healthy normal villi of the small intestine(as seen under the microscope)

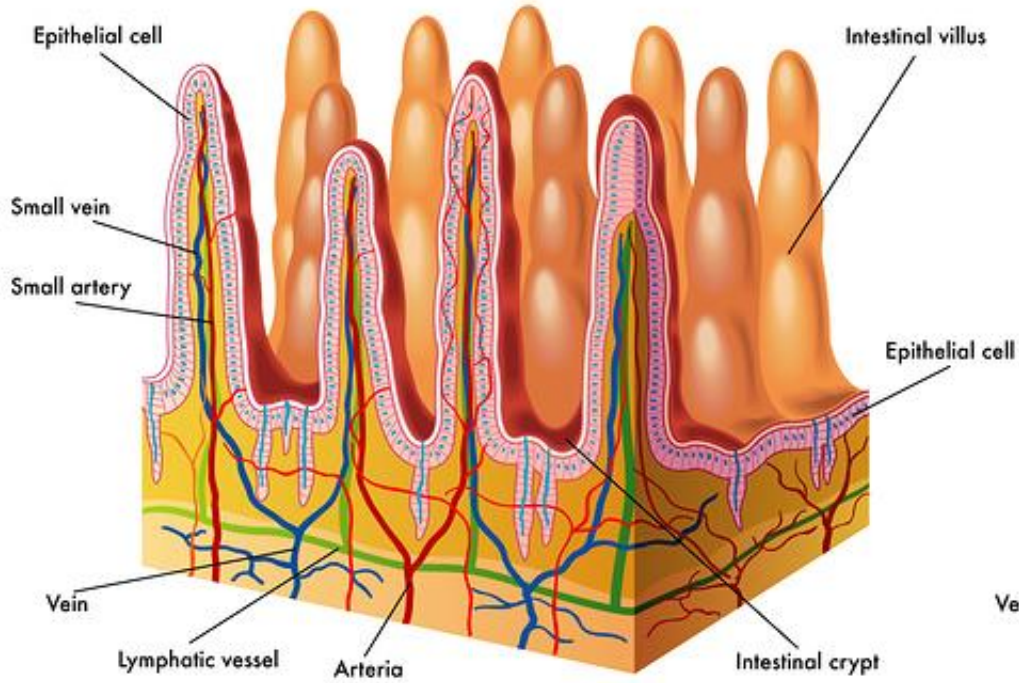


Damaged villi of the small intestine

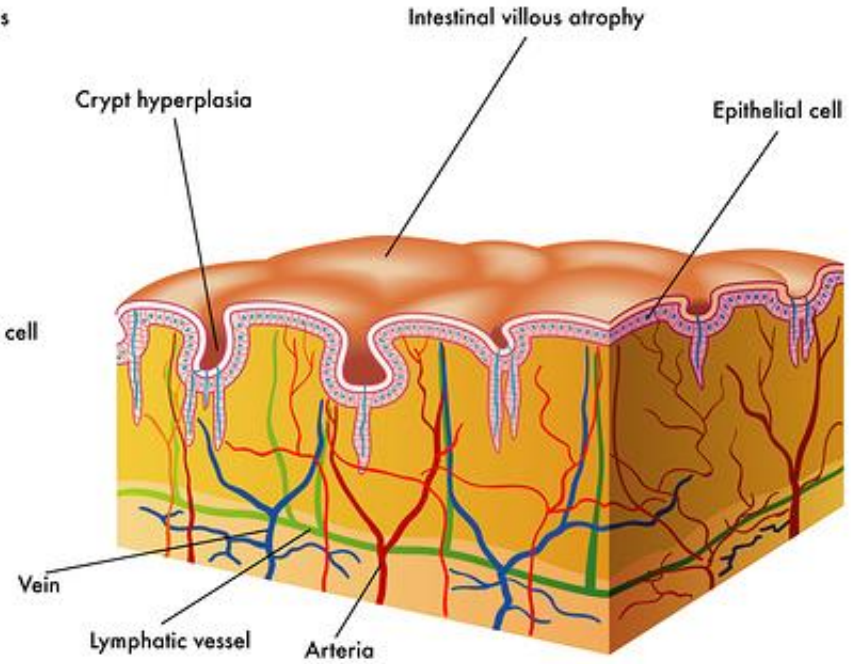


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NORMAL



CELIAC DISEASE



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Summary of histologic classifications frequently used for celiac disease

