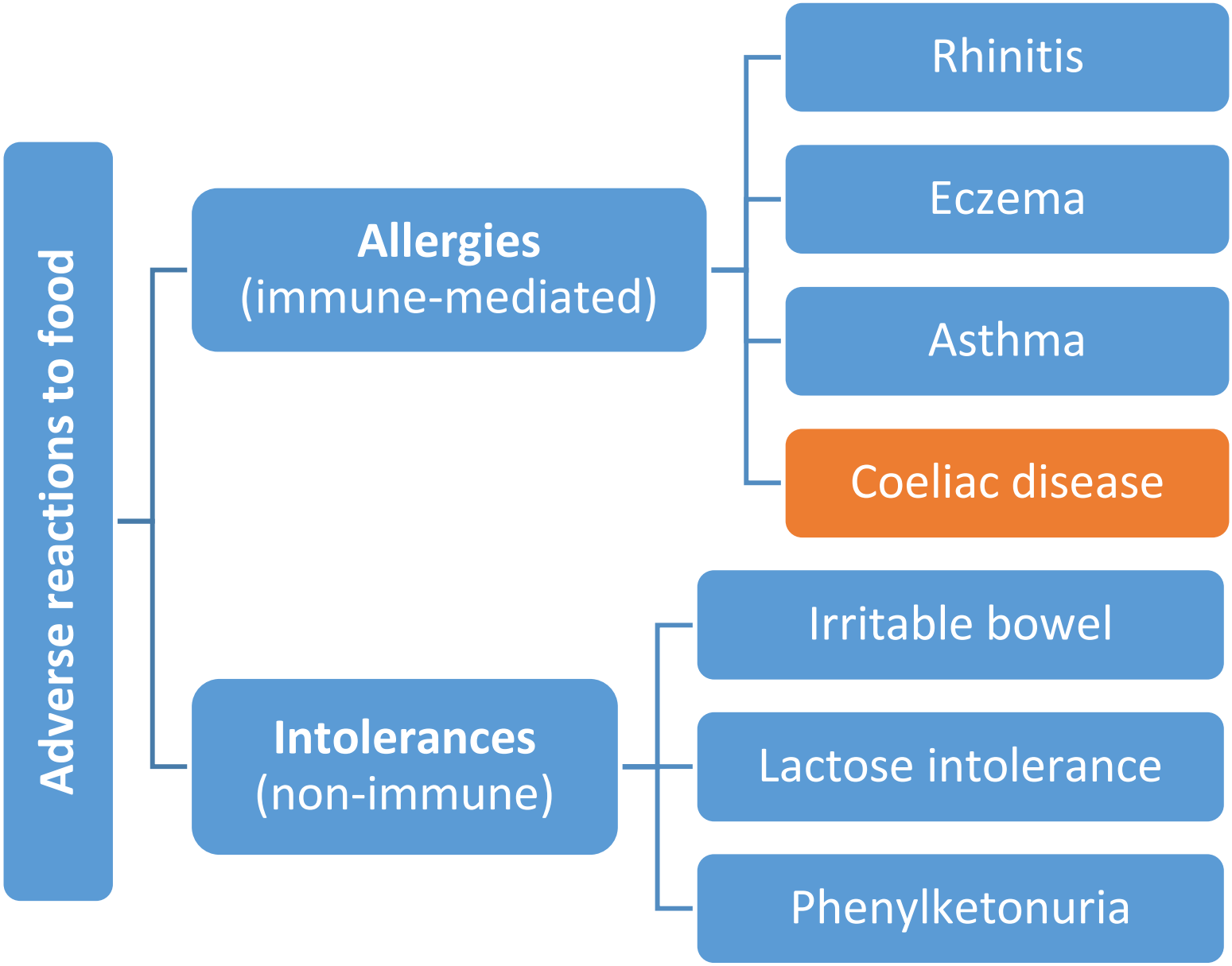
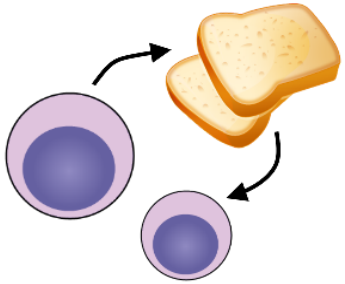
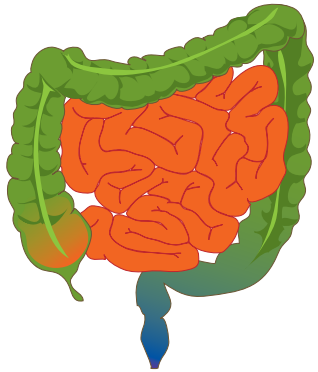

Adverse reactions to food
Allergies
(immune-mediated)
Rhinitis
Eczema
Asthma
Coeliac disease
Intolerances
(non-immune)
Irritable bowel
Lactose intolerance
Phenylketonuria

Definition

- **Immune response** to dietary **gluten**
- Damage to proximal **small intestine epithelium**
- **Malabsorption** features
- Responds to gluten-free diet



