UNIVERSITA' DEGLI STUDI DI PERUGIA
DIPARTIMENTO DI MEDICINA E CHIRURGIA

SANU AA 2023/24

Celiachia – Malabsorption syndromes

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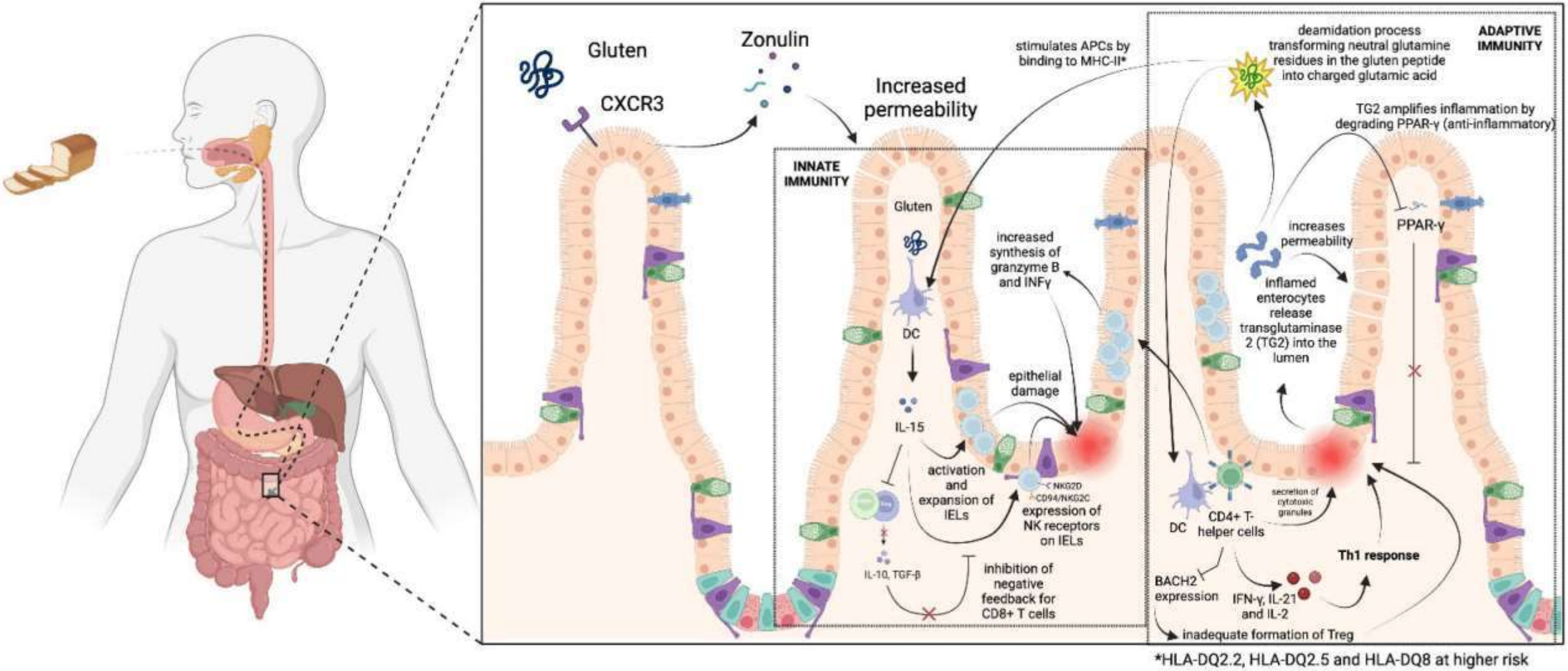

Gluten
Zonulin
CXCR3
Increased permeability
stimulates APCs by binding to MHC-II*
deamidation process transforming neutral glutamine residues in the gluten peptide into charged glutamic acid
ADAPTIVE IMMUNITY
TG2 amplifies inflammation by degrading PPAR-γ (anti-inflammatory)
INNATE IMMUNITY
Gluten
DC
IL-15
increased synthesis of granzyme B and INFγ
epithelial damage
activation and expansion of IELs
NKG2D
CD94/NKG2C
expression of NK receptors on IELs
IL-10, TGF-β
inhibition of negative feedback for CD8+ T cells
increases permeability
Inflamed enterocytes release transglutaminase 2 (TG2) into the lumen
PPAR-γ
DC
CD4+ T-helper cells
secretion of cytotoxic granules
Th1 response
BACH2 expression
IFN-γ, IL-21 and IL-2
inadequate formation of Treg
*HLA-DQ2.2, HLA-DQ2.5 and HLA-DQ8 at higher risk

Malabsorption syndrome

Malabsorption

- Disorders of absorption constitute a broad spectrum of conditions with multiple etiologies and varied clinical manifestations.
- Almost all of these clinical problems are associated **with *diminished* intestinal absorption** of one or more dietary nutrients and are often referred to as the ***malabsorption syndrome*.**

- Malabsorption is a clinical term that encompasses defects occurring during the **digestion and absorption** of food nutrients **(maldigestion vs malabsorption)**

- Impairment can be of single or multiple nutrients depending on the abnormality.

Gastric Diseases
Atrophic gastritis
Autoimmune gastritis (pernicious anemia)
Gastric resection or bypass surgery

Pancreatic Diseases
Congenital pancreatic enzyme deficiencies:
- Colipase deficiency
- Lipase deficiency
- Trypsinogen deficiency

Pancreatic insufficiency:
- Chronic pancreatitis
- Cystic fibrosis
- Johanson-Blizzard syndrome
- Pearson's marrow-pancreas syndrome
- Shwachman's syndrome

Pancreatic tumors

Liver Diseases
Inborn errors of bile acid biosynthesis and transport
Cirrhosis and other liver diseases
Portal hypertension

Obstructive Biliary Diseases
Biliary tumors
Primary and secondary sclerosing cholangitis

Intestinal Diseases
Amyloidosis
Autoimmune enteropathy
Celiac disease
Collagenous sprue
Congenital intestinal defects (see Table 104-10)
Crohn's disease
Enteroendocrine cell deficiency:
- Autoimmune polyglandular syndrome type 1
- Enteric anendocrinosis

Enterokinase deficiency
Eosinophilic gastroenteritis
Fistulas
Food allergy
Graft-versus-host disease
Hypolactasia
Ileal bile acid malabsorption
Intestinal infections:
- AIDS (HIV infection): cryptosporidiosis, *Mycobacterium avium* complex infection, viral infections
- Giardiasis
- Helminthic infections
- Tuberculosis
- Whipple's disease

Immunoproliferative small intestinal disease
Intestinal ischemia
Intestinal lymphoma
Intestinal resections or bypass
Mastocytosis
Nongranulomatous chronic idiopathic enterocolitis
Postinfection malabsorption
Primary immunodeficiency diseases
Radiation enteritis
Refractory sprue
Sarcoidosis
SIBO
Tropical sprue

Lymphatic Diseases
Primary intestinal lymphangiectasia
Secondary intestinal lymphangiectasia:
- Lymphoma
- Solid tumors
- Thoracic duct trauma, damage, or obstruction

Neuroendocrine Tumors
Carcinoid syndrome
Glucagonoma
Somatostatinoma
Zollinger-Ellison syndrome

Cardiac and Vascular Diseases
Constrictive pericarditis
Heart failure

Endocrine Causes
Addison's disease
Diabetes mellitus
Hyperthyroidism

Systemic Diseases
Cronkhite-Canada syndrome
Mixed connective tissue disease
Neurofibromatosis type 1
Protein-calorie malnutrition
Scleroderma
SLE

Malabsorptive disorders can be categorized into

1-Generalized mucosal abnormalities

resulting in multiple nutrient malabsorption

2-Specific nutrient disorder

(carbohydrate, fat, protein, vitamin and mineral malabsorption)

Malabsorption

Most, but not all, malabsorption syndromes are associated with ***steatorrhea***, an increase in stool fat excretion of >6% of dietary fat intake.

Some malabsorption disorders are not associated with steatorrhea: primary lactase deficiency, a congenital absence of the small intestinal brush border disaccharidase enzyme lactase, is associated with lactose "malabsorption," and pernicious anemia is associated with a marked decrease in intestinal absorption of cobalamin (vitamin B_{12}) due to an absence of gastric parietal cell intrinsic factor required for cobalamin absorption

Pathophysiologic Mechanism	Malabsorbed Substrate(s)	Representative Causes
Maldigestion		
Conjugated bile acid deficiency	Fat Fat-soluble vitamins Calcium Magnesium	Hepatic parenchymal disease Biliary obstruction SIBO with bile acid deconjugation Ileal bile acid malabsorption CCK deficiency
Pancreatic insufficiency	Fat Protein Carbohydrate Fat-soluble vitamins Vitamin B_{12} (cobalamin)	Congenital defects Chronic pancreatitis Pancreatic tumors Inactivation of pancreatic enzymes (e.g., ZES)
Reduced mucosal digestion	Carbohydrate Protein	Congenital defects (see Table 104-10) Acquired lactase deficiency Generalized mucosal disease (e.g., celiac disease, Crohn's disease)
Intraluminal consumption of nutrients	Vitamin B_{12} (cobalamin)	SIBO Helminthic infections (e.g., *Diphyllobothrium latum* infection)
Malabsorption		
Reduced mucosal absorption	Fat Protein Carbohydrate Vitamins Minerals	Congenital transport defects (see Table 104-10) Generalized mucosal diseases (e.g., celiac disease, Crohn's disease) Previous intestinal resection or bypass Infections Intestinal lymphoma
Decreased transport from the intestine	Fat Protein	Intestinal lymphangiectasia Primary Secondary (e.g., solid tumors, Whipple's disease, lymphomas) Venous stasis (e.g., from heart failure)
Other Mechanisms		
Decreased gastric acid and/or intrinsic factor secretion	Vitamin B_{12}	Pernicious anemia Atrophic gastritis Previous gastric resection
Decreased gastric mixing and/or rapid gastric emptying	Fat Calcium Protein	Previous gastric resection Autonomic neuropathy
Rapid intestinal transit	Fat	Autonomic neuropathy Hyperthyroidism

Clinical manifestations

Diarrhea – bulky, floating, malodorous stool – difficult to flush.

Weight loss – may be profound, usually associated with anorexia.

Anaemia – B12, iron, folate malabsorption.

Patient may complain of dizziness, dyspnoea and fatigue

TABLE 104-3 Symptoms and Signs of Malabsorption and Relevant Pathophysiology

Symptom or Sign	Pathophysiologic Explanation
Gastrointestinal	
Diarrhea	Osmotic activity of carbohydrates or short-chain fatty acids Secretory effect of bile acids and fatty acids Decreased absorptive surface Intestinal loss of conjugated bile acids: Ileal resection Severe ileal mucosal disease Congenital defects of the ileal sodium-bile acid cotransporter
Abdominal distention, flatulence	Bacterial gas production from carbohydrates in colon, SIBO
Foul-smelling flatulence or stool	Malabsorption of proteins or intestinal protein loss
Pain	Gaseous distention of intestine
Ascites	Protein loss or malabsorption
Musculoskeletal	
Tetany, muscle weakness, paresthesias	Malabsorption of vitamin D, calcium, magnesium, and phosphate
Bone pain, osteomalacia, fractures	Protein, calcium, or vitamin D deficiency; secondary hyperparathyroidism
Cutaneous and Mucosal	
Easy bruisability, ecchymoses, petechiae	Vitamin K deficiency, vitamin C deficiency (scurvy)
Glossitis, cheilosis, stomatitis	Vitamin B complex, vitamin B_{12}, folate, or iron deficiency
Edema	Protein loss or malabsorption
Acrodermatitis, scaly dermatitis	Zinc and essential fatty acid deficiency
Follicular hyperkeratosis	Vitamin A deficiency
Hyperpigmented dermatitis	Niacin deficiency (pellagra)
Thin nails with spoon-shaped deformity	Iron deficiency
Perifollicular hemorrhage	Malabsorption of vitamin C
Spiral or curly hair	Malabsorption of vitamin C
Other	
Weight loss, hyperphagia	Nutrient malabsorption
Growth and weight retardation, infantilism	Nutrient malabsorption in childhood and adolescence
Anemia	Iron, folate, or vitamin B_{12} deficiency
Kidney stones	Increased colonic oxalate absorption
Amenorrhea, impotence, infertility	Multifactorial (including protein malabsorption, secondary hypopituitarism, anemia)
Night blindness, xerophthalmia	Vitamin A deficiency
Peripheral neuropathy	Vitamin B_{12} or thiamine deficiency
Fatigue, weakness	Calorie depletion, iron and folate deficiency, anemia
Neurologic symptoms, ataxia	Vitamin B_{12}, vitamin E, or folate deficiency

Malasportion syndrome

Diagnosis

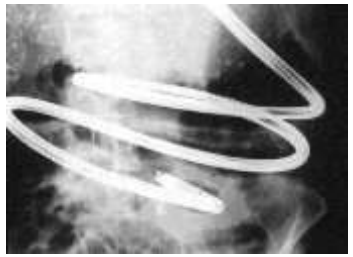
Malabsorption

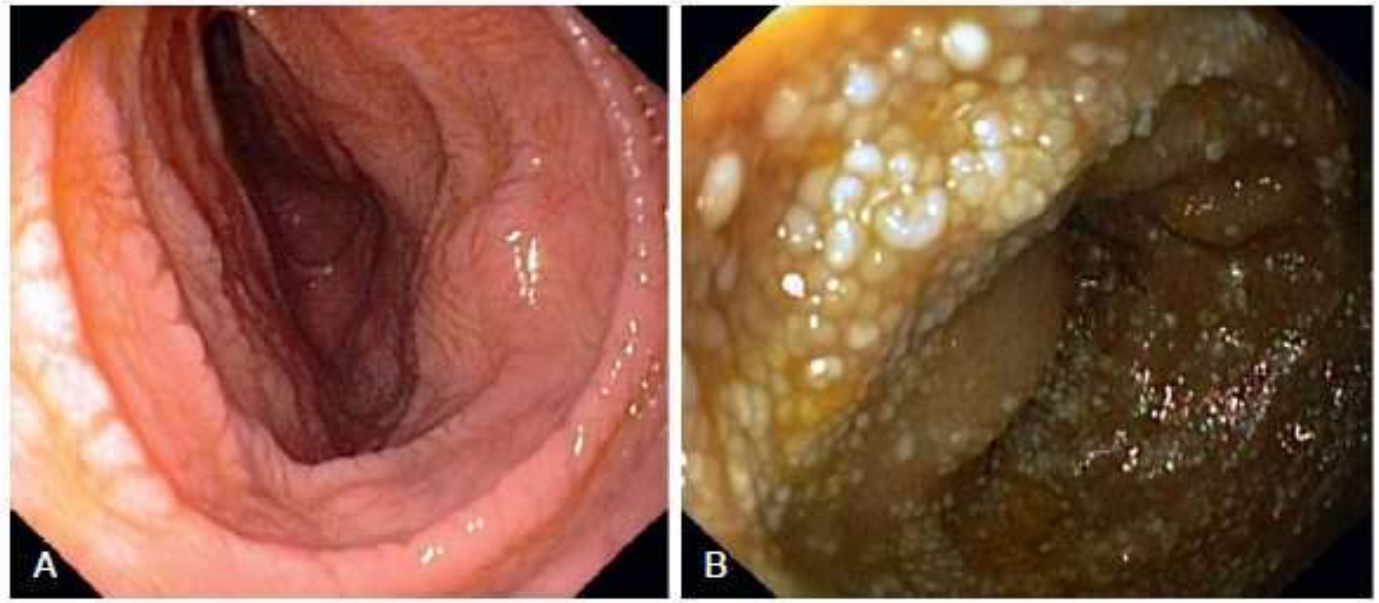
TABLE 104-4 Useful Laboratory Tests for Patients with Suspected Malabsorption and for Establishing Possible Nutrient Deficiencies

Test	Comment(s)
Blood Cell Count	
Hematocrit, hemoglobin	Decreased in iron, vitamin B_{12}, and folate malabsorption or with blood loss
Mean corpuscular hemoglobin or mean corpuscular volume	Decreased in iron malabsorption; increased in folate and vitamin B_{12} malabsorption
White blood cells, differential	Decreased in vitamin B_{12} and folate malabsorption; low lymphocyte count in lymphangiectasia
Biochemical Tests (Serum)	
TGs	Decreased in severe fat malabsorption
Cholesterol	Decreased in bile acid malabsorption or severe fat malabsorption
Albumin	Decreased in severe malnutrition, lymphangiectasia, protein-losing enteropathy
Alkaline phosphatase	Increased in calcium and vitamin D malabsorption (severe steatorrhea); decreased in zinc deficiency
Calcium, phosphorus, magnesium	Decreased in extensive small intestinal mucosal disease, after extensive intestinal resection, or in vitamin D deficiency
Zinc	Decreased in extensive small intestinal mucosal disease or intestinal resection
Iron, ferritin	Decreased in celiac disease, in other extensive small intestinal mucosal diseases, and with chronic blood loss
Other Serum Tests	
Prothrombin time	Prolonged in vitamin K malabsorption
β-Carotene	Decreased in fat malabsorption from hepatobiliary or intestinal diseases
Immunoglobulins	Decreased in lymphangiectasia, diffuse lymphoma
Folic acid	Decreased in extensive small intestinal mucosal diseases, with anticonvulsant use, in pregnancy; may be increased in SIBO
Vitamin B_{12}	Decreased after gastrectomy, in pernicious anemia, terminal ileal disease, SIBO, and infection with *Diphyllobothrium latum*
Methylmalonic acid	Markedly elevated in vitamin B_{12} deficiency
Homocysteine	Markedly elevated in vitamin B_{12} or folate deficiency
Citrulline	May be decreased in destructive small intestinal mucosal disease or intestinal resection
Stool Tests	
Fat	Qualitative or quantitative increase in fat malabsorption
Elastase, chymotrypsin	Decreased concentrations and output in exocrine pancreatic insufficiency
pH	Less than 5.5 in carbohydrate malabsorption

Endoscopy

- **Gross morphology – gives diagnostic clue**
  - Reduced duodenal folds and scalloping of duodenal mucosa – celiac disease
    - Use of vital dyes to identify villous atrophy
- **Biopsy – to establish Dx**
  - For patients with documented steatorrhea or chronic Diarrhea
- **Lesions seen – classified in to three**
  - Diffuse,specific e.g. Whipple's Disease
  - Patchy, specific – Crohn's D., lymphoma infectious causes
  - Diffuse,non-specific – celiac sprue, Tropical sprue autoimmune enteropathy
- **Suspected distal pathology** - push enteroscopy wireless capsule endoscopy

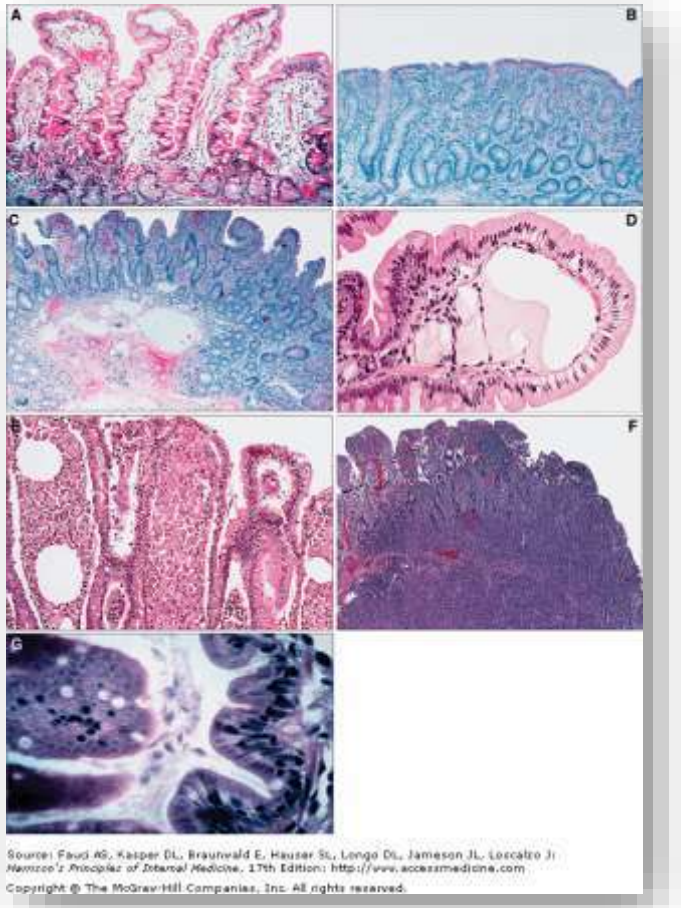



A
B

Small Bowel Biopsy

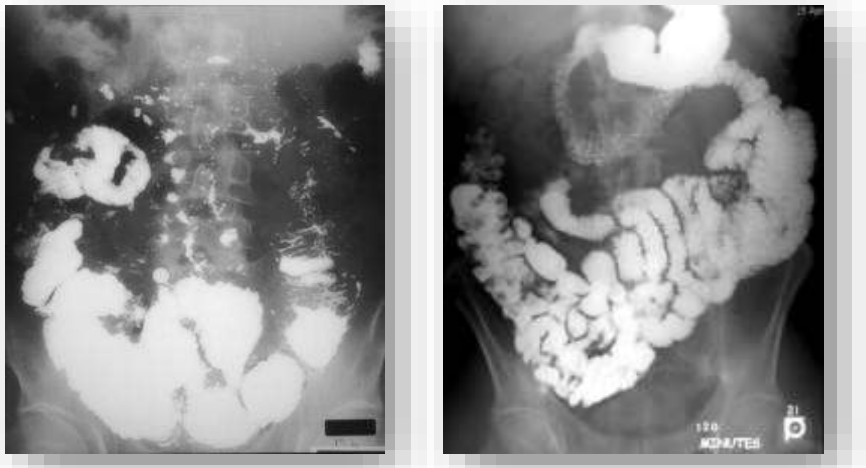
Causes of villous atrophy in the duodenum