Marsh Modified	Histologic criterion			Corazza
	Increased intraepithelial lymphocytes*	Crypt hyperplasia	Villous atrophy	
Type 0	No	No	No	None
Type 1	Yes	No	No	Grade A
Type 2	Yes	Yes	No	
Type 3a	Yes	Yes	Yes (partial)	Grade B1
Type 3b	Yes	Yes	Yes (subtotal)	
Type 3c	Yes	Yes	Yes (total)	Grade B2

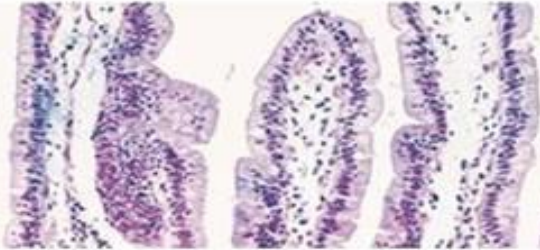


* > 40 intraepithelial lymphocytes per 100 enterocytes for Marsh modified (Oberhuber); > 25 intraepithelial lymphocytes per 100 enterocytes for Corazza

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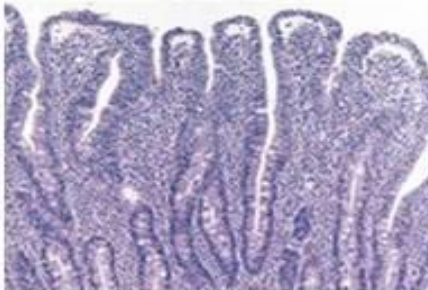
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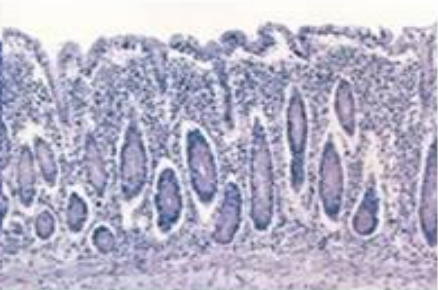
3A



3B



3C



PRE-INFILTRATIVE

INFILTRATIVE

INFILTRATIVE
HYPERPLASTIC

FLAT
DESTRUCTIVE

ATYPIC
HYPERPLASTIC

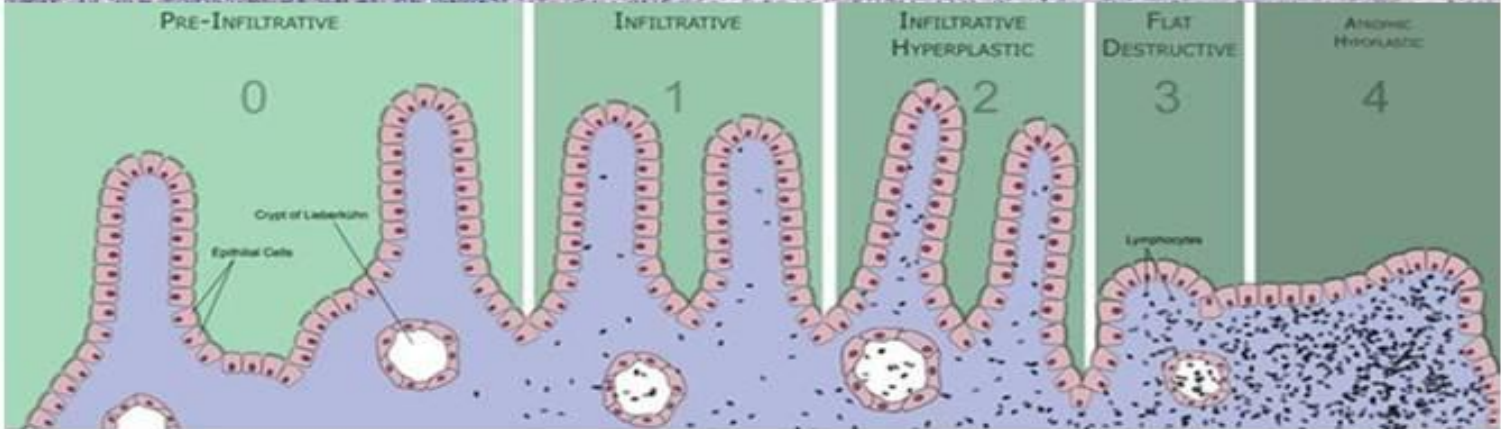
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Biopsy for Pediatrics?