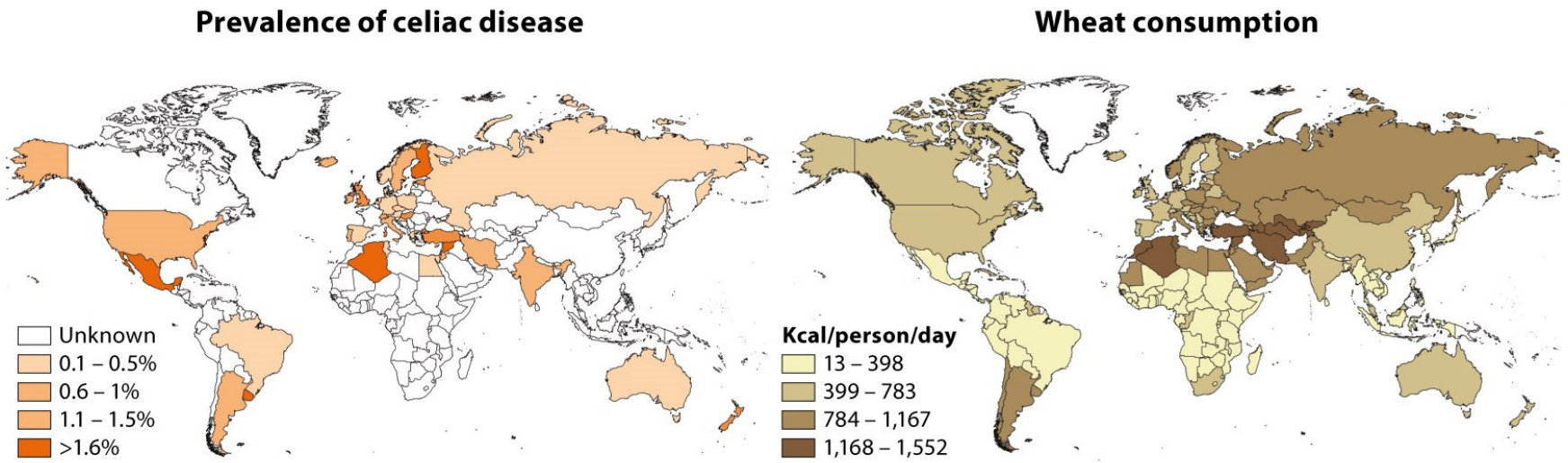


Other Names

- ***Coeliac sprue***
- ***Gluten-sensitive enteropathy***

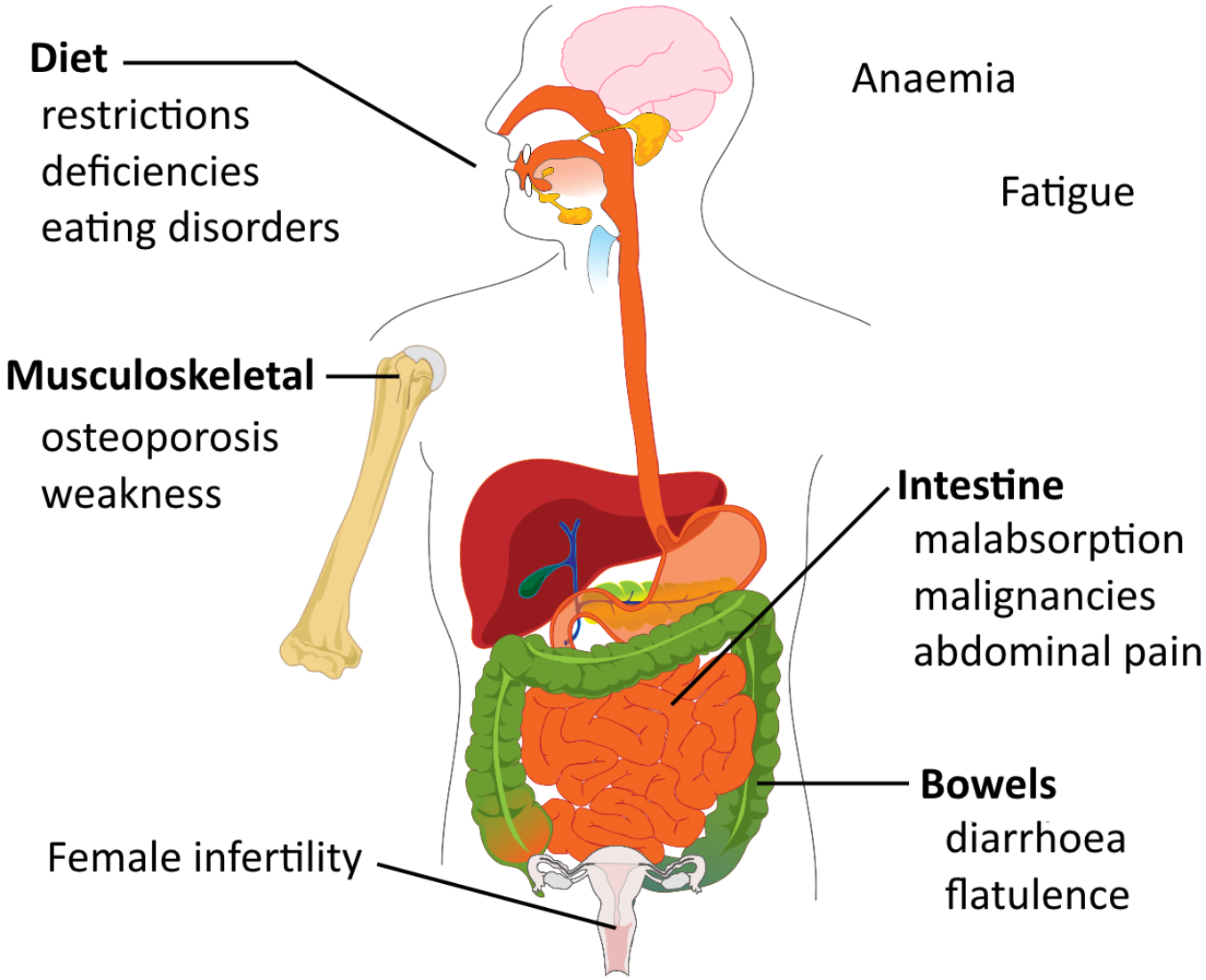
Prevalence

- **0.5 to 1%** among those of White European ancestry
- Most commonly **30-60y** with peaks in infancy and in **50s**



Abadie, V. et al., 2011

Morbidity


Diet
restrictions
deficiencies
eating disorders
Anaemia
Fatigue
Musculoskeletal
osteoporosis
weakness
Intestine
malabsorption
malignancies
abdominal pain
Bowels
diarrhoea
flatulence
Female infertility