- Celiac disease
- Tropical sprue
- Small-bowel bacterial overgrowth
- Autoimmune enteropathy
- Hypogammaglobulinemic sprue
- Drug-associated enteropathy (e.g., olmesartan)
- Whipple disease
- Collagenous sprue
- Crohn's disease
- Eosinophilic enteritis
- Intestinal lymphoma Intestinal tuberculosis
- Infectious enteritis (e.g., giardiasis)
- Graft versus host disease
- Malnutrition
- Acquired immune deficiency syndrome enteropathy



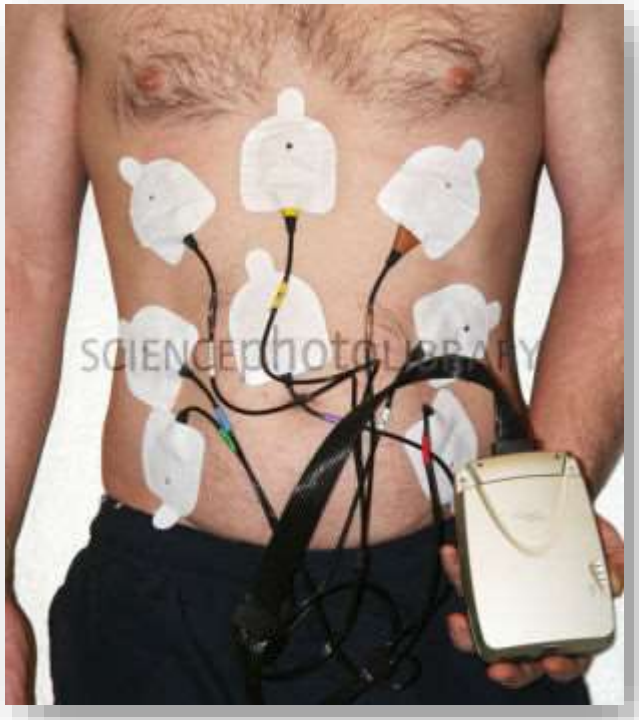
Barium studies

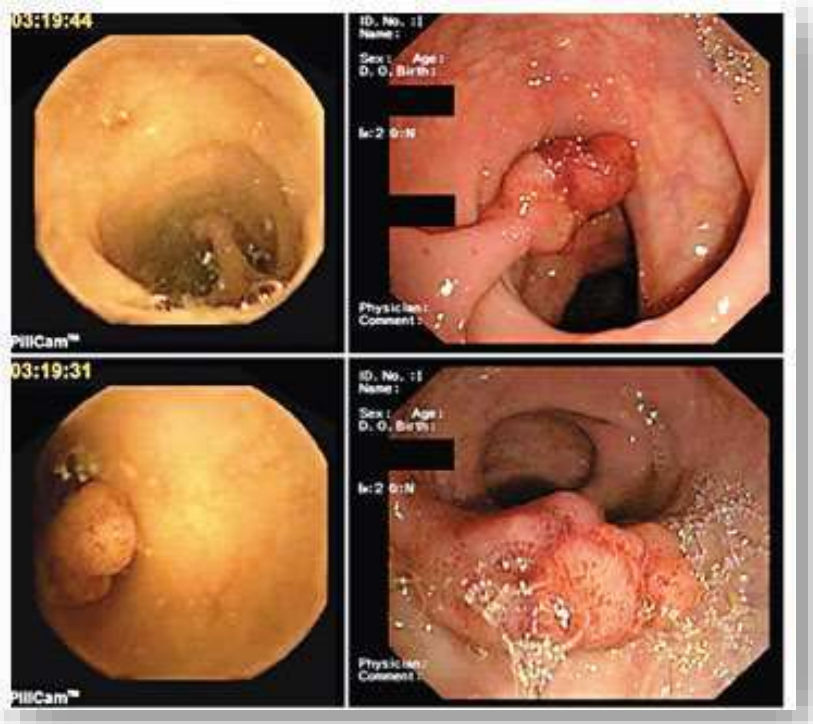
- **Important information about the gross anatomy and morphology of SB**
  - Upper GI series with small bowel follow through
  - Duodenal tube, double contrast study by passing a tube into proximal SB and injecting barium+ methylcellulose



- **Normal study doesn't exclude small bowel disease**

Wireless video-capsule





Functional tests for malabsorption

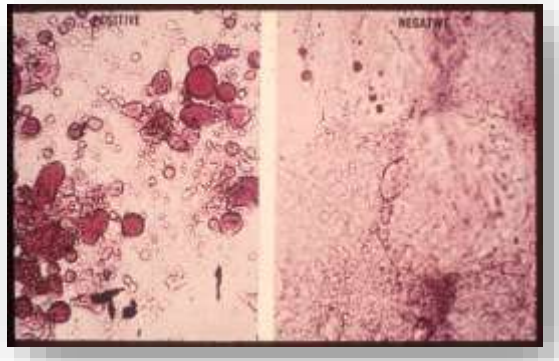
(excluding pancreatic causes)

Disease or Condition	Diagnostic Test(s)*	Comment(s)
Lactose malabsorption	Lactose hydrogen breath test Lactose tolerance test	Tests do not differentiate between primary and secondary lactose malabsorption.
Incomplete fructose absorption	Fructose hydrogen breath test	
SIBO (see Chapter 105)	^{14}C-D-xylose breath test Glucose hydrogen breath test Schilling test with and without antibiotics	A predisposing factor should be sought if the result of any of the tests is positive.
Bile acid malabsorption	SeHCAT test, ^{14}C-TCA test	Does not differentiate between primary and secondary causes.
Exocrine pancreatic insufficiency	Quantitative fecal fat determination Fecal elastase or chymotrypsin, tubeless tests (see Chapters 56 and 59)	Used to establish malabsorption in chronic pancreatitis Variable sensitivity and specificity, depending on the type of test and stage of the disease.
Vitamin B_{12} malabsorption	Schilling test	The test is performed without intrinsic factor and, depending on the result with intrinsic factor, with antibiotics or pancreatic enzymes (see text). Further tests are necessary if SIBO, terminal ileal disease, or pancreatic disease is suspected.

*See text for diagnostic accuracy of the different tests listed.
SeHCAT, selenium-75-homotaurocholic acid test; TCA, taurocholic acid.

Tests for steatorrhea

- **Quantitative test**
  - 72hr stool fat collection – gold standard
    - > 6gm/day – pathologic
    - P’ts with steatorrhea - >20gm/day
    - Modest elevation in diarrheal disease (may not necessarily indicate Malabsorption)
- **Qualitative tests**
  - **Sudan lll stain**
    - Detect clinically significant steatorrhea in >90% of cases
  - Acid steatocrit – a gravimetric assay
    - Sensitivity – 100%, specificity – 95% , PPV – 90%
  - NIRA (near infra reflectance analysis)
    - Equally accurate with 72hr stool fat test
    - Allows simultaneous measurement of fecal fat, nitrogen, CHO



Functional tests for malabsorption

(excluding pancreatic causes)

TABLE 104-8 Malabsorptive Diseases or Conditions in Which Noninvasive Tests Can Establish Malabsorption or Provide a Diagnosis

Disease or Condition	Diagnostic Test(s)*	Comment(s)
Lactose malabsorption	Lactose hydrogen breath test Lactose tolerance test	Tests do not differentiate between primary and secondary lactose malabsorption.
Incomplete fructose absorption	Fructose hydrogen breath test	
SIBO (see Chapter 105)	^{14}C-D-xylose breath test Glucose hydrogen breath test Schilling test with and without antibiotics	A predisposing factor should be sought if the result of any of the tests is positive.
Bile acid malabsorption	SeHCAT test, ^{14}C-TCA test	Does not differentiate between primary and secondary causes.
Exocrine pancreatic insufficiency	Quantitative fecal fat determination Fecal elastase or chymotrypsin, tubeless tests (see Chapters 56 and 59)	Used to establish malabsorption in chronic pancreatitis Variable sensitivity and specificity, depending on the type of test and stage of the disease.
Vitamin B_{12} malabsorption	Schilling test	The test is performed without intrinsic factor and, depending on the result with intrinsic factor, with antibiotics or pancreatic enzymes (see text). Further tests are necessary if SIBO, terminal ileal disease, or pancreatic disease is suspected.

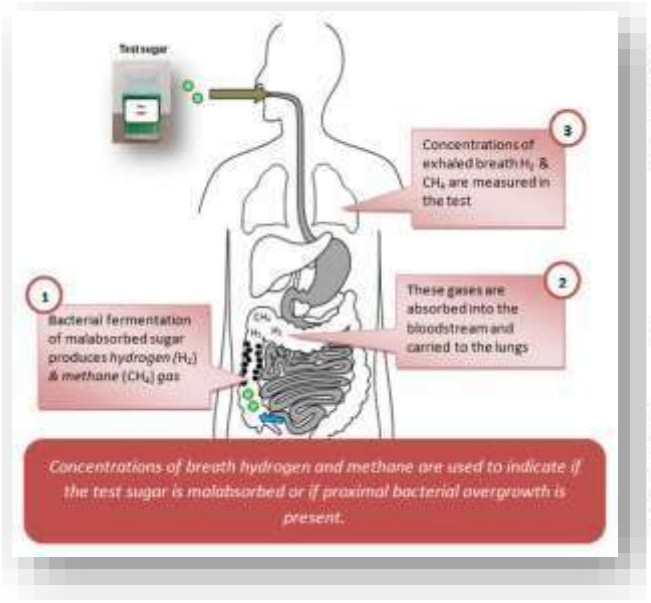
*See text for diagnostic accuracy of the different tests listed.
SeHCAT, selenium-75-homotaurocholic acid test; TCA, taurocholic acid.

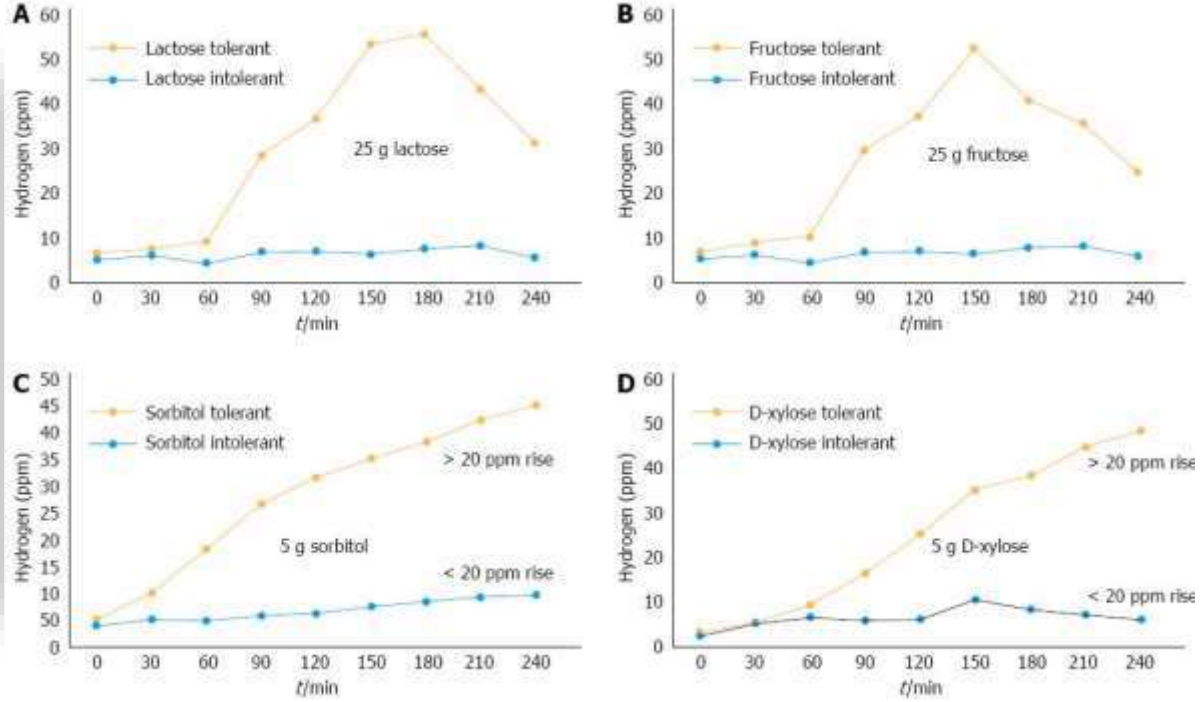
D-xylose test

- **D-xylose**
  - A Pentose monosacharide absorbed exclusively at the proximal SB
  - Used to asses proximal SB mucosal function
- **The test**
  - After overnight fast, 25 gm D-xylose p.o.
  - Urine collected for next 5 hrs
  - **Abnormal test - <4.5 gm (duodenal / jejunal mucosal injury)**
  - False +ve results:
    - Renal dysfunction
    - Inadequate urine sample
    - Impaired gastric empyting,
    - Ascites
    - Drugs(ASA, indometacin, Neomycin)

- **Carbohydrate malabsorbtion**
  - Lactose tolerance test
    - P.o. 50 gm lactose
    - Blood glucose at 0,60,120 min.
    - BG <20mg/l + dev't of Sxs – diagnostic

- **Breath tests hydrogen (also detects bacterial overgrowth)**

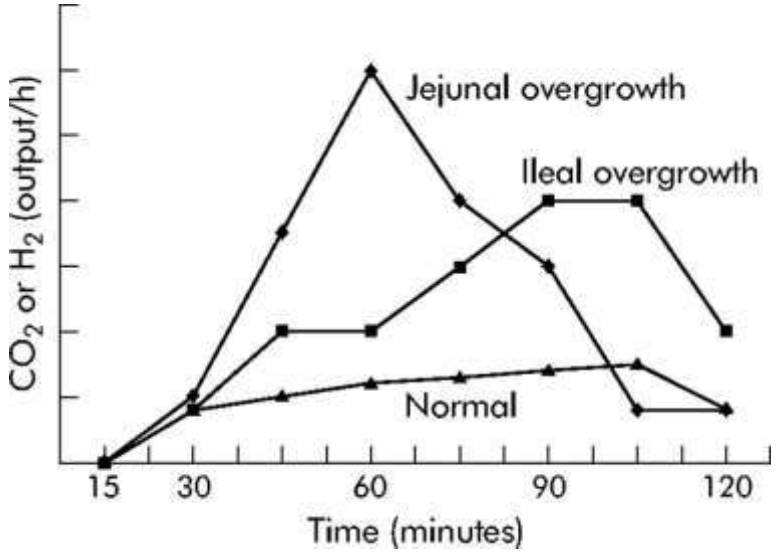


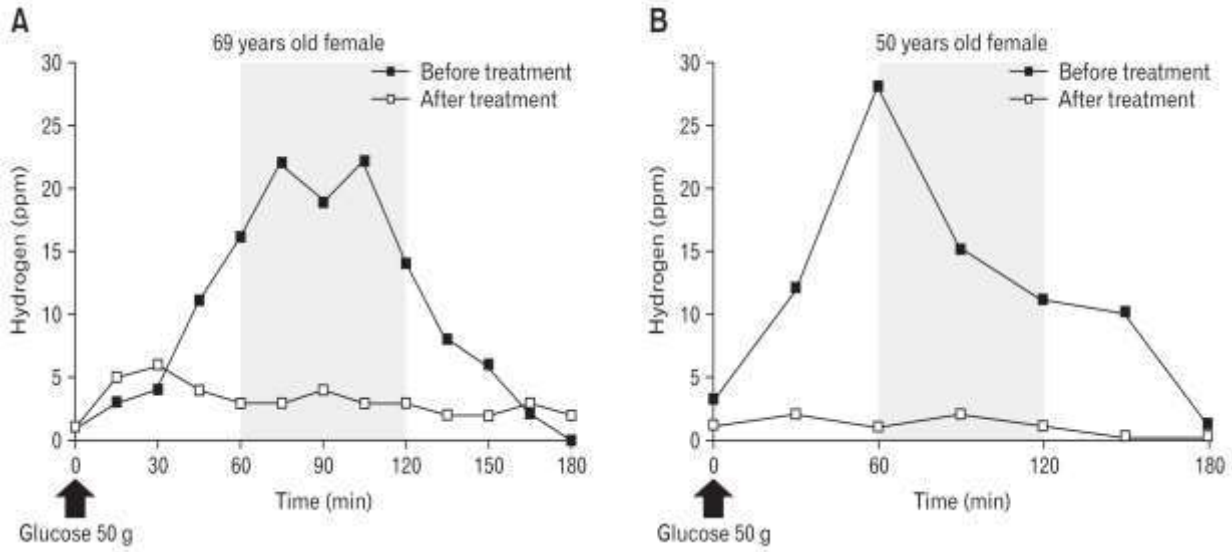


The hydrogen breath tests and lactose tolerance tests have Sensitivity and Specificity >95% in detecting in lactose intolerance

H2 breath test is easier

Bacterial overgrowth (SIBO)





Celiac Disease

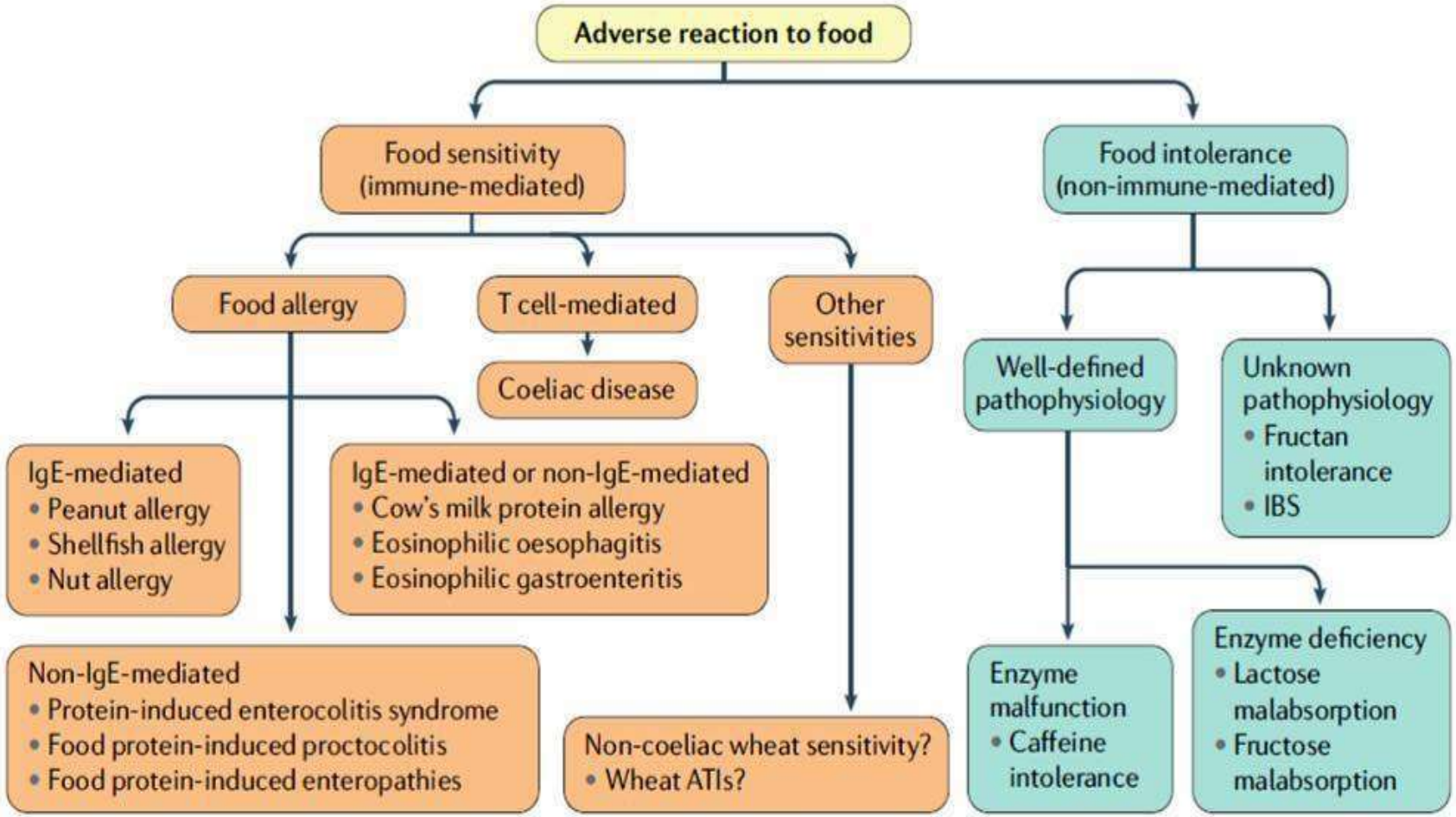


Fig. 1 | **Classification of adverse reaction to food according to underlying pathophysiology.** Adverse reactions to food can be divided into food intolerances (non-immune mediated) and food sensitivities (immune mediated) according to their underlying pathophysiology. Both types can be subclassified into specific diseases on the basis of their pathophysiology. ATI, α-amylase-trypsin inhibitor; IgE, immunoglobulin E.