Recent guideline from the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (**ESPGHAN**) proposed that it may be possible to avoid any intestinal biopsy in children who meet the following criteria:

- Characteristic symptoms of CD
- TTG IgA levels >10x upper limit of normal (confirmed with + EMA in different blood sample)
- Positive HLA-DQ 2/8

D/D of Biopsy

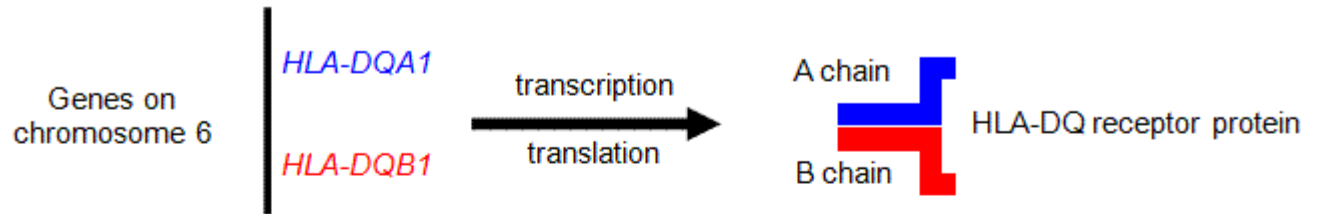
- NSAIDs
- SIBO
- IBD
- H-Pylori,
- Giardia
- CVID
- Lymphoma
- Viral Gastroenteritis
- Tropical sprue,
- Whipple's Disease
- Non-gluten proteins
- Drugs (Olmesatzen, Benicar)



HLA testing

- HLA DQ- 2 (95%) HLA DQ- 8 (5%)
- 30-40% of the population
- Necessary, But not enough
- Negative predictive value 99-100%
- Celiac Disease prevalence 1%