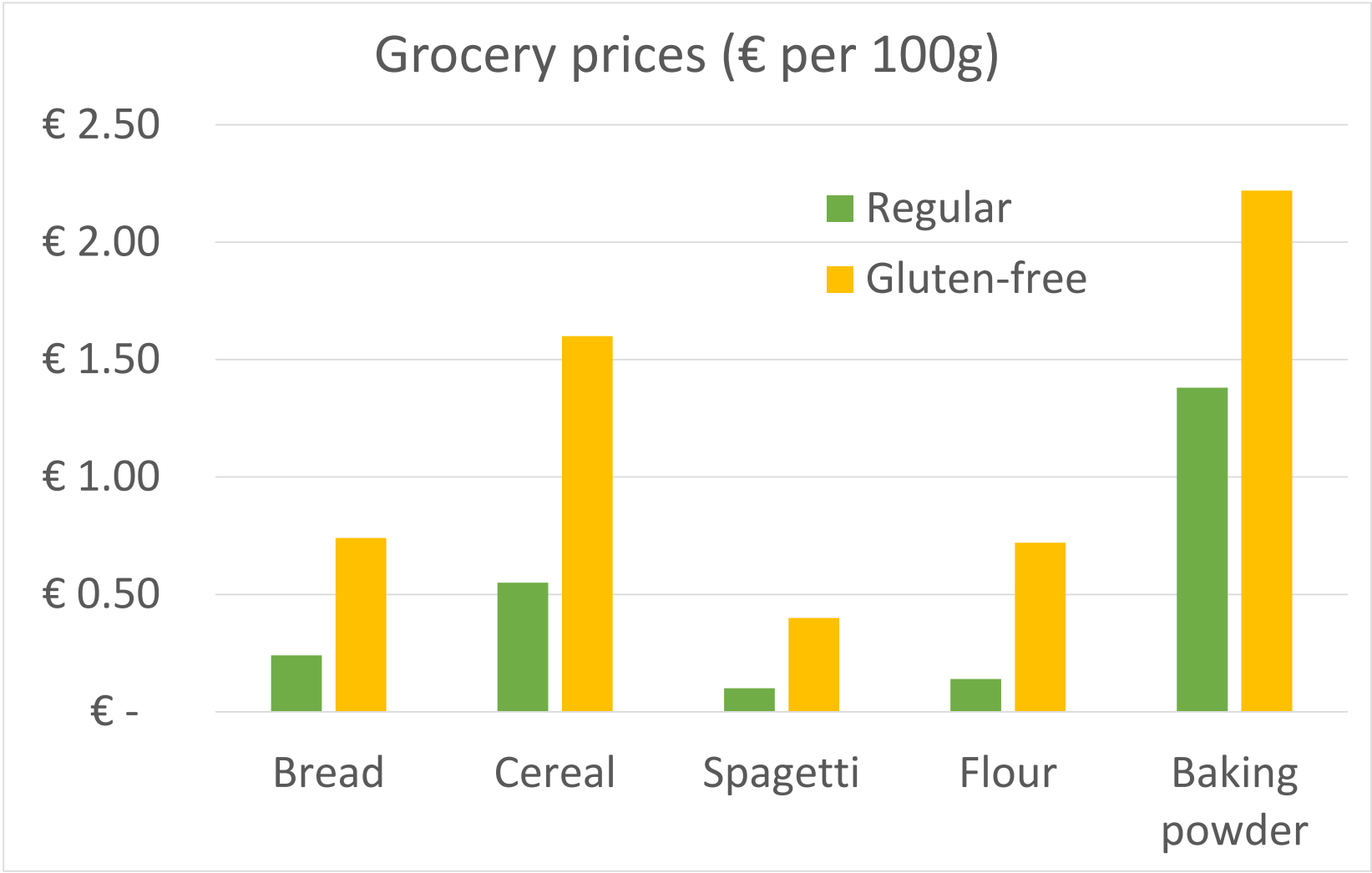
Patient perceptions

Whitaker, J.K.H., et al., 2009

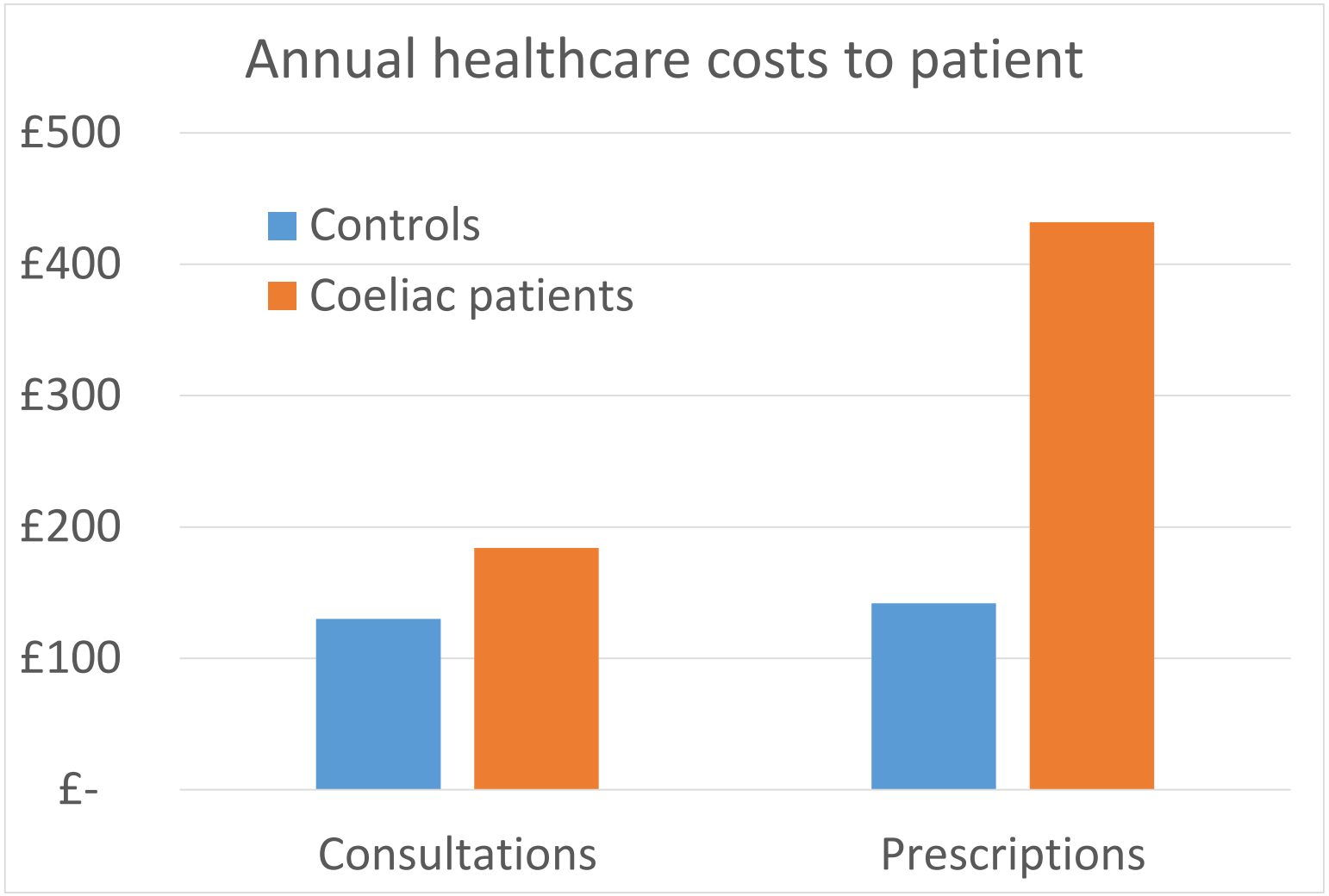
Complaint	**% reporting**
Reduced enjoyment of food	68%
Food costs >£10 per week extra	46%
Food costs a problem	21%
Doing enjoyable things less often	54%
Regret not being diagnosed earlier	66%

Mortality

- Mainly in **undiagnosed** and **untreated**
- Most mortality from **malignancies**
- **Long-term survival** when properly treated