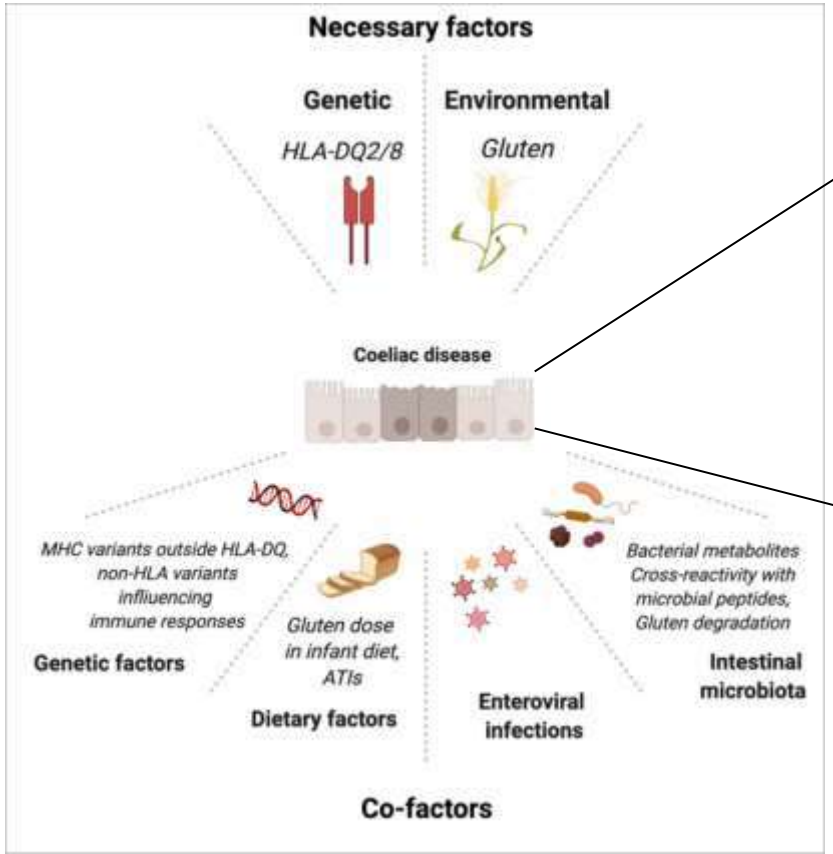
Gluten-related diseases

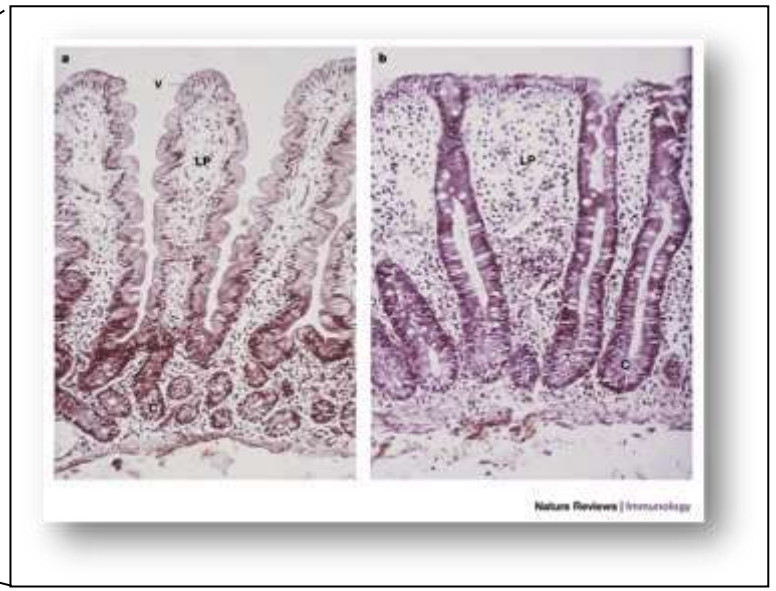
	Celiac Disease	Non-Celiac Gluten Sensitivity	Wheat Allergy
Definition	Genetic, autoimmune disorder; gluten ingestion triggers damage to small intestine	Intolerance to gluten or other wheat components without damage to small intestine	Immune response to one or more of the proteins found in wheat (can include gluten)
Gastrointestinal symptoms	Diarrhea, bloating, abdominal pain	Diarrhea, bloating, abdominal pain	Nausea, vomiting, diarrhea, bloating, irritation of mouth or throat
Extra-intestinal findings (e.g. anemia, bone loss)	Weight loss, malnutrition, iron deficiency, dental caries, bone loss, skin issues, neurological disorders, liver dysfunction, joint pain, hair loss, fatigue	Brain fog, neurological disorders, joint pain, fatigue	Hives, rash, nasal congestion, eye irritation, difficulty breathing
Positive antibody test	Yes	Variable	No
Abnormal intestinal biopsy	Yes	No	No
Treatment	Strict adherence to a gluten free lifestyle	Adherence to a wheat free/gluten free diet (level of adherence variable)	Strict adherence to a wheat free lifestyle

Fasano A, Sapone A, Zevallos V, Schuppan D. Nonceliac gluten sensitivity. Gastroenterology. 2015 May;148(6):1195-204. doi: 10.1053/j.gastro.2014.12.049.

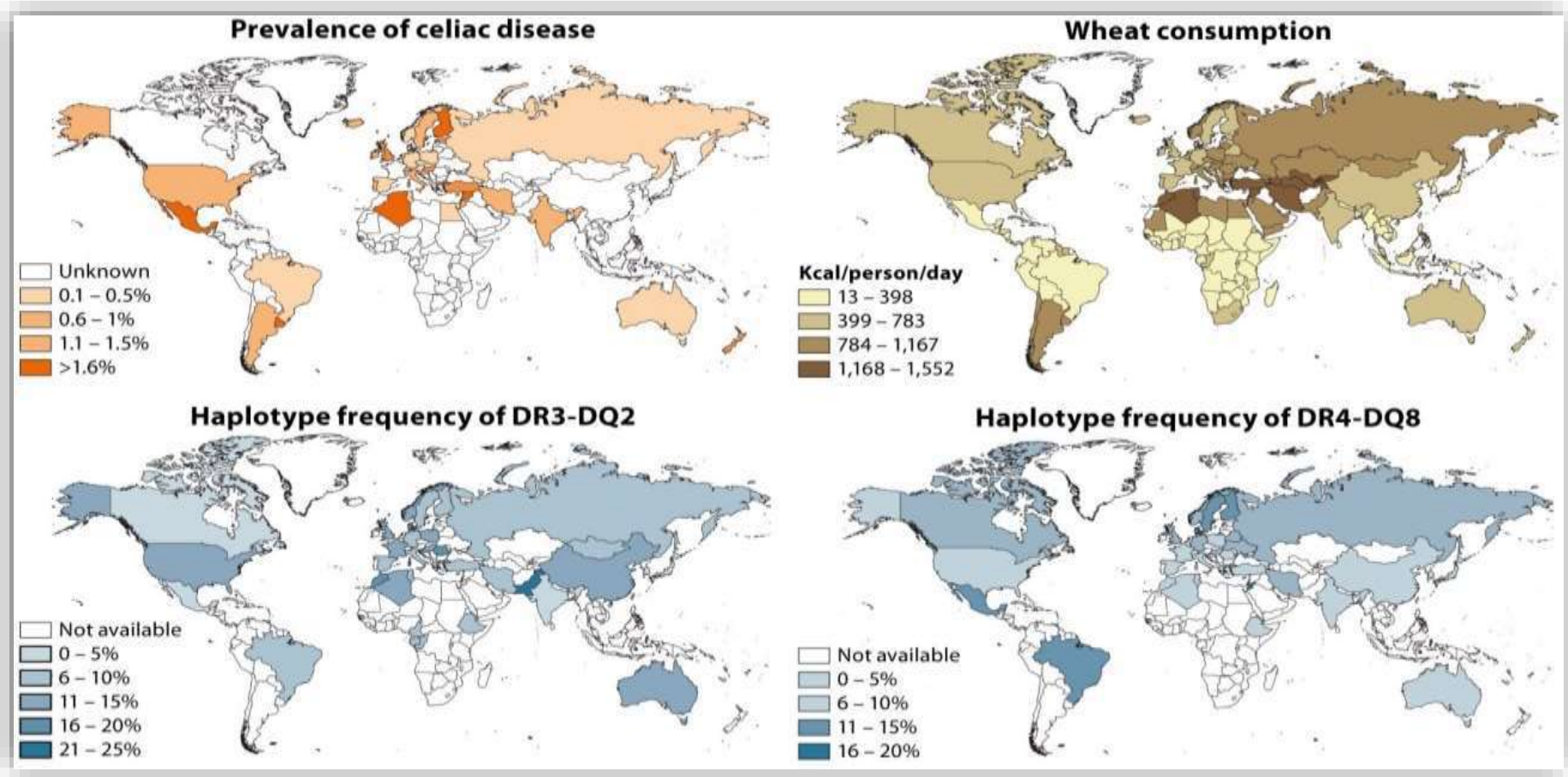
Celiac Disease

The celiac disease as an (auto)- immune disorder that is triggered by an environmental agent (**the gliadin component of gluten**) in genetically predisposed individuals

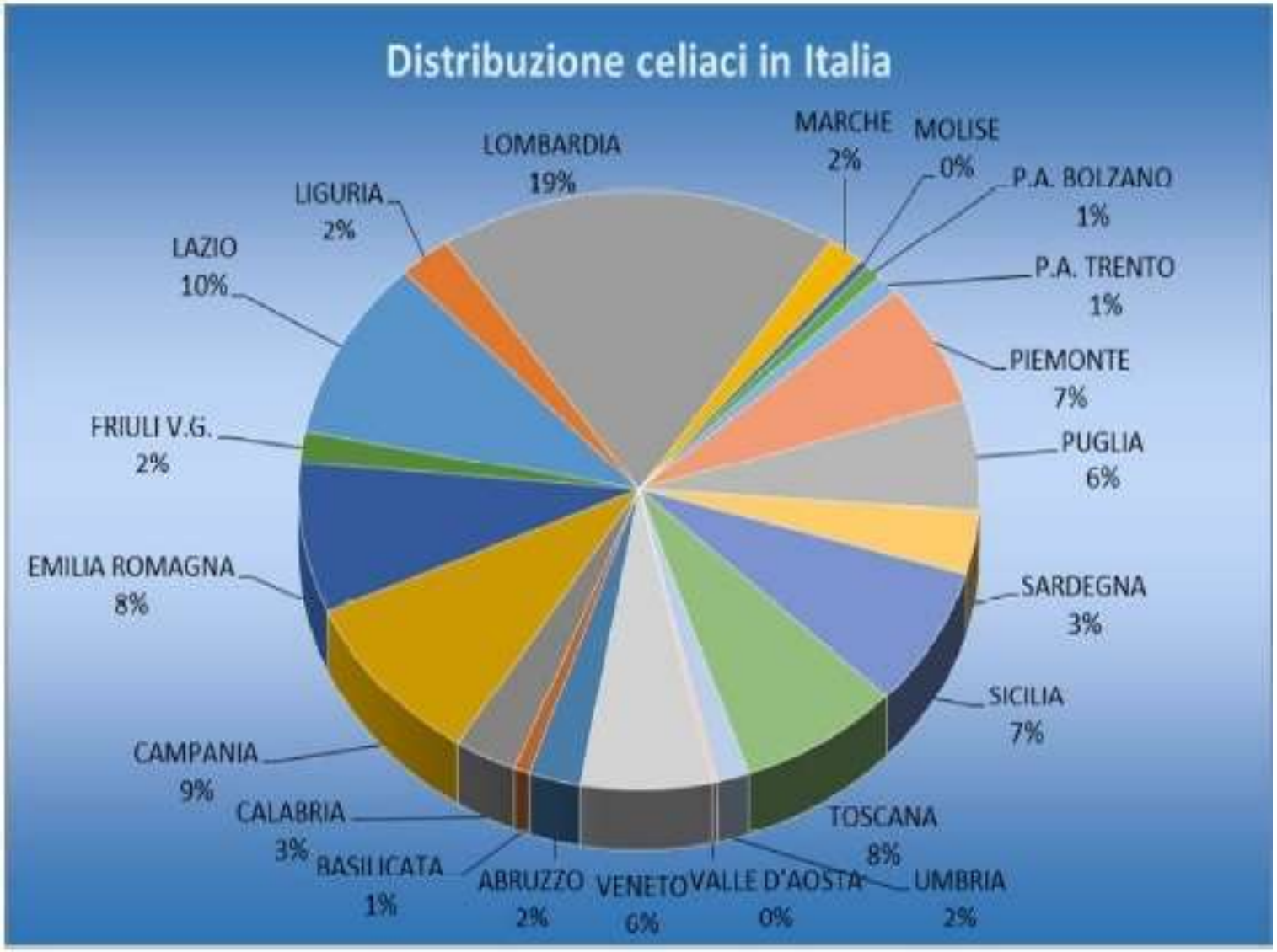




Celiac Disease

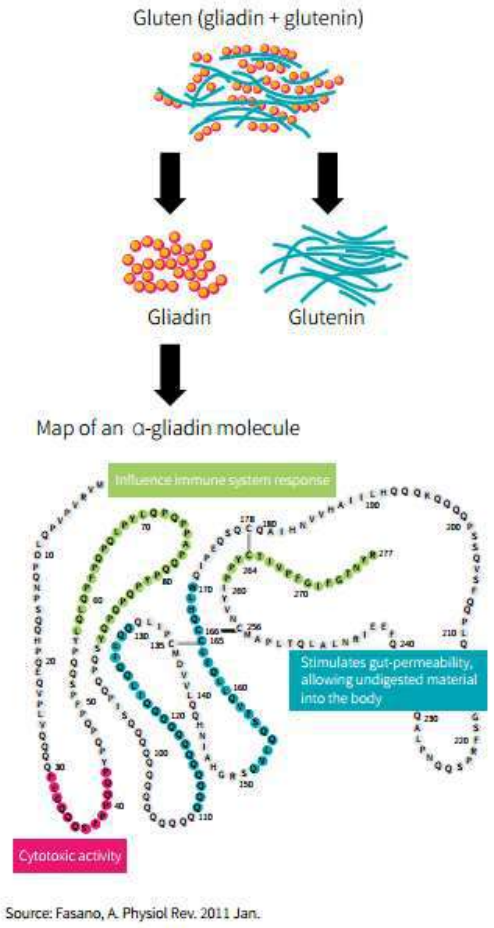


La celiachia è un'enteropatia infiammatoria, la stima della sua prevalenza si aggira intorno all'1%: è stato calcolato che nella popolazione italiana il numero totale di celiaci si aggiri intorno ai 600.000 contro gli oltre 233.000 ad oggi diagnosticati (2016)



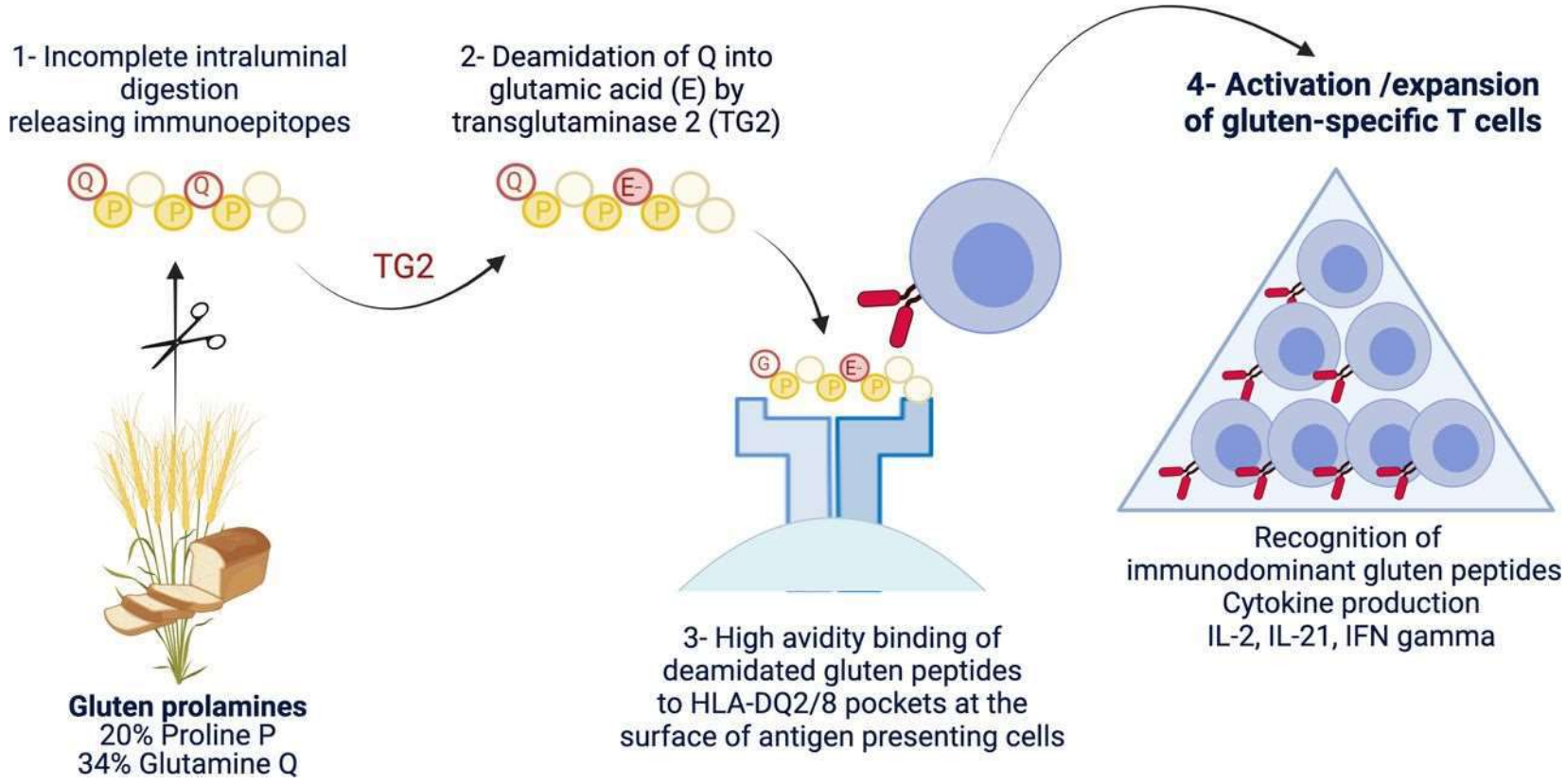
Gliadin protein

Gliadins, which are a component of gluten, are essential for giving bread the ability to rise properly during baking. Gliadins and glutenins are the two main components of the gluten fraction of the wheat seed. This gluten is found in products such as wheat flour.



Mapping of α-gliadin motifs. Those exerting cytotoxic activity are shown in red, immunomodulatory activity in yellow, **zonulin release and gut permeating activity in blue**, **and CXCR3-dependent** IL-8 release in celiac disease patients in dark green. Partially modified from Sapone *et al. BMC Medicine* 2012 **10**:13 doi:10.1186/1741-7015-10-13

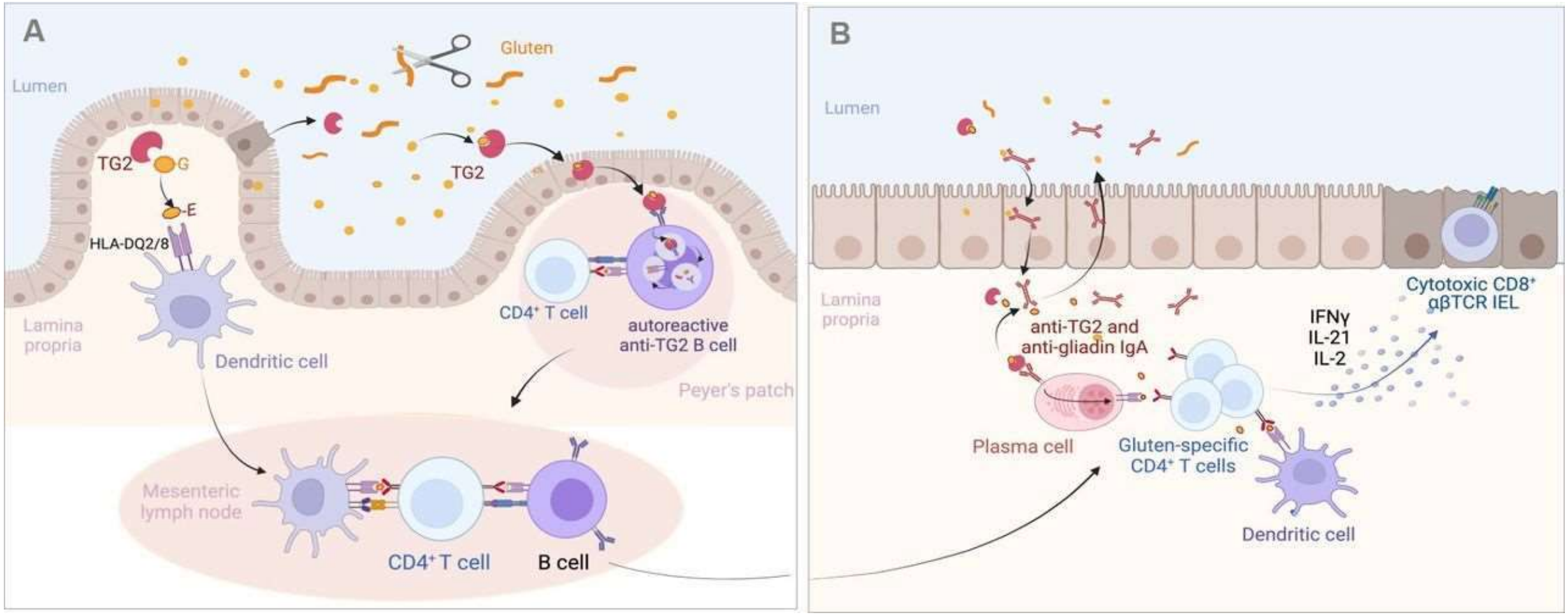
Schematic representation of the driver antigluten response.