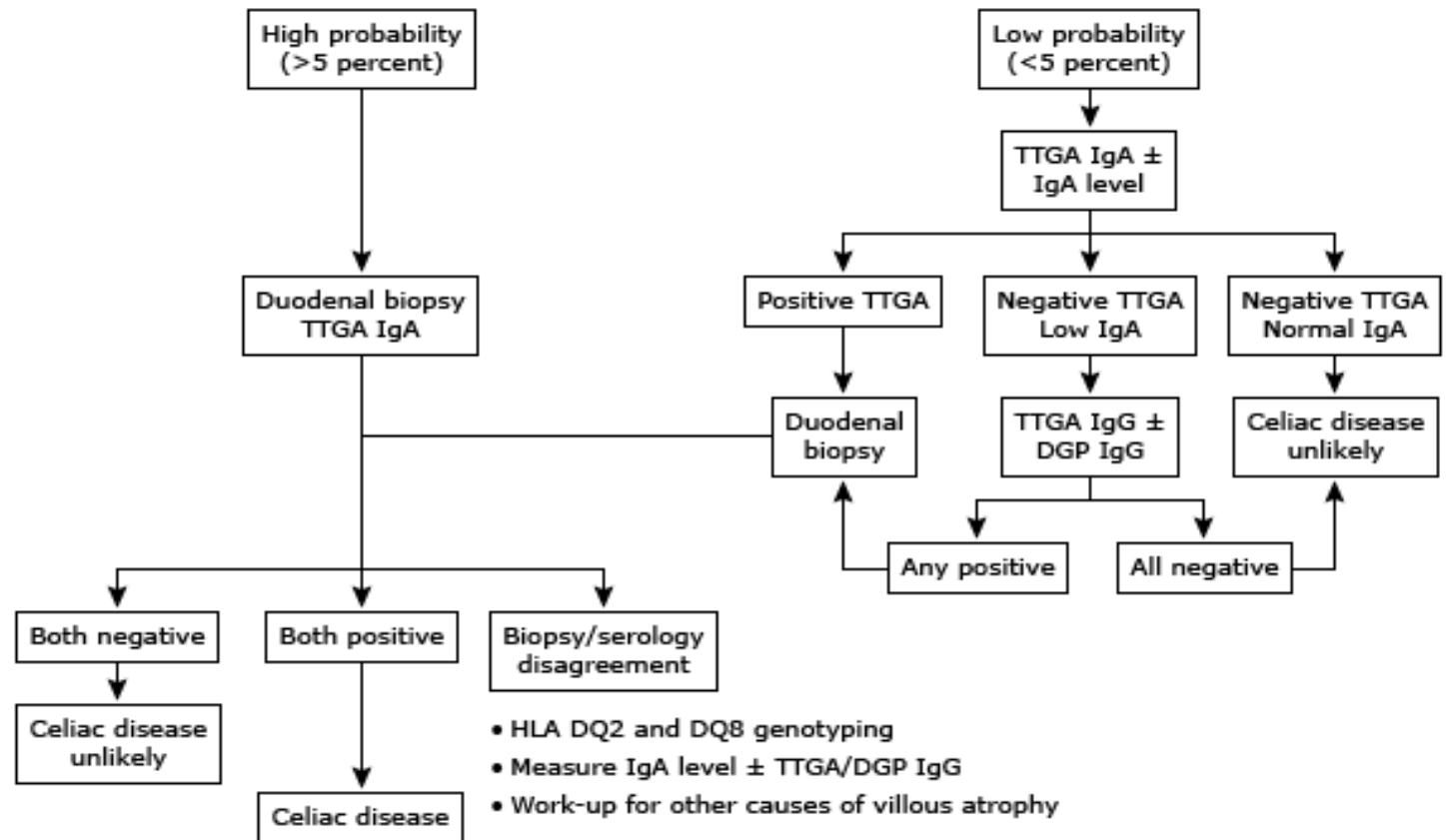


There are a range of possible HLA-DQ protein types, from DQ1 to DQ9, that are located on the surface of cells to act as receptors of antigen molecules.



HLA-DQ2 and HLA-DQ8 bind gluten peptide fragment more strongly and can trigger an immune response more easily

Celiac disease testing algorithm



- HLA DQ2 and DQ8 genotyping
- Measure IgA level ± TTGA/DGP IgG
- Work-up for other causes of villous atrophy



Treatment

- Gluten free diet life long
- Skilled Dietician.
- Labs.
 - CBC, (ferritin, B12,folate)
 - LFT, Vit D, TSH, Ca++
 - INR, Vit A, E, copper, zinc, etc.
- Bone Density.
- Vaccine for encapsulated
 - May be functionally A splenic





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Diet Compliance

- Lower Compliance
 - Diagnosis at older age
 - Teens
 - Asymptomatic
 - Detection via family screening.



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Clinical response time line

- Symptom relief is quick:
 - 67% notice complete response in 6 months.
 - Mean time is 4 weeks
- Serologies:
 - Significant by 6 months
- Histology:
 - May take 6-24 months, Slower in adults



Follow up

- Baseline
 - Dietician, labs
- 3-6 months
 - Assess symptoms and repeat serologies
- Yearly Follow-up



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- Repeat biopsies?