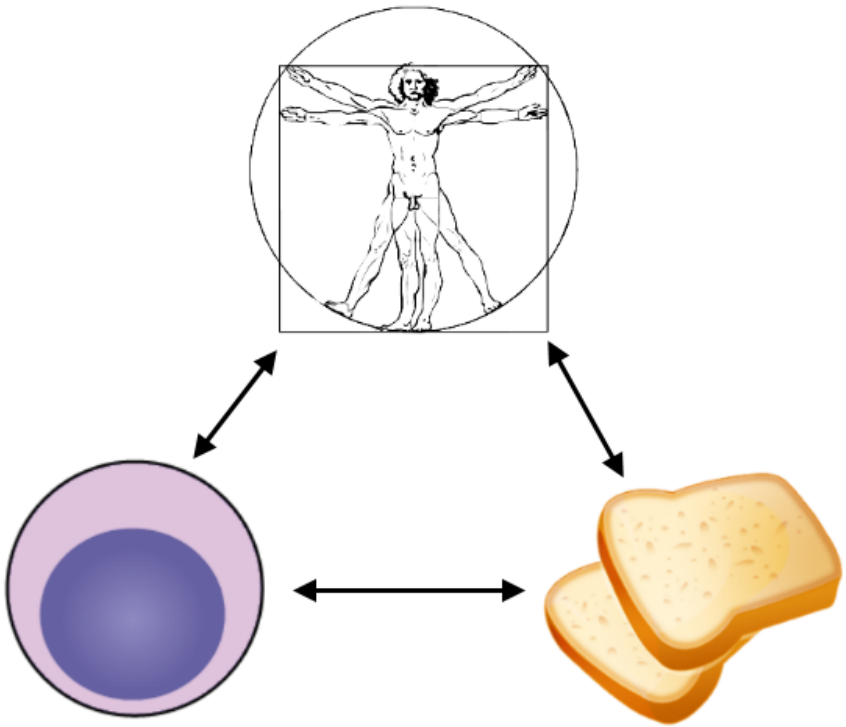
Data: Coeliac Society of Ireland



Data: Violata, M. et al., 2012

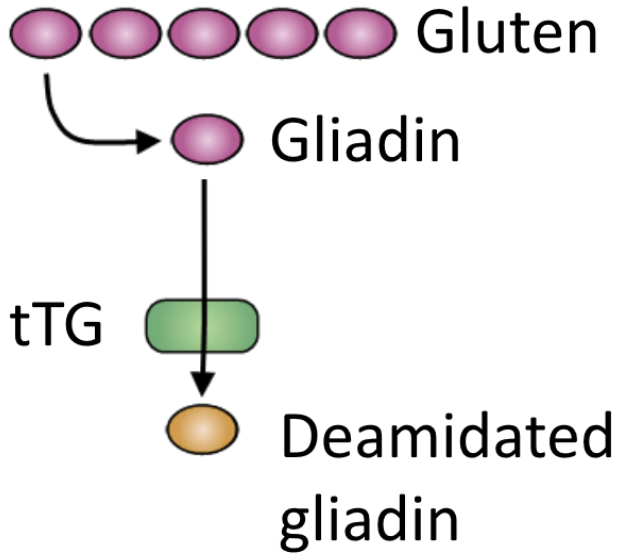
Pathogenesis

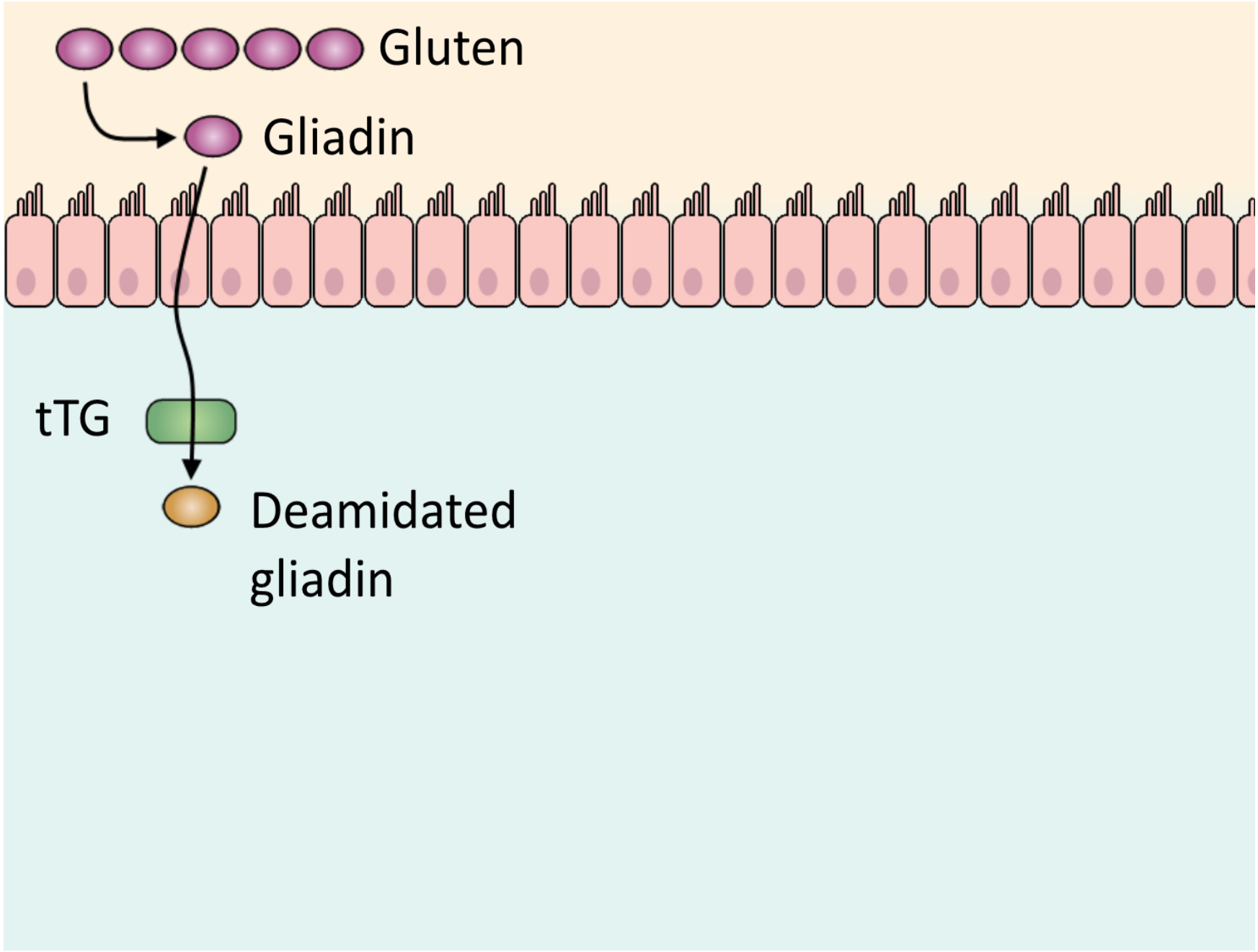
- **Immune-mediated reaction** to **gluten** in intestine
- Most people have no problem with gluten
- Thus **<u>disease attributable mainly to host factors</u>**