Anais Levescot et al. Gut 2022;71:2337-2349

GUT

Proposed mechanisms of the antigluten and antitransglutaminase 2 (TG2) responses in the coeliac intestine.



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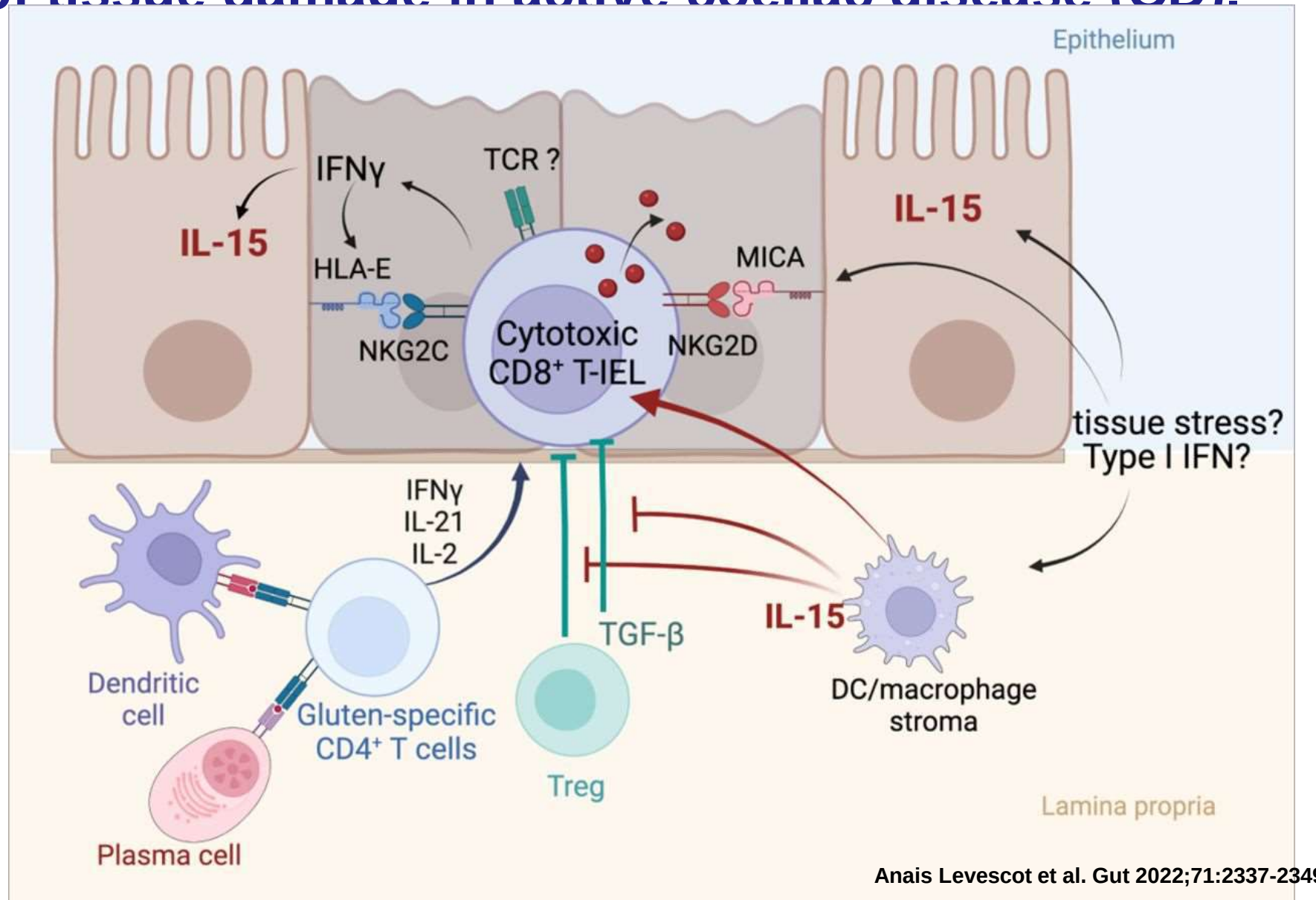
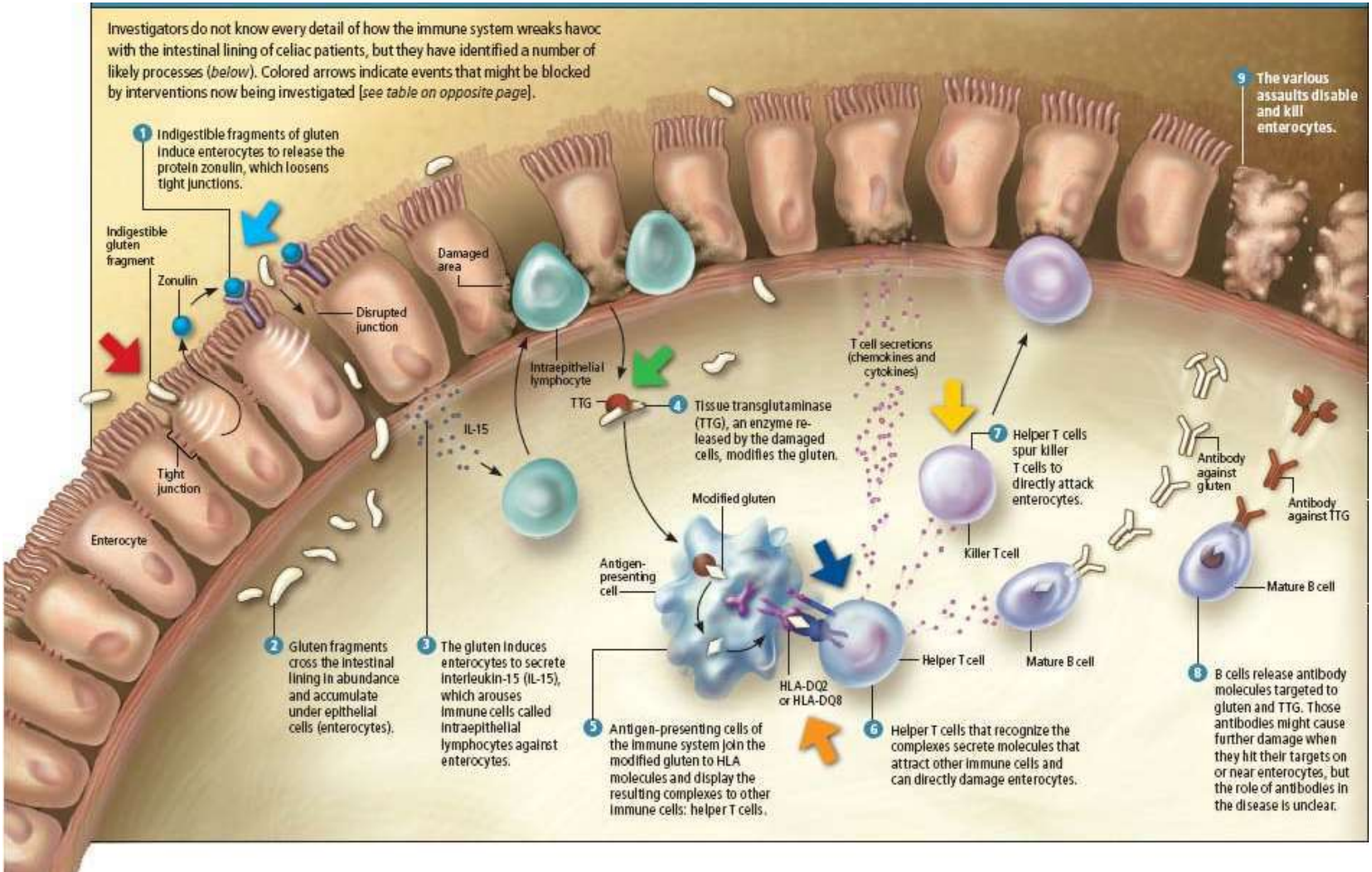
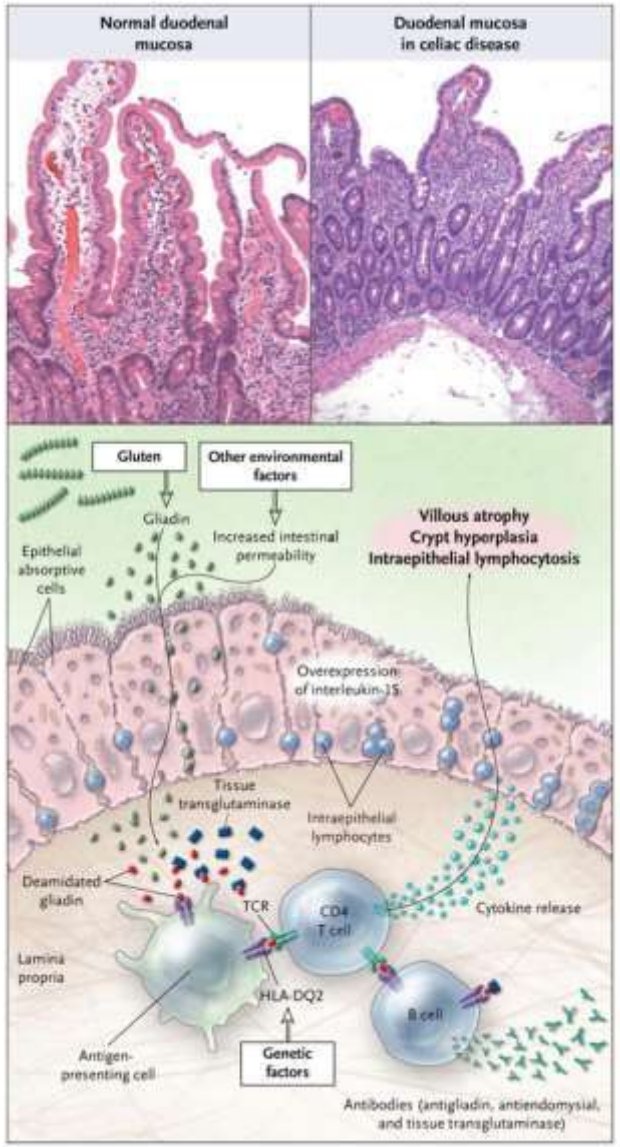
Activation of cytotoxic intraepithelial lymphocytes and induction of tissue damage in active coeliac disease (CD).



Anais Levescot et al. Gut 2022;71:2337-2349


Investigators do not know every detail of how the immune system wreaks havoc with the intestinal lining of celiac patients, but they have identified a number of likely processes (*below*). Colored arrows indicate events that might be blocked by interventions now being investigated [*see table on opposite page*].
1 Indigestible fragments of gluten induce enterocytes to release the protein zonulin, which loosens tight junctions.
Indigestible gluten fragment
Zonulin
Disrupted junction
Damaged area
Intraepithelial lymphocyte
TTG
4 Tissue transglutaminase (TTG), an enzyme released by the damaged cells, modifies the gluten.
IL-15
Tight junction
Enterocyte
Modified gluten
Antigen-presenting cell
T cell secretions (chemokines and cytokines)
7 Helper T cells spur killer T cells to directly attack enterocytes.
Killer T cell
Antibody against gluten
Antibody against TTG
Mature B cell
9 The various assaults disable and kill enterocytes.
2 Gluten fragments cross the intestinal lining in abundance and accumulate under epithelial cells (enterocytes).
3 The gluten induces enterocytes to secrete interleukin-15 (IL-15), which arouses immune cells called intraepithelial lymphocytes against enterocytes.
HLA-DQ2 or HLA-DQ8
Helper T cell
Mature B cell
5 Antigen-presenting cells of the immune system join the modified gluten to HLA molecules and display the resulting complexes to other immune cells: helper T cells.
6 Helper T cells that recognize the complexes secrete molecules that attract other immune cells and can directly damage enterocytes.
8 B cells release antibody molecules targeted to gluten and TTG. Those antibodies might cause further damage when they hit their targets on or near enterocytes, but the role of antibodies in the disease is unclear.

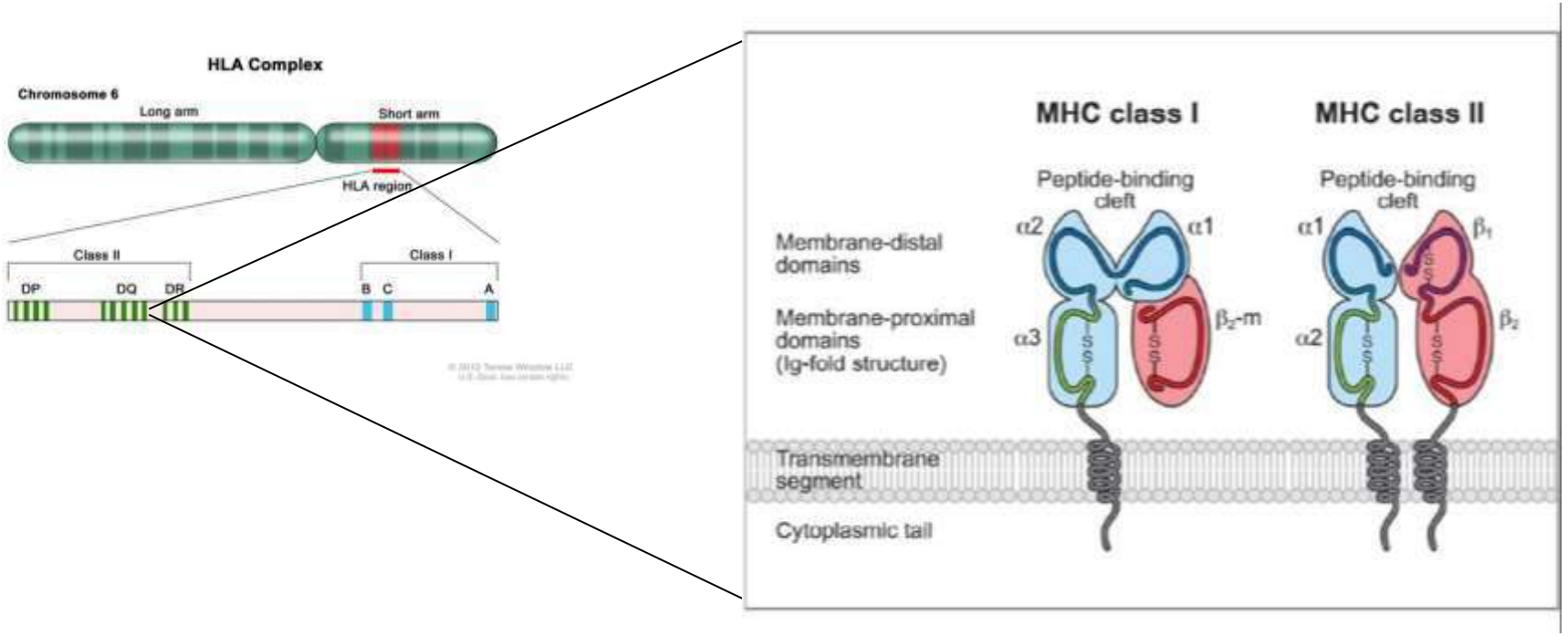
Celiac Disease



Gliadin-sensitive T cells in genetically predisposed individuals recognize gluten-derived peptide epitopes and develop an inflammatory response which produces mucosal damage

Celiac disease: HLA genes

Celiac disease **is a multigenic disorder**, in which the most dominant genetic risk factors are the genotypes encoding the HLA class II molecules **HLA-DQ2** **(**encoded by ***HLA-DQA1*0501*** **and** ***HLA-DQB1*02***) and **HLA-DQ8** (encoded by *HLA-DQA1*0301* and *HLA-DQB1*0302*).



Celiac disease: HLA genes

Individual are predisposed to celiac disease if they have any of the following results:

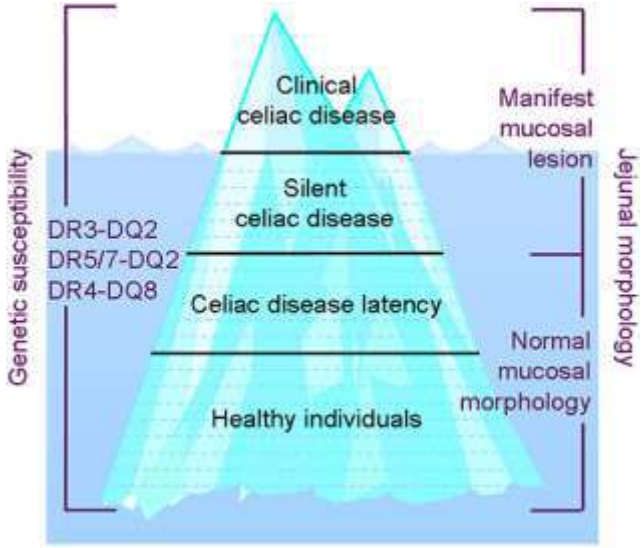
- **DQ2-positive** (HLA-DQA1*0501 or *0505 **and** HLA-DQB1*0201 or *0202)
- Half **DQ2-positive** (HLA-DQA1*0501 or 0505 **or** HLA-DQB1*0201 or 0202)
- **DQ8-positive (**HLA-DQA1*0301 **and** HLA-DQB1*0302)

Deamidated gliadin peptides have a **high binding affinity t**o **HLA-DQ2 and HLA-DQ8** molecules, but not to other HLA class II molecules, which explains the immunogenicity of gluten in carriers of HLA-DQ2 and HLA-DQ8.

Celiac disease: HLA genes

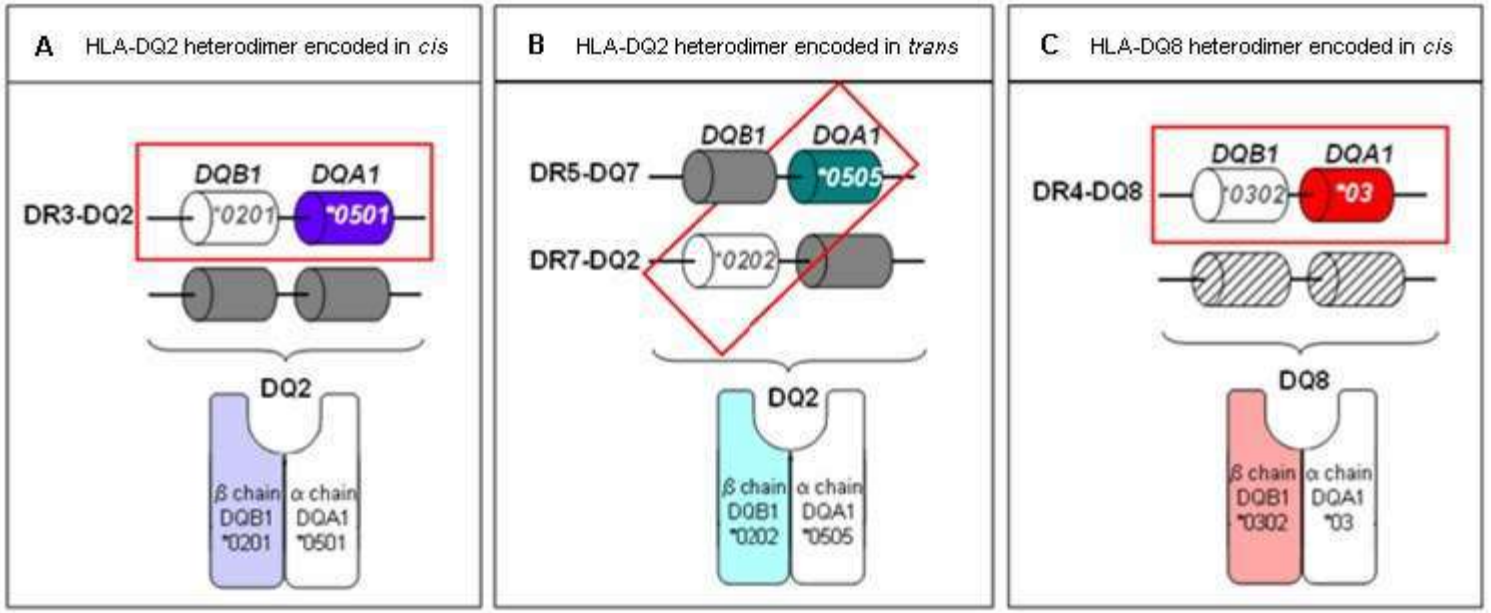
The presence of these HLA alleles **is necessary but not sufficient** to cause celiac disease.

- DQ2 is found in more than **90%** of individuals with celiac disease and in **20%-30% of the general population**
- 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).**
- DQ8 is found **in 5%-10%** of individuals with celiac disease and approximately 10% of the general population



A correlation has been found between **homozygosity** for the genes encoding the HLA-DQ2 molecule and the development of serious complications of celiac disease, in particular **RCD** and EATL (**enteropathy associated T cell lymphoma)**, which implies a gene–dose effect.