Celiac Disease Complications

- Nonresponsive celiac disease
- Refractory celiac disease
- Ulcerative jejunitis
- Lymphoma
- Skin conditions



Refractory sprue

- **Type 1:**
 - Normal population of intraepithelial lymphocytes.
- **Type 2:**
 - Aberrant or premalignant population of intraepithelial lymphocytes based upon clonality analysis of T-cell receptors and immunophenotyping.
 - Type 2 can progress to enteropathy-associated T-cell lymphoma, which may present clinically as ulcerative jejunitis. The diagnosis can be established on biopsy; CT, MRI, and 18F-FDG PET scans can help identify suspicious areas



Summary

- Mono symptomatic or non classic features are more common than classic Celiac disease
- Clinical History, serologies and Small bowel biopsy substantiate the diagnosis.
- GFD is life long, challenging and expensive.
- If not responding than verify the diagnosis, check compliance, consider complication
- Screening at risk population. Mass screening is not endorsed



The Lighter Side of Celiac Disease:

PERMANENT WRINKLE

From the constant smile when we assure people "It's not that bad!"

HARD OF HEARING

From years of trying to tune out fried chicken and doughnut shop commercials.

TEETH LOST

From eating too many nuts in an effort to put more fiber in the diet.

ULCERS

From holding back the urge to punch out the cereal companies for sneaking gluten into most of their products.

FINGER CANCER

From pointing repeatedly (sometimes for years) to "where it hurts" before we finally got the right diagnosis.

HAIR FRAZZLED

From constantly having to answer to "Celiac Disease, what's that??"

BAD POSTURE

From bending over the typewriter when writing to manufacturers.

TACKY CLOTHES

From spending too much money on expensive gluten-free products

HAND LOST

From excessive fingernail biting when planning a trip to a restaurant.

TENNIS SHOES

For running to the bathroom quickly after making a mistake on the diet (intentional or accidental) and for running to our celiac meetings because our food budget is higher than our "new car" budget!

Thank You
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Professional level information

- Academy of Nutrition and Dietetics (formerly American Dietetic Association)
 - (www.eatright.org)
- American Celiac Disease Alliance
 - (www.americanceliac.org)
- American Gastroenterological Association
 - (http://www.gastro.org/info_for_patients/2013/6/6/understanding-celiac-disease)
- Celiac Disease Foundation
 - (www.celiac.org)
- Gluten Intolerance Group of North America
 - (www.gluten.net)
- National Foundation for Celiac Awareness (NFCA)
 - (www.celiaccentral.org)
- National Institute of Diabetes and Digestive and Kidney Diseases
 - (www.niddk.nih.gov)
- National Library of Medicine
 - (www.nlm.nih.gov/medlineplus/ceciacdisease.html)
- North American Society for the Study of Celiac Disease
 - (www.nasscd.org)
- US Food and Drug Administration
 - (<http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm059116.htm>)
- FDA and USDA labeling:
 - Thompson T. ADA Pocket Guide to Gluten-Free Strategies for Clients with Multiple Diet Restrictions, American Dietetic Association, Chicago 2011.
 - <http://www.glutenfreedietitian.com/labeling-of-usda-regulated-foods>



PATHOGENESIS

- Genetic factors

- The frequent intrafamilial occurrence and the remarkably close association with the HLA-DQ2 and/or DQ8 gene loci provide the basis of our current understanding of celiac disease
- HLA typing for DQ2 (DQA1*05; DQB1*02) and DQ8 (DQA1*03; DQB1*0302) may be useful in individuals with equivocal small bowel histologic findings since celiac disease is unlikely if neither is present
- Homozygosity for HLA DQ2 has been associated with an increased risk for celiac disease and enteropathy-associated T-cell lymphoma