Digestion, Ingestion

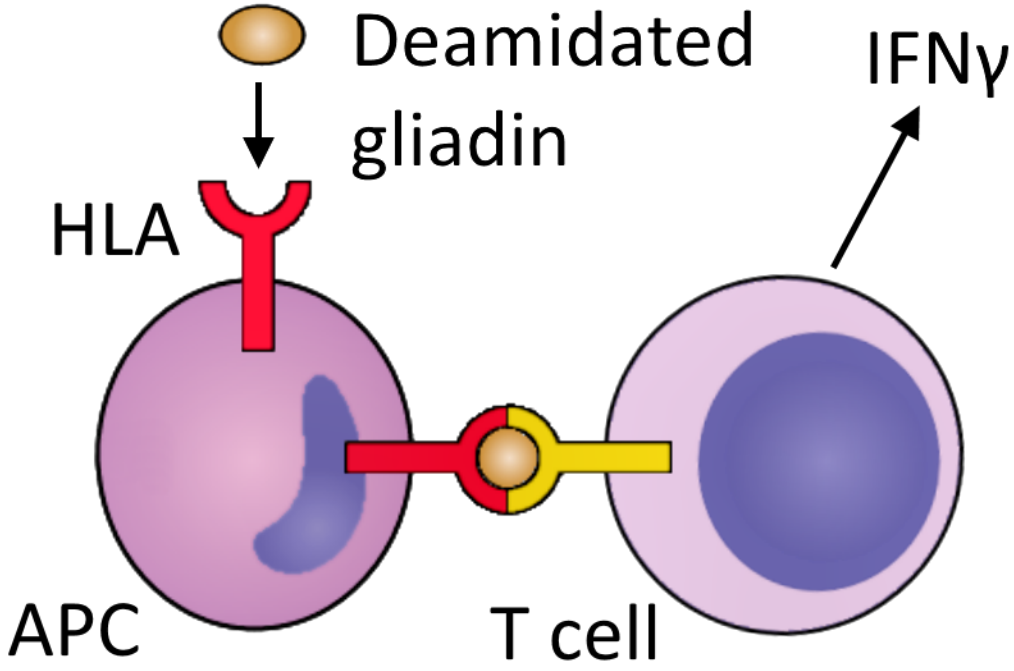
- **Gluten** is ingested in **cereal grains** (wheat, rye, barley).
- Gluten is digested by intestinal enzymes to amino acids and peptides.
- A peptide, **gliadin**, remains, which cannot be degraded by regular enzymes
- Gliadin is instead *deamidated* (has an amide group removed) by **tissue transglutaminase (tTG).**