Figure 1

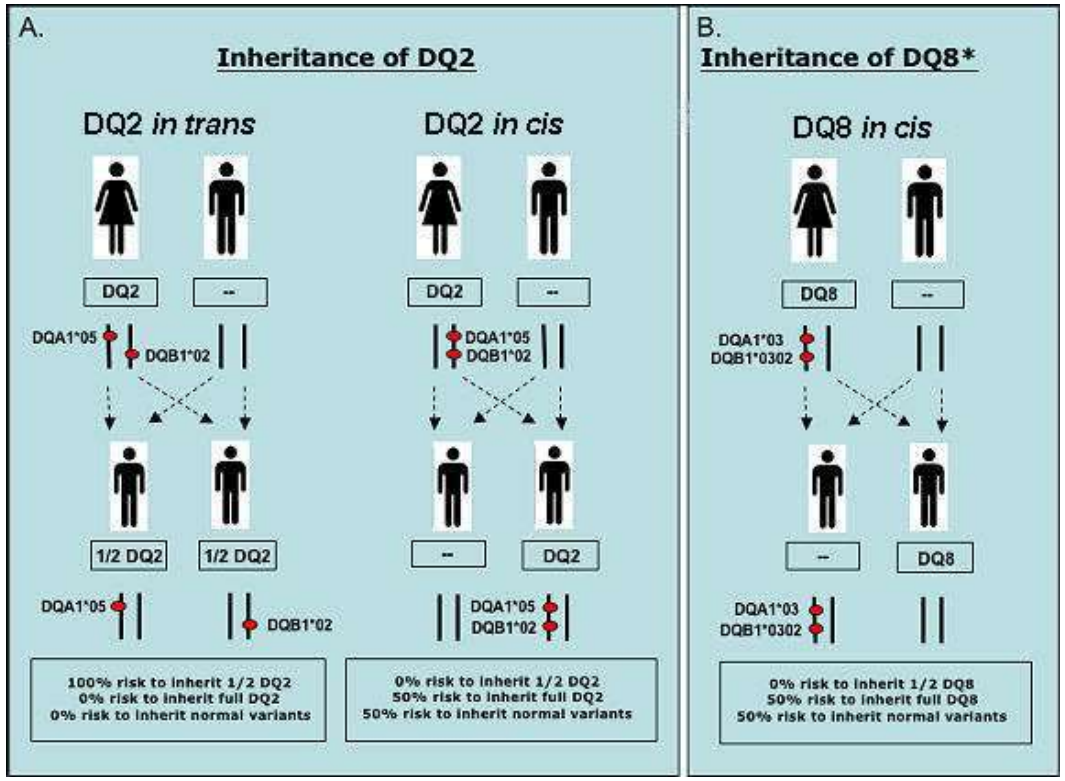


- Formation of DQ2 and DQ8
- A. **The DQ2 molecule**, consisting of the α-chain protein encoded by the HLA-DQA1*0501 allele and the β-chain protein encoded by the HLA-DQB1*0201 allele on the same parental chromosome (i.e., in cis configuration).
- B. **The DQ2 molecule**, consisting of the α-chain protein encoded from the HLA-DQA1*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**).

Celiac disease genetic counseling

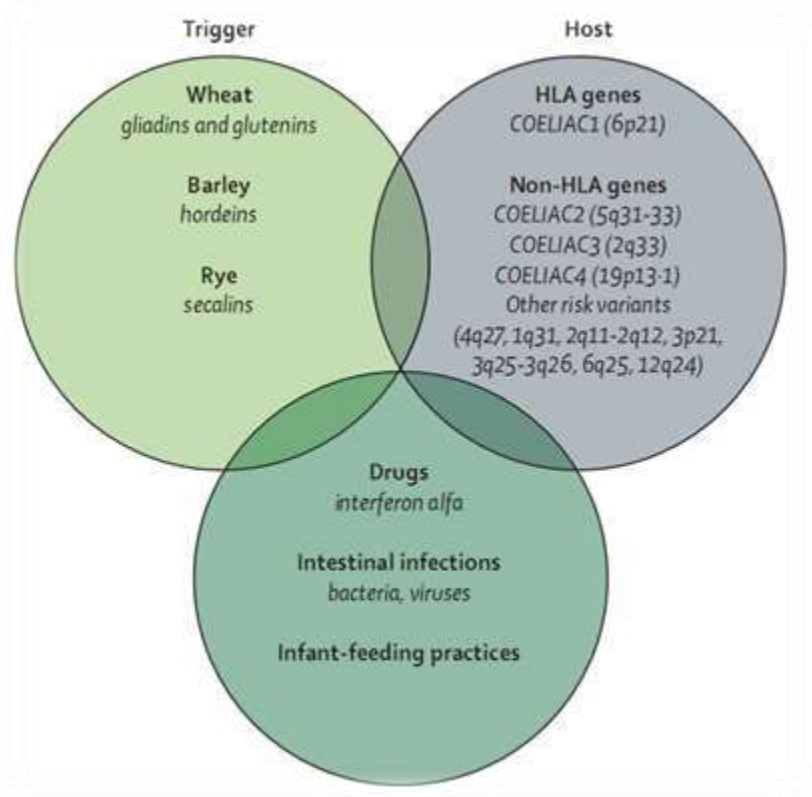
Mode of Inheritance

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



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**.

Genetic Risk from HLA-DQ2 and/or DQ8



HLA DQ2/DQ8 Genotype [1]	Risk [1]
DQ2+DQ8	1:7 (14.3%)
DQ2+DQ2 OR DQ2 Homozygous DQB1*02	1:10 (10%)
DQ8+DQ8 [2]	1:12 (8.4%) [2]
DQ8+DQB1*02	1:24 (4.2%)
Homozygous DQB1*02	1:26 (3.8%)
DQ2 alone	1:35 (2.9%)
DQ8 alone	1:89 (1.1%)
Population risk	1:100 (1%)
½ DQ2: DQB1*02	1:210 (0.5%)
½ DQ2: DQA1*05	1:1842 (0.05%)
No HLA-DQA/DQB celiac susceptibility alleles	1:2518 (<0.04%)

Celiac disease: genetic non HLA

Currently, **several susceptibility loci not related to HLA have been identified by genome-wide association studies**, each of which is estimated to be associated with only a small risk of developing celiac disease.

Most of these loci contain immune-related genes.

Table 1 | **Coeliac disease susceptibility loci**

Locus*	Most likely candidate gene(s)	Function of proteins encoded by candidate gene(s)	Probable immune function	Associated with type 1 diabetes?	Refs
6p21	*HLA*	MHC is important for antigen presentation	Yes	Yes	11
2q33	*CTLA4*	CTLA4 is a receptor on T cells for CD80 and CD86 and is a negative regulator of T cell activation	Yes	Yes	119
4q27	*IL2* and *IL21*	IL-2 is a growth factor for T cells; IL-21 is a cytokine that enhances B cell, T cell and NK cell functions	Yes	Yes	14
1q31	*RGS1*	RGS1 is involved in cell signalling and is expressed by intraepithelial lymphocytes	Yes	Yes	15
2q12	*IL1R1*, *IL18R1* and *IL18RAP*	The α-chain and β-chain of the IL-18 receptor are encoded by *IL18R1* and *IL18RAP*, respectively; IL-18 promotes interferon-γ production	Yes	Yes	15
3p21	*CCR1*, *CCR3*, *CCR2* and *CCR5*	The chemokine receptors CCR1, CCR3, CCR2 and CCR5 are encoded at this locus; there are probably two independent coeliac disease risk factors at this locus	Yes	Yes	15
3q25	*IL12A*	The p35 subunit of the cytokine IL-12 is encoded at this locus; IL-12 favours T_H1 cell differentiation	Yes	No	15
3q28	*LPP*	Unknown	No	No	15
6q25	*TAGAP*	TAGAP is expressed by activated T cells and is important for modulating cytoskeletal changes	Yes	Yes	15
12q23	*SH2B3*	Lymphocyte adaptor protein (LNK) is encoded at this locus and is involved in signalling in lymphocytes, including T cells	Yes	Yes	15
18p11	*PTPN2*	The T cell protein tyrosine phosphatase is a negative regulator of inflammation	Yes	Yes	19
6q23	*TNFAIP3*	TNFαIP3 is a zinc-finger protein that inhibits nuclear factor-κB activity and tumour necrosis factor-mediated programmed cell death	Yes	Yes	120
2p13	*REL*	REL is a component of the nuclear factor-κB transcription complex	Yes	No	120

CCR, CC-chemokine receptor; CTLA4, cytotoxic T lymphocyte antigen 4; IL, interleukin; LPP, LIM domain containing preferred translocation partner in lipoma; NK, natural killer; PTPN2, protein tyrosine phosphatase, non-receptor type 2; R, receptor; RAP, receptor accessory protein; RGS1, regulator of G protein signalling 1; TAGAP, T cell activation RhoGTPase activating protein; T_H1, T helper 1; TNFAIP3, tumour necrosis factor, α-induced protein 3. *The odds ratios of the strongest associated markers of the non-HLA loci range from 0.7–1.4.

Celiac Disease:
Clinical Manifestations

Celiac Disease: Clinical Manifestations in Children

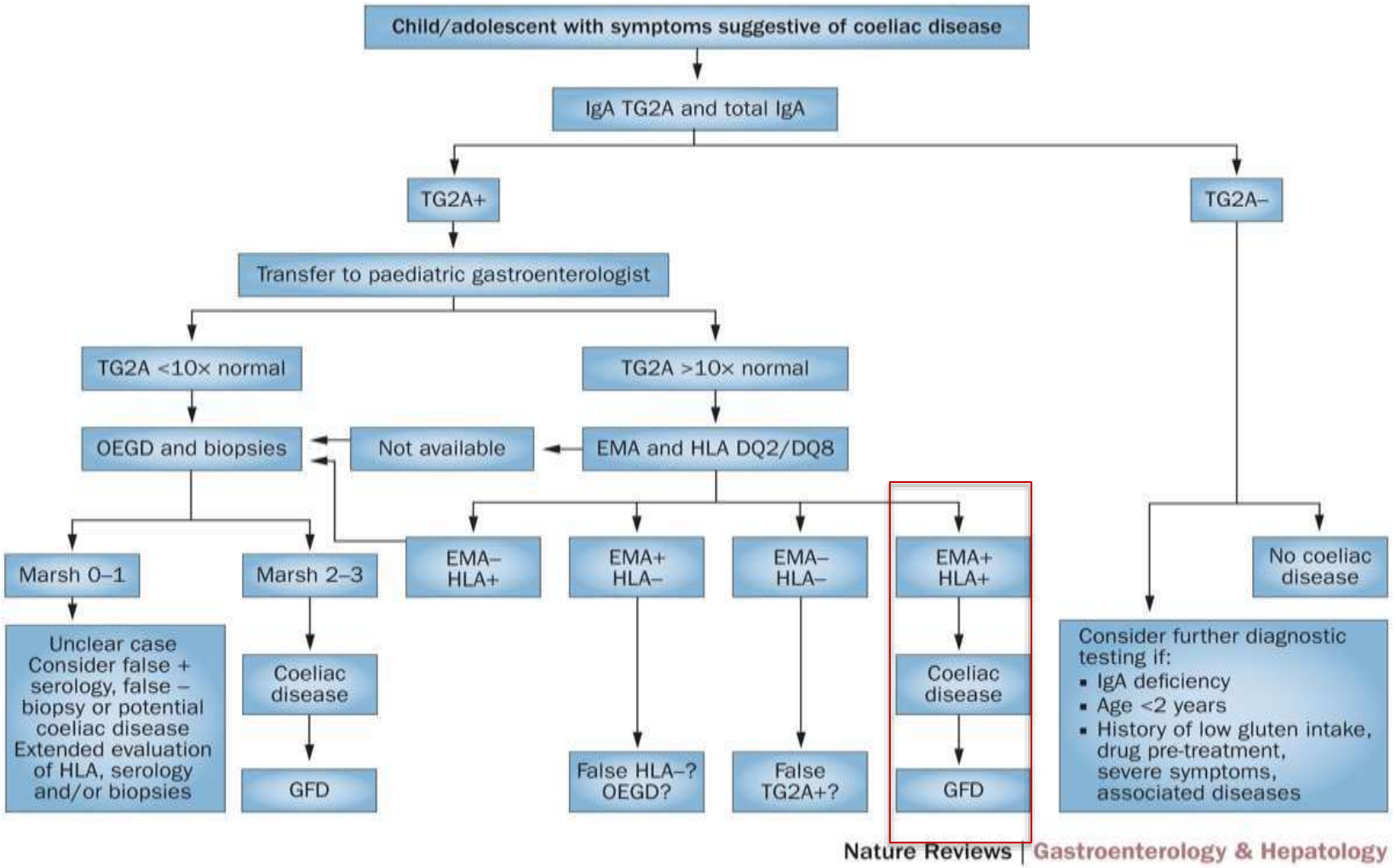
The classical presentation is in children after weaning and introduction of cereals into the diet:

- Failure to thrive
- Apathy
- Pallor
- Anorexia
- Muscle wasting with generalized hypotonia
- Abdominal bloating and distention
- Soft, bulky, clay-colored, offensive stools

Celiac Disease: Clinical Manifestations in Children

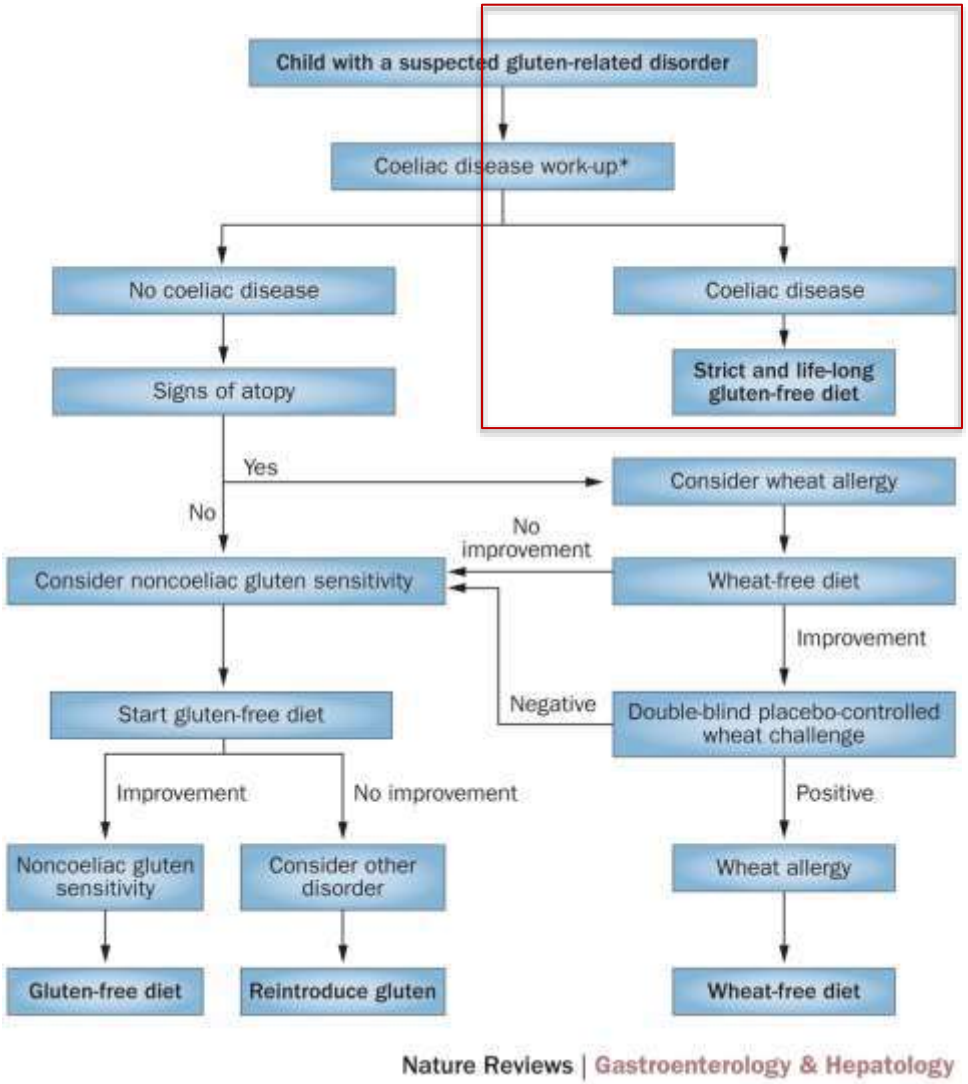
Symptoms and signs at presentation	Overall prevalence (%)
Iron deficiency with anemia	29
Iron deficiency without anemia	27
Recurrent Abdominal Pain	24
Mood Changes	17
Recurrent Aphthous Stomatitis	11
Poor appetite	10
Recurrent diarrhea	9
Short stature	7
Abdominal distension	5
Constipation	2
Pubertal delay	2
Hypoalbuminemia	2

Figure 3 ESPGHAN algorithm for the diagnosis of coeliac disease in children and adolescents with symptoms



Vriezinga, S. L. *et al.* (2015) Coeliac disease and gluten-related disorders in childhood
Nat. Rev. Gastroenterol. Hepatol. doi:10.1038/nrgastro.2015.98

Figure 1 Flow-chart of the diagnostic process in a child with a suspected gluten-related disorder



Vriezinga, S. L. *et al.* (2015) Coeliac disease and gluten-related disorders in childhood
Nat. Rev. Gastroenterol. Hepatol. doi:10.1038/nrgastro.2015.98

Celiac Disease: Clinical Manifestations in Adults

- **Majority of individuals were diagnosed in their 4th to 6th decades.**
- **Women predominated (2.9:1)- the female predominance was less marked in the elderly.**
- **Diarrhea** was the main presenting symptom occurring in 50%.
- **36% had a previous diagnosis of irritable bowel syndrome.**
- Symptoms were present a mean of 11 years before diagnosis.

Celiac Disease in adult

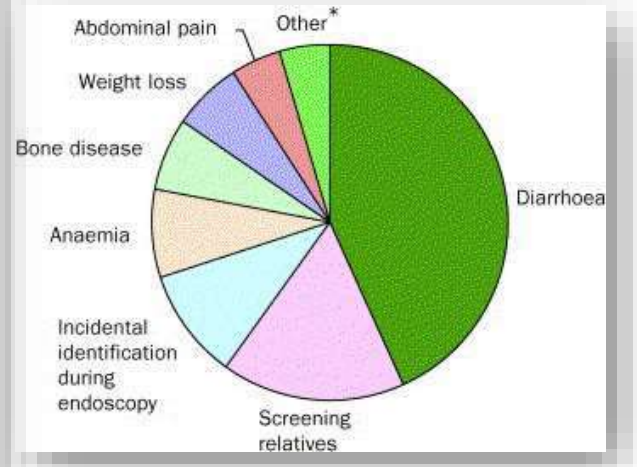
Symptoms And Complications Associated with Celiac Disease*

Gastrointestinal
Recurring abdominal pain
Bloating
Gas
Chronic diarrhea
Constipation

Systemic
Persistent anemia
Chronic fatigue
Weight loss
Osteopenia, osteoporosis
Fractures
Amenorrhea
Infertility
Muscle cramps
Discoloration and loss of Tooth enamel

Autoimmune Associations
Dermatitis herpetiformis (DH)
Aphthous stomatitis/ulcers
Peripheral neuropathy, ataxia
Epilepsy
Arthritis
Thyroid disease
Sjogren's syndrome
Chronic active hepatitis, Primary biliary cirrhosis, Sclerosing Cholangitis

Malignancies
Non-Hodgkin lymphoma (intestinal and extra intestinal, T- and B-cell types)
Small intestinal Adenocarcinoma
Esophageal carcinoma
Papillary thyroid cancer
Melanoma



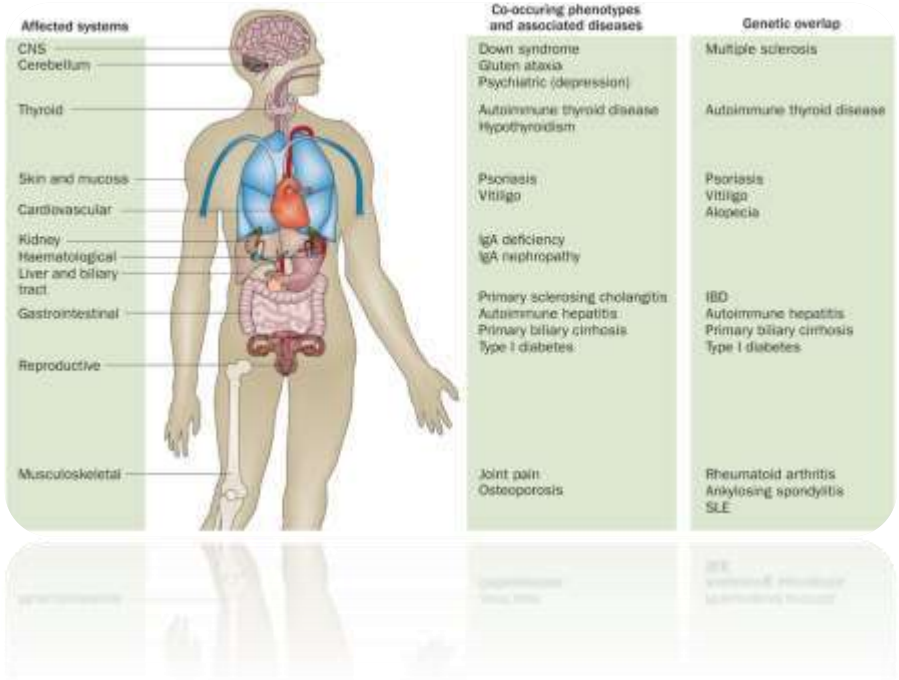
Spectrum of Celiac Disease

Few if any GI symptoms — **Marked GI symptoms**

Fatigue
Depression, irritability
Menstrual irregularity
Weakness
Infertility
Neurologic Complaints

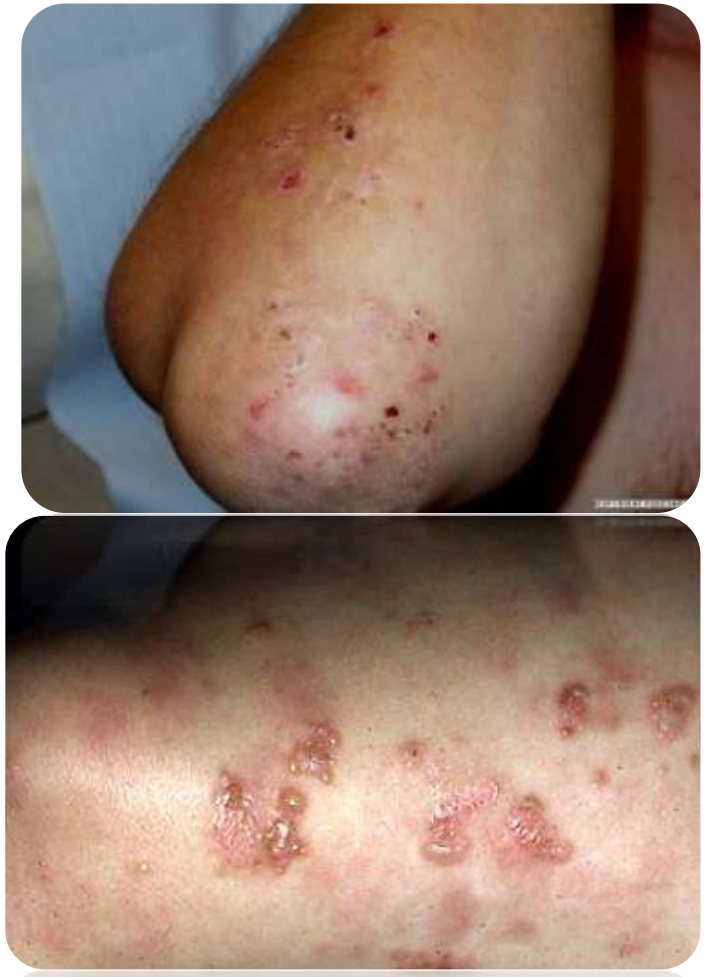
Diarrhea
Bulky, Pale, Foul stools
Abdominal Distension, Bloating
Abdominal cramps
Weight loss
Loss of or increased appetite

Multi-organ autoimmune disease



At-Risk Groups	
Type 1 diabetes	3-12
Autoimmune thyroid disease	3
Autoimmune liver disease	13.5
Down syndrome	5.5
Turner syndrome	6.5
Williams syndrome	9.5
IgA deficiency	3
IgA nephropathy	4
Juvenile idiopathic arthritis	1.5-2.5

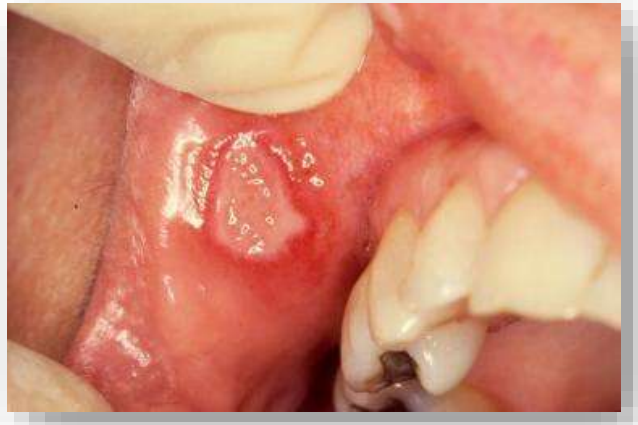
Celiac Disease:
Dermatitis Herpetiformis

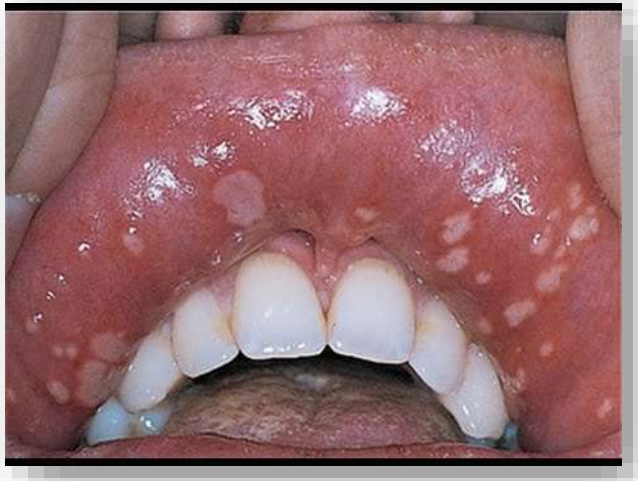


Symmetric vesicles, crusts and erosions distributed over the extensor areas of the elbows, knees, buttocks, shoulders and scalp, with a tendency to grouping of individual lesions

It has been reported that up to 10 percent of individuals with celiac will also have dermatitis herpetiformis

Celiac Disease: Associated Disorders





- Aphthous stomatitis- unexplained oral ulcers have been reported as the sole presenting feature
- Glossitis, angular stomatitis, and cheilosis have also been associated

Celiac Disease: Type 1 Diabetes

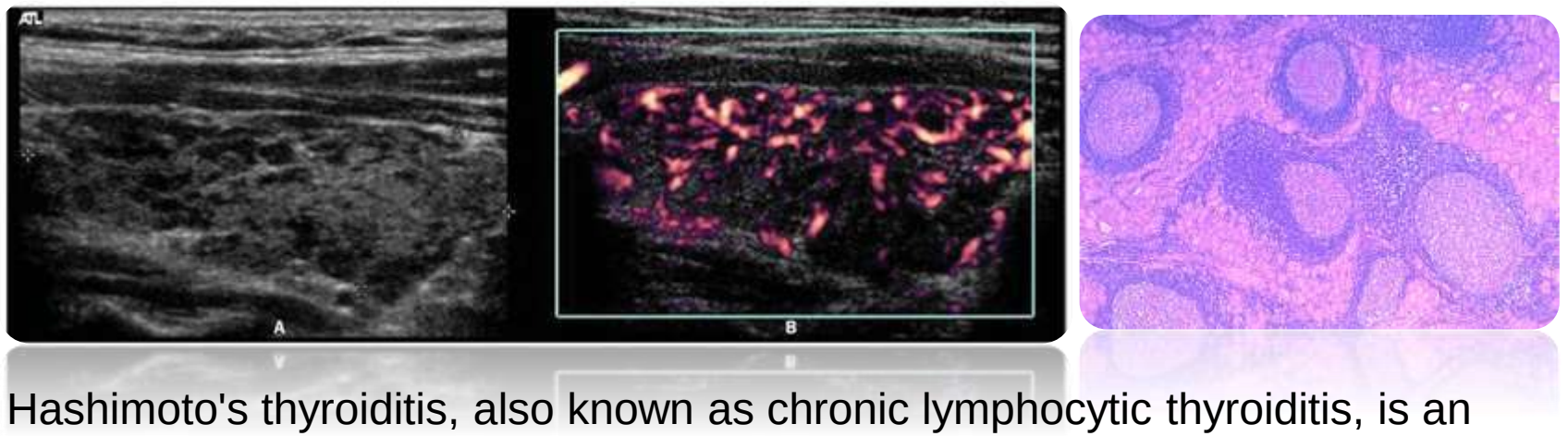
- An association between CD and type 1 diabetes mellitus (T1DM) has been recognized for decades

- Several studies in children and adults, have shown that there is a **1.5% to 7%** prevalence of CD in type 1 diabetes

- A community-based study of type 1 diabetics of all ages in Olmsted County, MN, revealed that 6.5% had celiac disease.

Celiac Disease:
Autoimmune Thyroid Disease

- Approximately 5-6% of the patients with celiac disease also had autoimmune thyroid disease (Hashimoto'a thyroiditis)

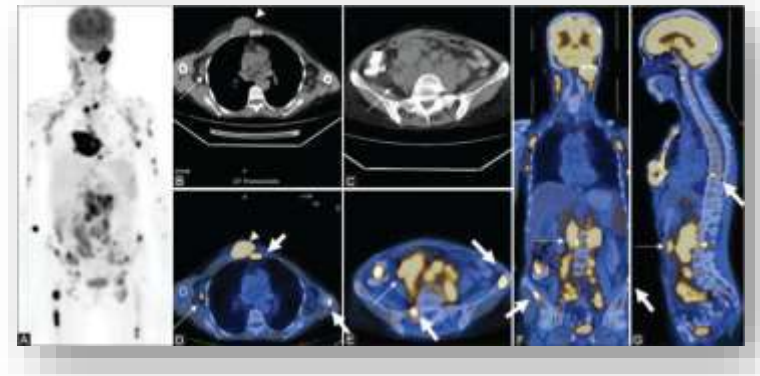


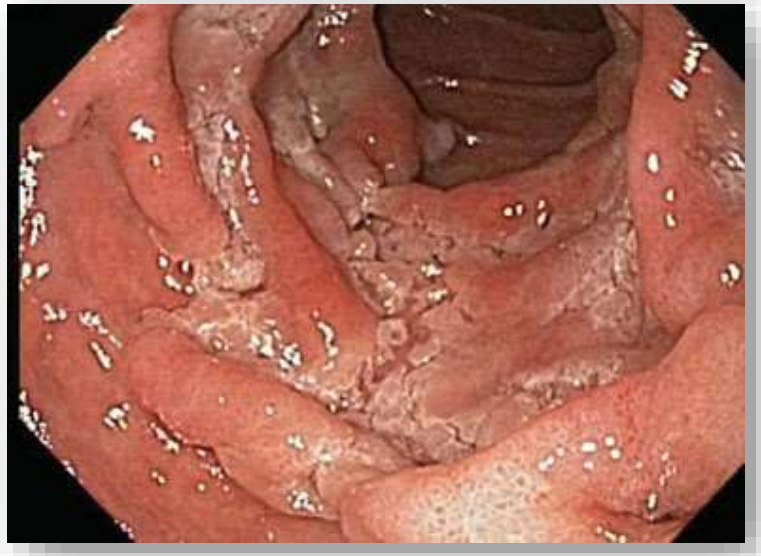
Hashimoto's thyroiditis, also known as chronic lymphocytic thyroiditis, is an autoimmune disease in which the thyroid gland is gradually destroyed. Some people eventually develop hypothyroidism with its accompanying weight gain, feeling tired, constipation, depression, and general pains

Celiac Disease: Neuropsychologic Features

- Depression- 10.6%
- Epilepsy- 3.5%
- Migraine headaches- 3.2%
- Anxiety- 2.6%
- Suicidal tendency- 2.1%
- Carpal tunnel- 1.8%
- Myopathy- 1.5%

Celiac Disease: Malignancies



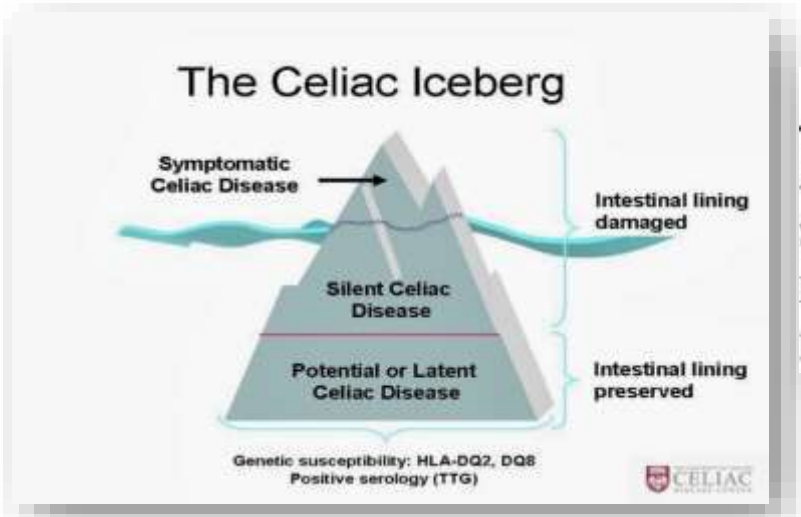


Malignancy	Overall Relative Risk
All cancers	2 to 3
Enteropathy -associated T-cell lymphomas	30 to 40 (w/o gluten free diet)
Small intestinal adenocarcinoma	83
Mouth, pharynx, esophagus cancer	23 (w/o gluten free diet)

American Gastroenterological Association, Ciclitra, PJ, Gastroenterology 2001; 120: 1526.

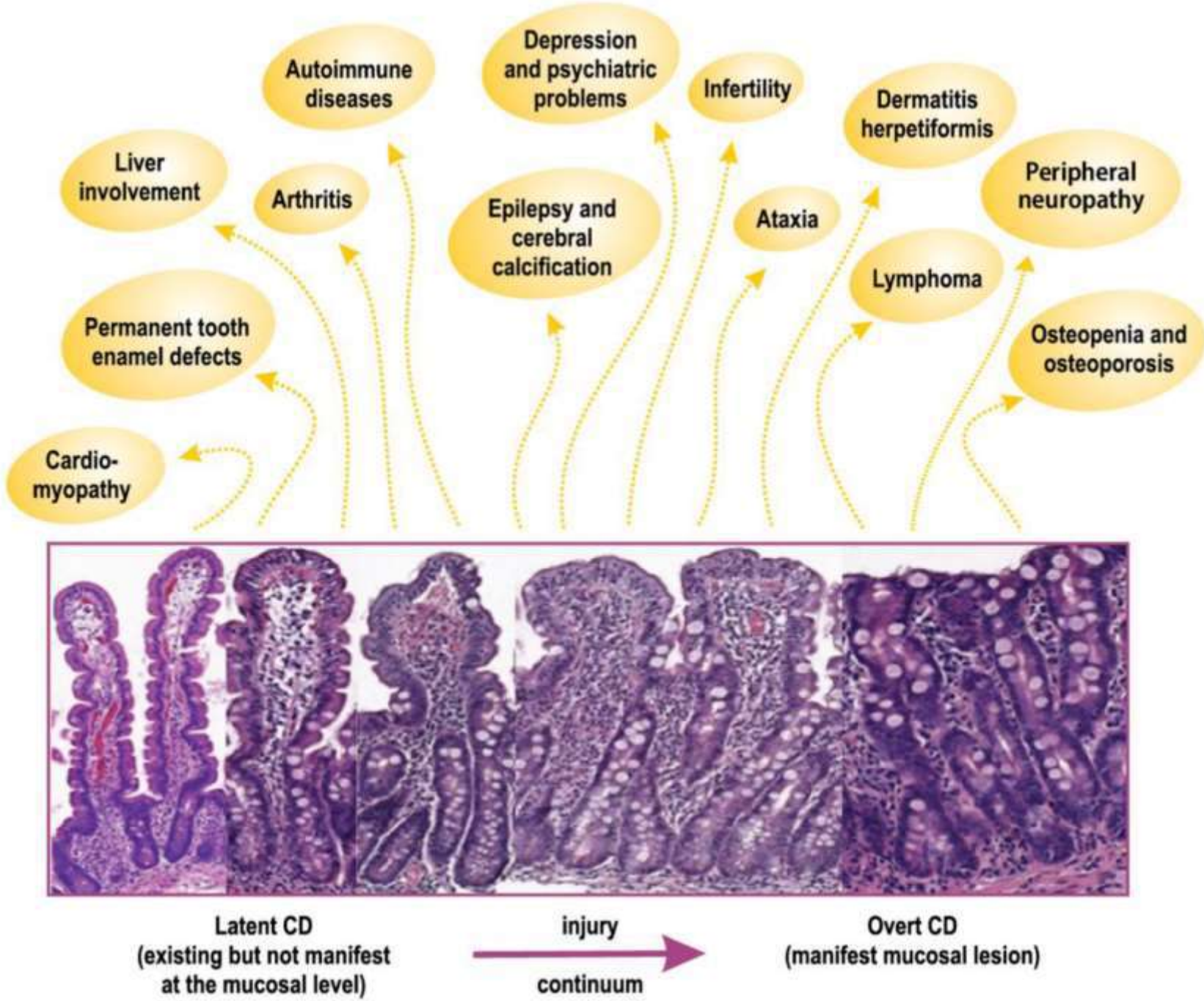
Classification of Celiac Disease

- Classical celiac disease
- Silent celiac disease
- Latent celiac disease



	DQ2/8	Antibodies	Histology	Symptoms
Active CD	+	+	+	+
Silent CD	+	+	+	–
Latent CD	+	–/+	– (+ in the past)	–/+
Potential CD	+	+	–	–/+

	DQ2/8	Antibodies	Histology	Symptoms
Active CD	+	+	+	+
Silent CD	+	+	+	−
Latent CD	+	−/+	– (+ in the past)	−/+
Potential CD	+	+	−	−/+


Autoimmune diseases
Depression and psychiatric problems
Infertility
Dermatitis herpetiformis
Liver involvement
Arthritis
Epilepsy and cerebral calcification
Ataxia
Peripheral neuropathy
Lymphoma
Permanent tooth enamel defects
Osteopenia and osteoporosis
Cardio-myopathy
Latent CD
(existing but not manifest at the mucosal level)
injury
continuum
Overt CD
(manifest mucosal lesion)

Diagnosis of Celiac Disease

Clinical & Laboratory Findings

Serologic testing

Small Intestines Mucosal Biopsy

Gluten Re-challenge

Diagnosis of Celiac disease: Serologic Testing

- IgA and IgG anti-deamidated-gliadin antibodies
- IgA endomysial antibodies
- IgA and IgG tissue transglutaminase antibodies

Table 3. Range of Sensitivity and Specificity and Use of Current Serologic Tests for Celiac Disease[a]

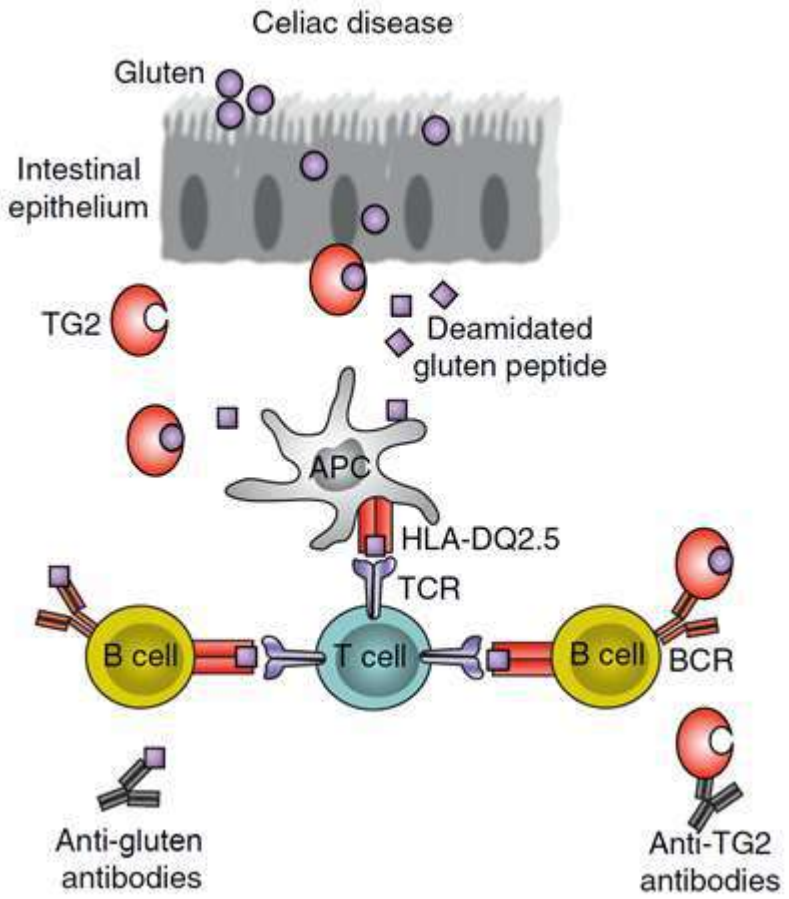
Serologic Study	% Sensitivity	% Specificity	Application in Clinical Practice
IgA tTG	73.9-100	77.8-100	First-line testing to screen for celiac disease[b]
IgG DGP	80.1-96.9	86.0-96.9	First-line testing for celiac disease in patients with IgA deficiency
IgA EMA	82.6-100	94.7-100	Second-line confirmatory test to screen for celiac disease
IgG tTG	12.6-99.3	86.3-100	Not recommended for routine use because of poor sensitivity compared with IgG DGP
IgA DGP	80.7-95.1	86.3-93.1	Not recommended for routine use because of poor sensitivity and specificity compared with IgA tTG and IgA EMA

Abbreviations: EMA, antiendomysial antibody; DGP, deamidated gliadin peptide; tTG, tissue transglutaminase.

[a] Adapted from Thawani et al.[41]

[b] Should be sent with a baseline IgA level initially to ensure there is no IgA deficiency.

Diagnosis of Celiac disease: anti-transglutaminase ab

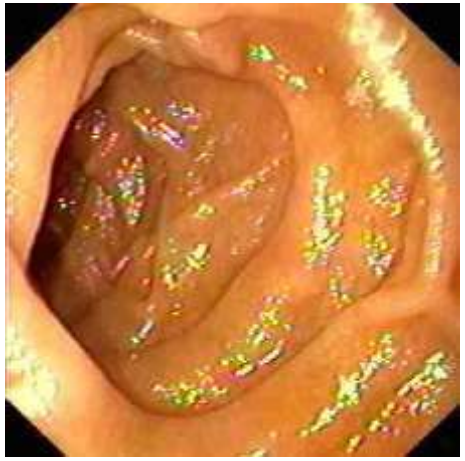


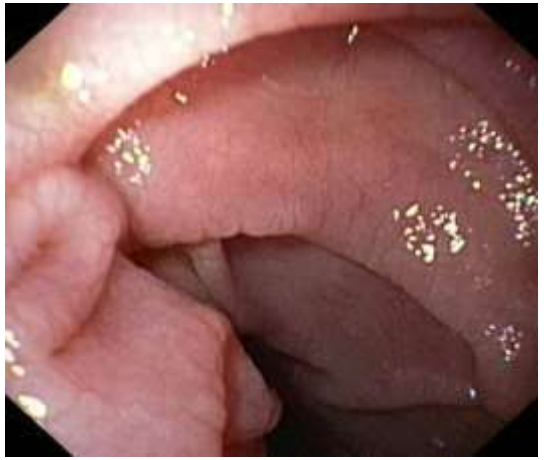
Tissue transglutaminase modifies gluten peptides into a form that may stimulate the immune system more effectively. These peptides are modified by tTG in two ways, deamidation or transamidation.