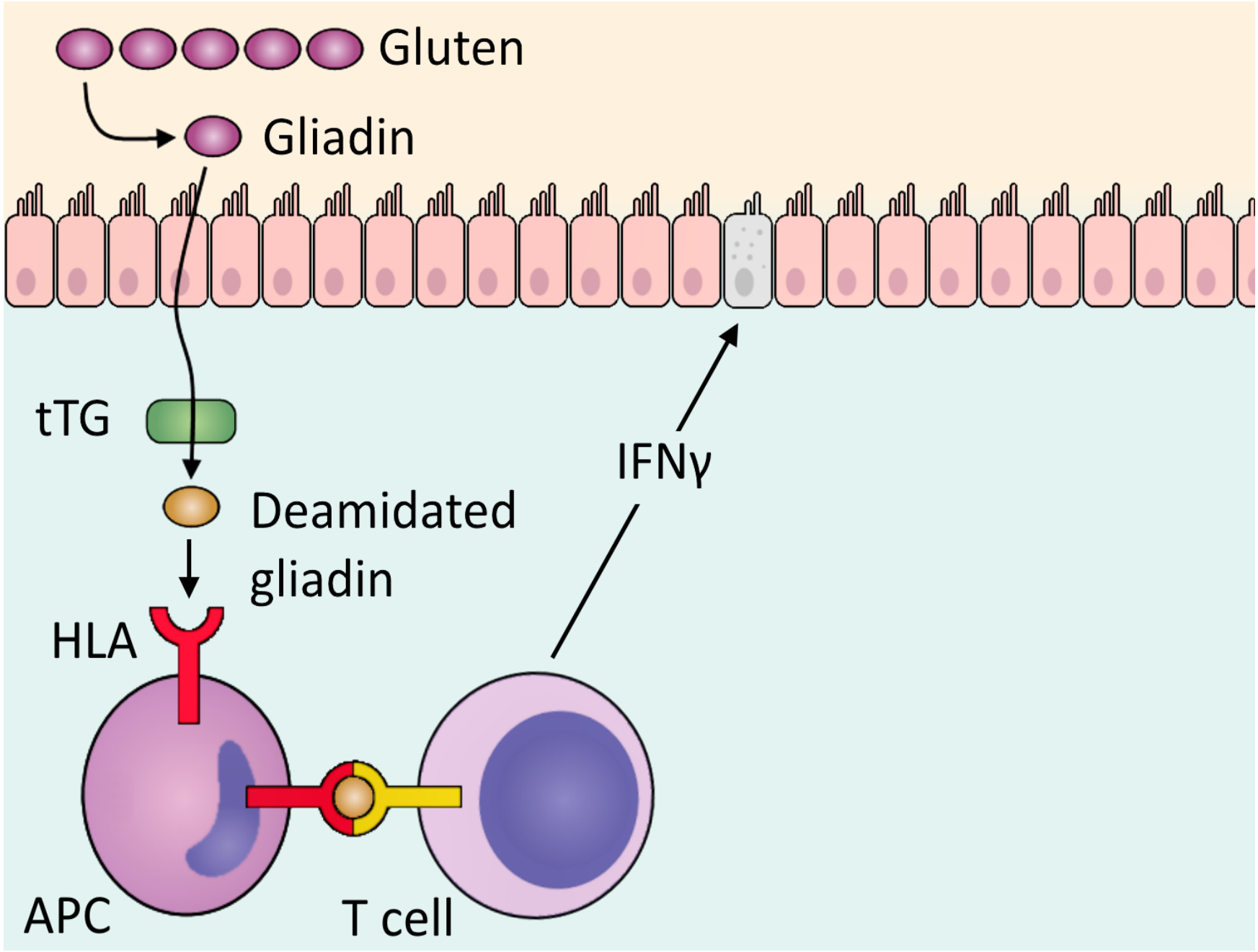



Gluten
Gliadin
tTG
Deamidated
gliadin

APC Presentation, T cell response

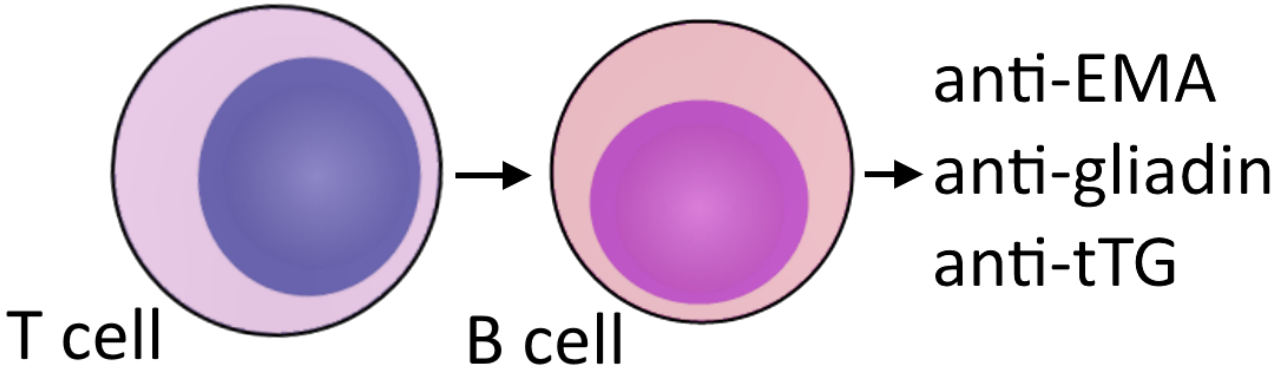
- **Deamidated gliadin** interacts with **HLA DQ2** or **HLA DQ8** on **antigen presenting cells (APCs)**.
- Deamidated gliadin is presented to **CD4 T cells**.
- CD4 T cells produce **cytokines** (such as IFNγ) which cause **tissue damage**.