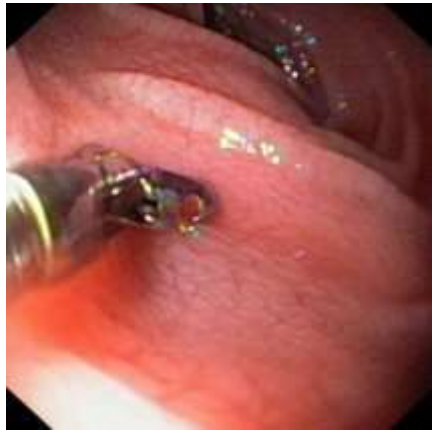
Deamidation is the reaction by which a glutamate residue is formed by cleavage of the epsilon-amino group of a glutamine side chain. Transamidation, which occurs three times more often than deamidation, is the cross-linking of a glutamine residue from the gliadin peptide to a lysine residue of tTg in a reaction which is catalysed by the transglutaminase. Crosslinking may occur either within or outside the active site of the enzyme. The latter case yields a permanently covalently linked complex between the gliadin and the tTg. This results in the formation of new epitopes which are believed to trigger the primary immune response by which the autoantibodies against tTg develop.

Diagnosis: Endoscopy

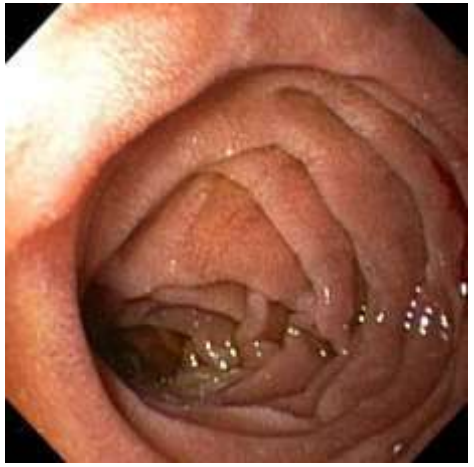
Normal

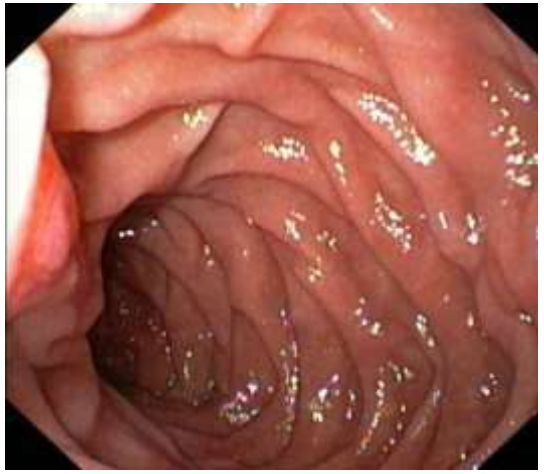


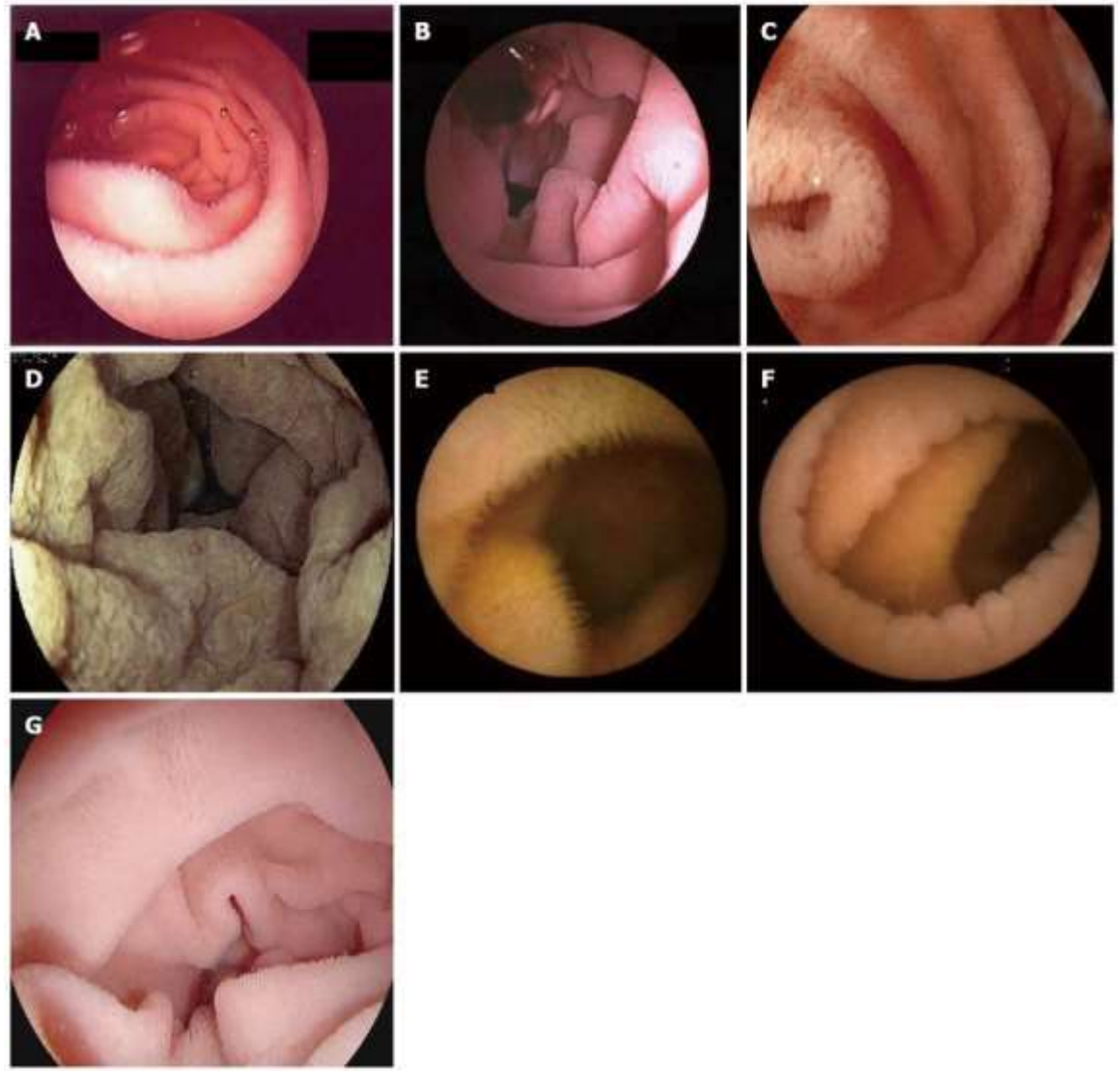




Celiac






A
B
C
D
E
F
G

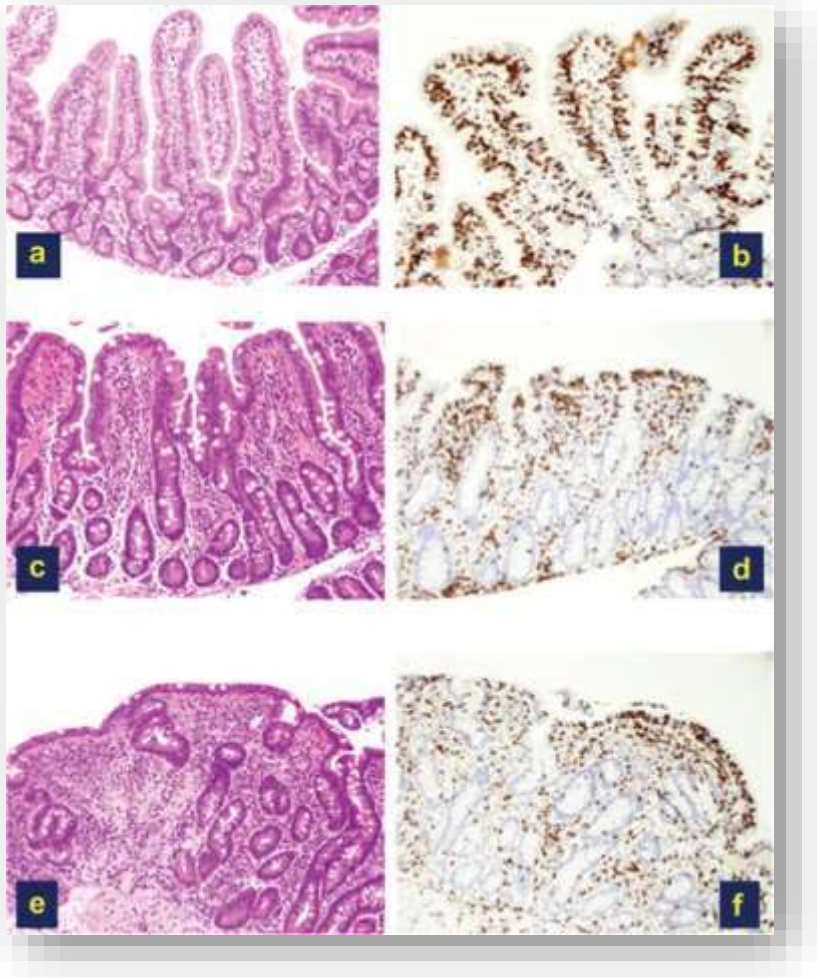
Marsh's classification

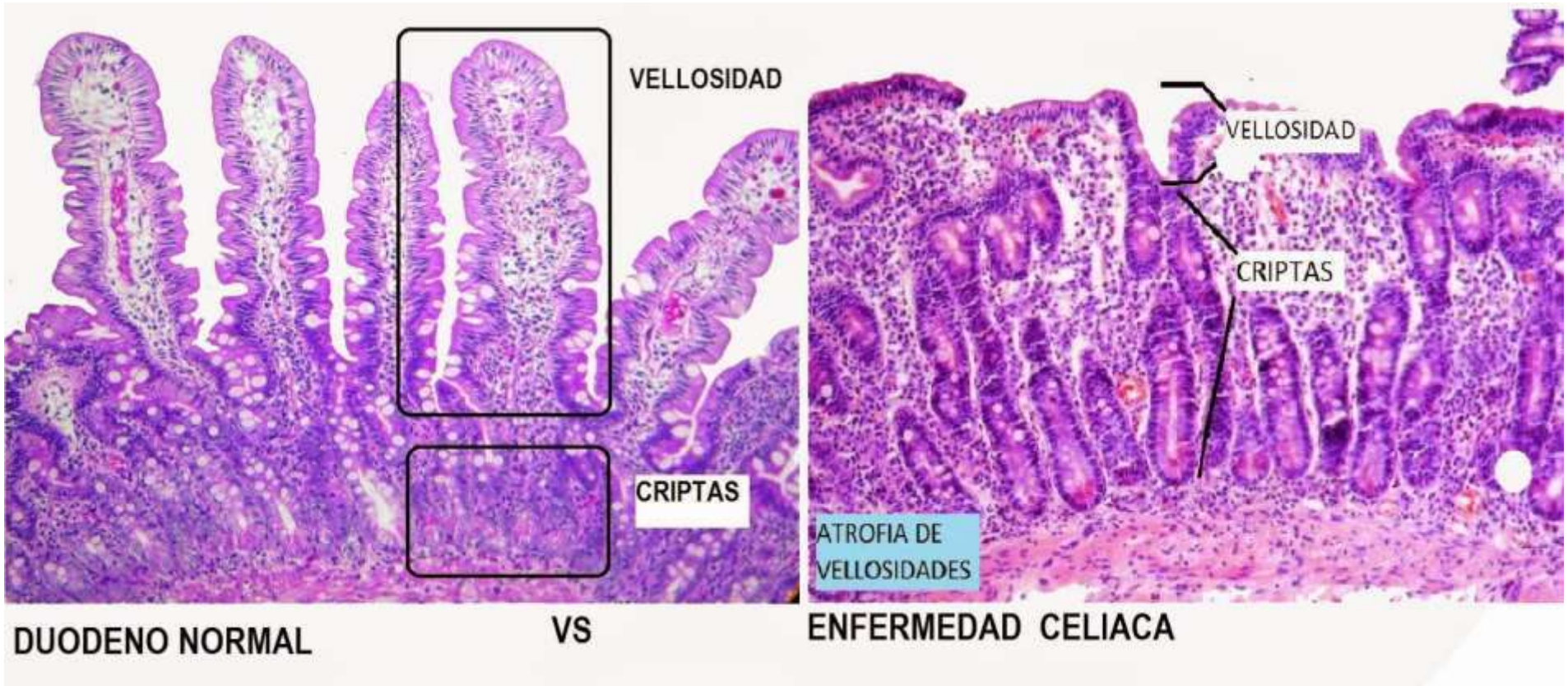
Stage 0
Preinfiltrative mucosa; 5% of patients with CD have small intestinal biopsy speciments that appear normal.

Stage I°
Increase in the number of intraepithelial lymhocytes (IELs) to more than 30 per 100 enterocytes.

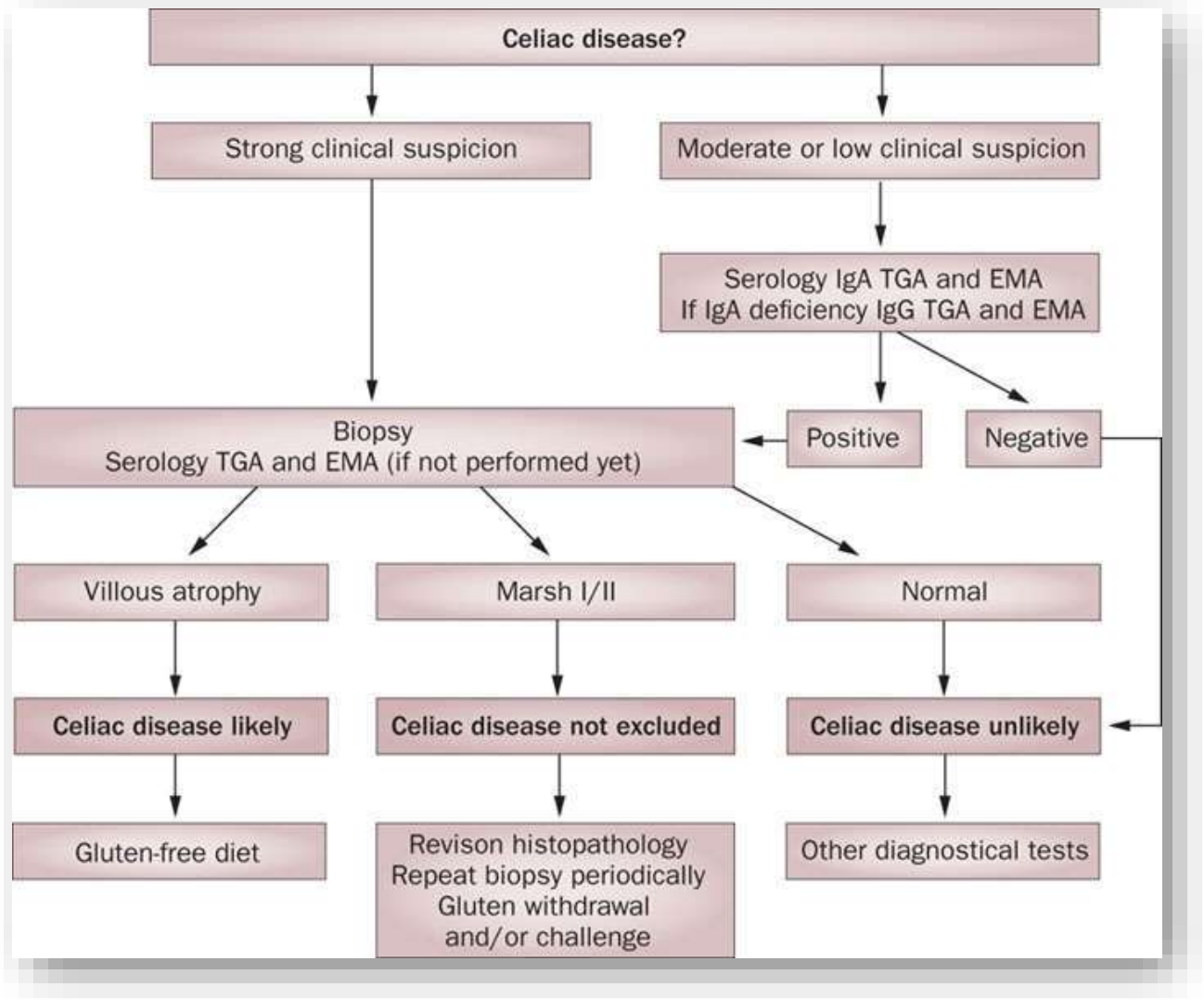
Stage II°
Criptic hyperplasia. In addition to the increased IELs, there is an increase in crypt depth without a reduction in villus height.

Stage III°
Villous atrophy; A partial, B subtotal, C total.
This lesion is characteristic of, but not diagnostic for, CD and can also been seen with severe giardiasis, infantile food sensitivities, graft-versus-host disease, chronic ischemia of the small intestine, tropical sprue, immunoglobulin deficiencies..




VELLOSIDAD
CRIPTAS
VELLOSIDAD
CRIPTAS
ATROFIA DE VELLOSIDADES
DUODENO NORMAL
VS
ENFERMEDAD CELIACA

Algorithm for diagnosis of uncomplicated celiac disease



Tack, G. J. *et al*. (2010) The spectrum of celiac disease: epidemiology, clinical aspects and treatment *Nat. Rev. Gastroenterol. Hepatol.* doi:10.1038/nrgastro.2010.23

La terapia della celiaca
È la dieta priva di glutine

Dieta priva di glutine

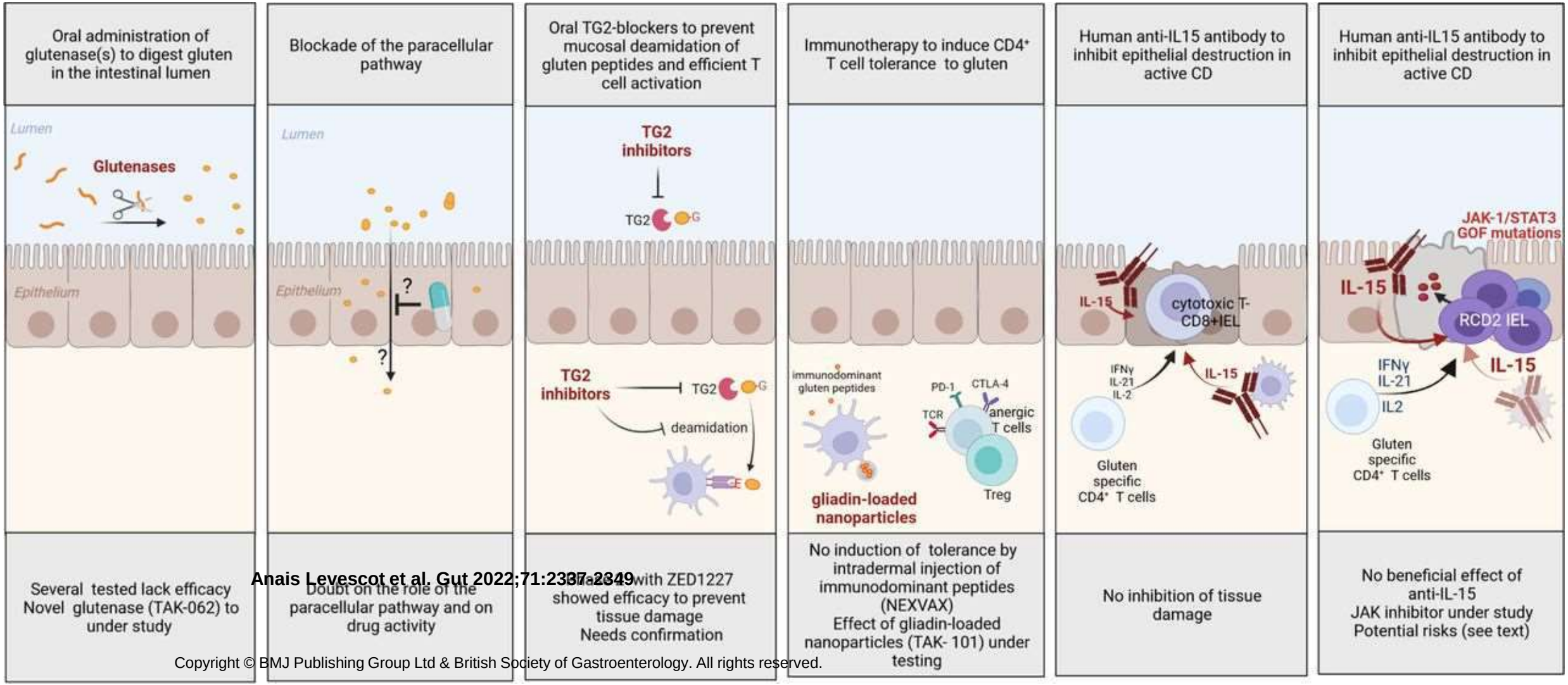
Perché un alimento si possa considerare senza glutine il 'Codex Alimentarius' europeo stabilisce che al massimo debba contenere lo 0.3% di glutine.

L’erogazione gratuita dei prodotti inseriti nel Registro rientra nei Livelli Essenziali di Assistenza sanitaria ed è garantita solo a coloro i quali, avendo ricevuto diagnosi di celiachia dai presidi accreditati con il SSN, ne fanno richiesta alla propria Azienda Sanitaria Locale. I limiti di spesa previsti dalla normativa attuale, per l’acquisto di tali prodotti, sono i seguenti:

EROGAZIONE GRATUITA

Fascia di età	Tetto mensile MASCHI	Tetto mensile FEMMINE
6 mesi – 1 anno	€ 45,00	€ 45,00
Fino a 3,5 anni	€ 62,00	€ 62,00
Fino a 10 anni	€ 94,00	€ 94,00
Età adulta	€ 140,00	€ 99,00

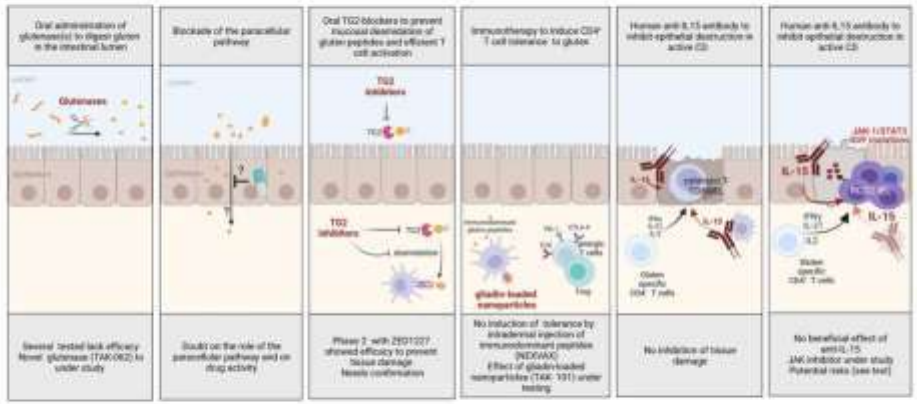
Proposed rationale-based therapies for celiac disease (CD).



Anais Levescot et al. Gut 2022;71:2337-2349

Therapy

Proposed rationale-based therapies for coeliac disease (CD).



Anais Levescot et al. Gut 2022;71:2337-2349

GUT

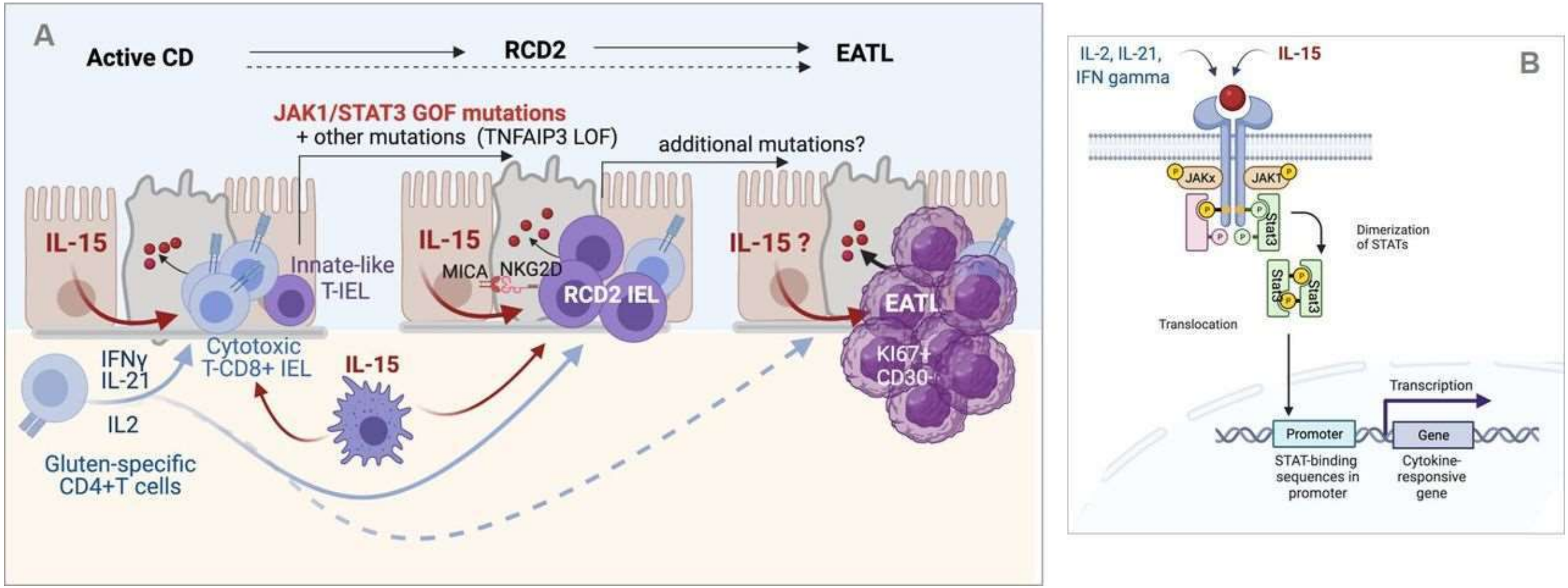
Celiac disease: refratory celiac disease

Refractory celiac disease (RCD) is defined by persistent or recurrent malabsorptive symptoms and villous atrophy despite strict adherence to a gluten-free diet (GFD) for at least 6–12 months in the absence of other causes of non-responsive treated celiac disease and overt malignancy.

Symptoms are often severe and require additional therapeutic intervention besides GFD.

RCD can be classified as **type 1 (normal intraepithelial lymphocyte phenotype), or type 2 (defined by the presence of abnormal** [clonal] intraepithelial lymphocyte phenotype).

Inflammation-driven lymphomagenesis in coeliac disease (CD).



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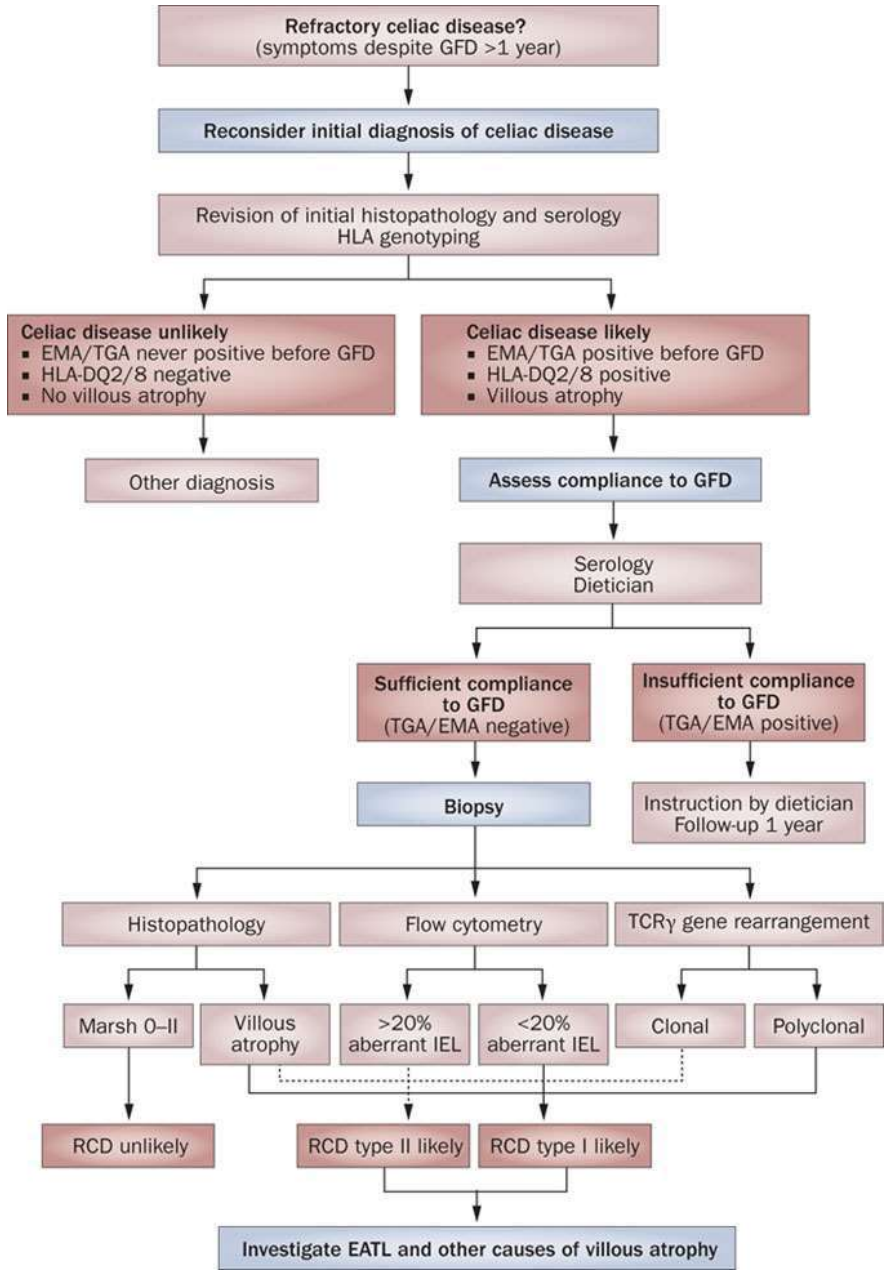
GUT

Algorithm for diagnosis of refractory celiac disease



Tack, G. J. *et al*. (2010) The spectrum of celiac disease: epidemiology, clinical aspects and treatment *Nat. Rev. Gastroenterol. Hepatol.* doi:10.1038/nrgastro.2010.23

RCD, refractory celiac disease; GFD, gluten-free diet; IELs, intraepithelial lymphocytes

Celiac disease refractory disease

Clinical Criteria	Disease Category	
	RCD type 1	RCD type 2
Abnormal immunophenotype of IELs with loss of normal surface markers CD4, CD8, and T-cell receptor: either >50 % by immunohistochemistry or >20–25% by flow cytometry	No	Yes
T-cell receptor chains (γ or δ) clonal rearrangement by molecular methods (<15% in normal state)	No	Yes
Clinical or histological response to steroids or other immunosuppressive drugs or ~~biologics~~	Yes	Variable
Lymphoma-genesis potential (especially T cell lymphoma development)	**Rare**	**Frequent**

Il TCR γδ non utilizza CD4 e CD8 come co-recettori, per cui i linfociti T γδ sono CD4- e CD8-.

Questa sottoclasse di linfociti, negli animali, è preponderante a livello epiteliale e nella mucosa intestinale, che ne è particolarmente ricca, assommano a non più del 15% del totale, mentre sono il 10% dei linfociti T totali.

I **TCR γδ si legano a proteine MHC di classe I non convenzionali e non sono ristretti a soli peptidi proteici, potendo riconoscere anche lipidi e molecole microbiche.**

Celiac disease:
refratory celiac disease

Prednisone (0.5–1 mg/kg/day), **budesonide** (9 mg/day), or a combination of prednisone and azathioprine (2 mg/kg/day) are clinically effective to induce clinical remission and mucosal recovery in most patients with RCD type Clinical response to steroids is observed in the majority (~75%) of patients with RCD type 2, however mucosal recovery is infrequent and progression to EATL is not prevented Steroid- dependence is observed in most patients with RCD type 1 or RCD type 2.[15]

Gluten sensitivity

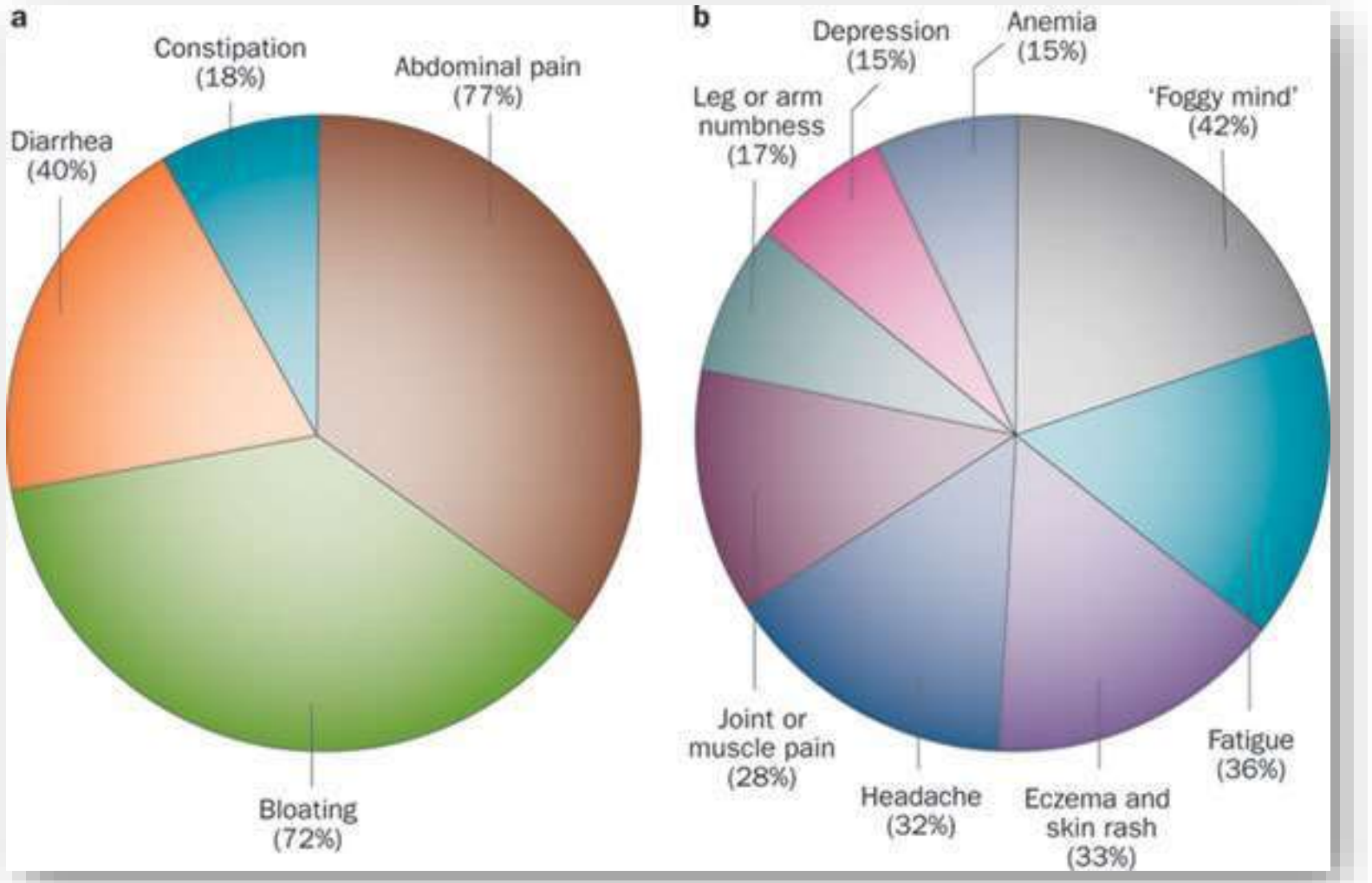
Unlike celiac disease, gluten sensitivity is not associated with ***serious conditions*** (referring to – autoimmune, cancer, osteoporosis, infertility, and neurological disease).

Common symptoms of gluten sensitivity include abdominal pain similar to irritable bowel syndrome, fatigue, headaches, “foggy mind” or tingling of the extremities.

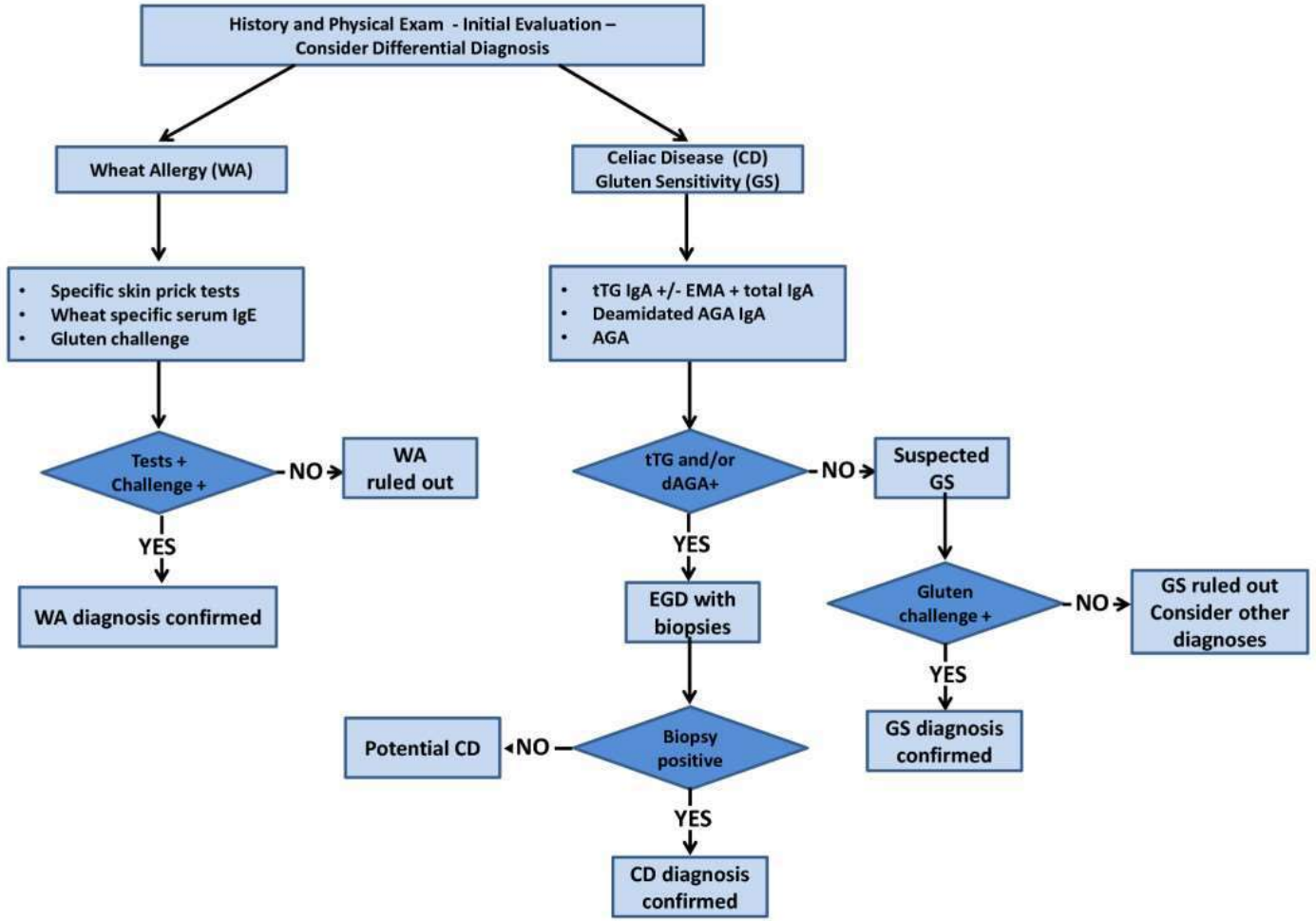
Table 2. Gastrointestinal and Extraintestinal Manifestations of Celiac Disease and Nonceliac Gluten Sensitivity[a]

Symptoms	Presence of Symptoms	
	Celiac Disease[b]	Nonceliac Gluten Sensitivity
Intestinal		
Abdominal pain, %	+ (27.8)	+
Anorexia	+	–
Bloating	+	+
Constipation, %	+ (20.2)	+
Diarrhea, %	+ (35.3)	+
Flatulence	+	+
Lactose intolerance	+	–
Nausea	+	–
Gastroesophageal reflux	+	–
Weight loss	+	–
Vomiting	+	–
Extraintestinal		
Anemia, %	+ (32)	+
Anxiety	+	+
Arthralgia, %	+ (29.3)	+
Arthritis, %	+ (1.5)	+
Ataxia	+	+
Dental enamel hypoplasia	+	–
Delayed puberty	+	–
Dermatitis herpetiformis	+	–
Depression	+	+
Elevated liver enzymes	+	–
Rash (eg, eczema)	+	+
Fatigue, %	+ (26.3)	+
Cloudiness of consciousness	+	+
Headache	+	+
Infertility	+ (1.5)	–
Irritability	+	+
Iron-deficiency anemia	+	–
Mouth sores	+	–
Myalgias	+	+
Osteoporosis, %	+ (5.5)	–
Pancreatitis	+	–
Peripheral neuropathy, %	+ (0.7)	+

Gluten sensitivity



The spectrum of wheat-associated diseases



Gluten sensitivity

	Gluten Sensitivity	Wheat Allergy	Celiac Disease
Prevalence	6 % of U.S. population	Less than 1% of children; some adults after exercise	1% of U.S. population
Symptoms	Some stomach issues, also headaches, balance problems, many others	Hives, nasal congestion, nausea, anaphylaxis	Bloating, diarrhea, malnutrition, osteoporosis, cancer
Triggers	Gluten, amount unknown	Wheat proteins, but may cross react with other grains	Even small amounts of gluten
Treatment	Gluten-free diet, although small amounts may be tolerable	Avoid wheat products	Strict gluten-free diet