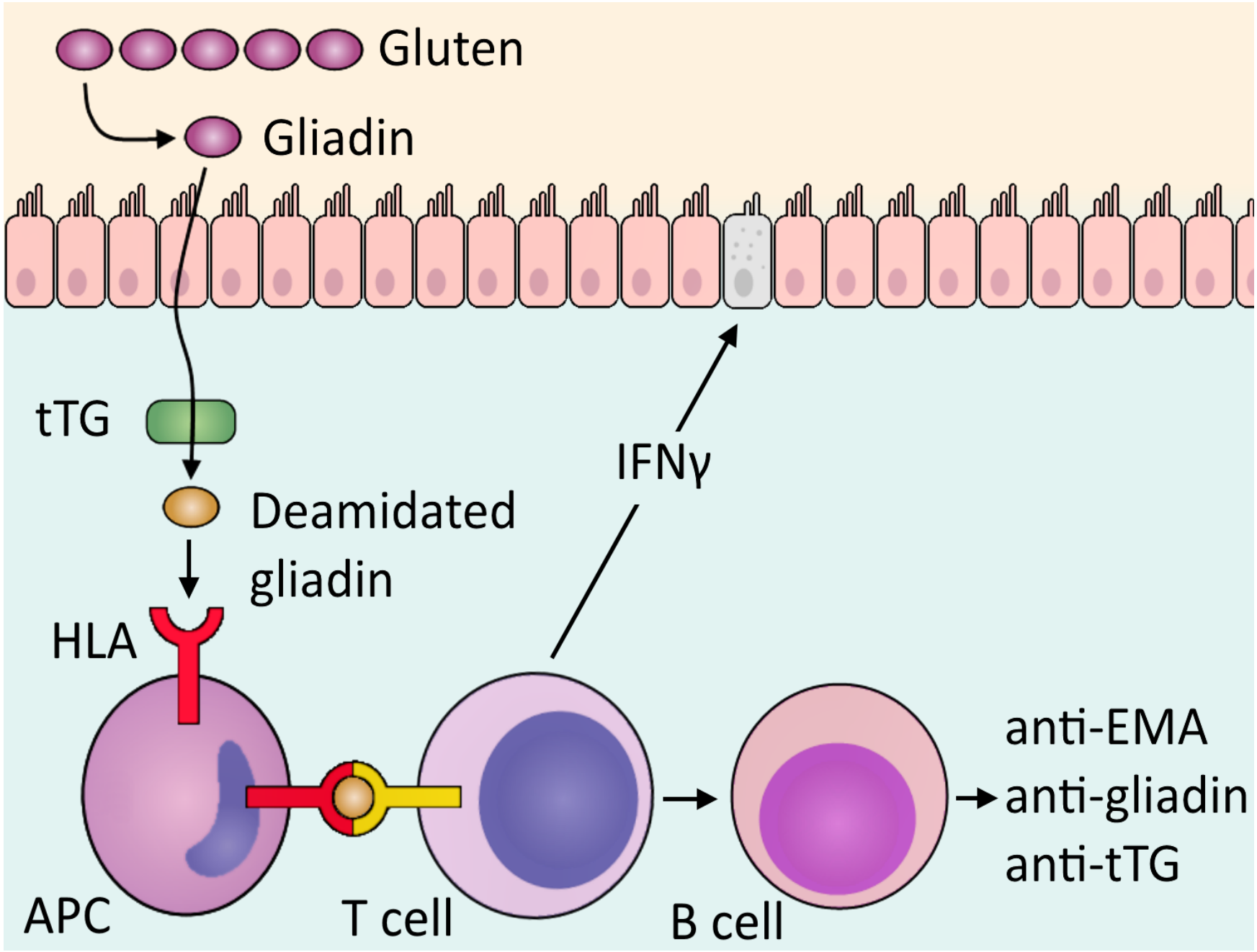



Gluten
Gliadin
tTG
Deamidated
gliadin
HLA
IFNγ
APC
T cell

B cell response

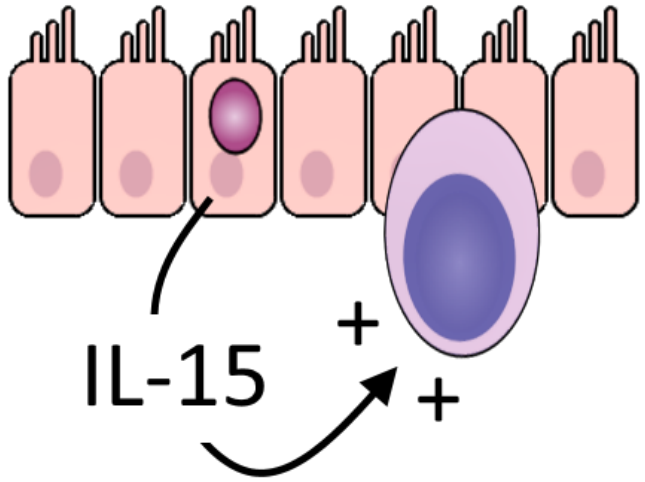
- T cells also elicit a **B cell response**.
- B cells produce the antibodies:
  - **Anti-tissue transglutaminase** (anti-tTG)
  - **Anti-deamidated gliadin**
  - **Anti-endomysial antibody** (anti-EMA)

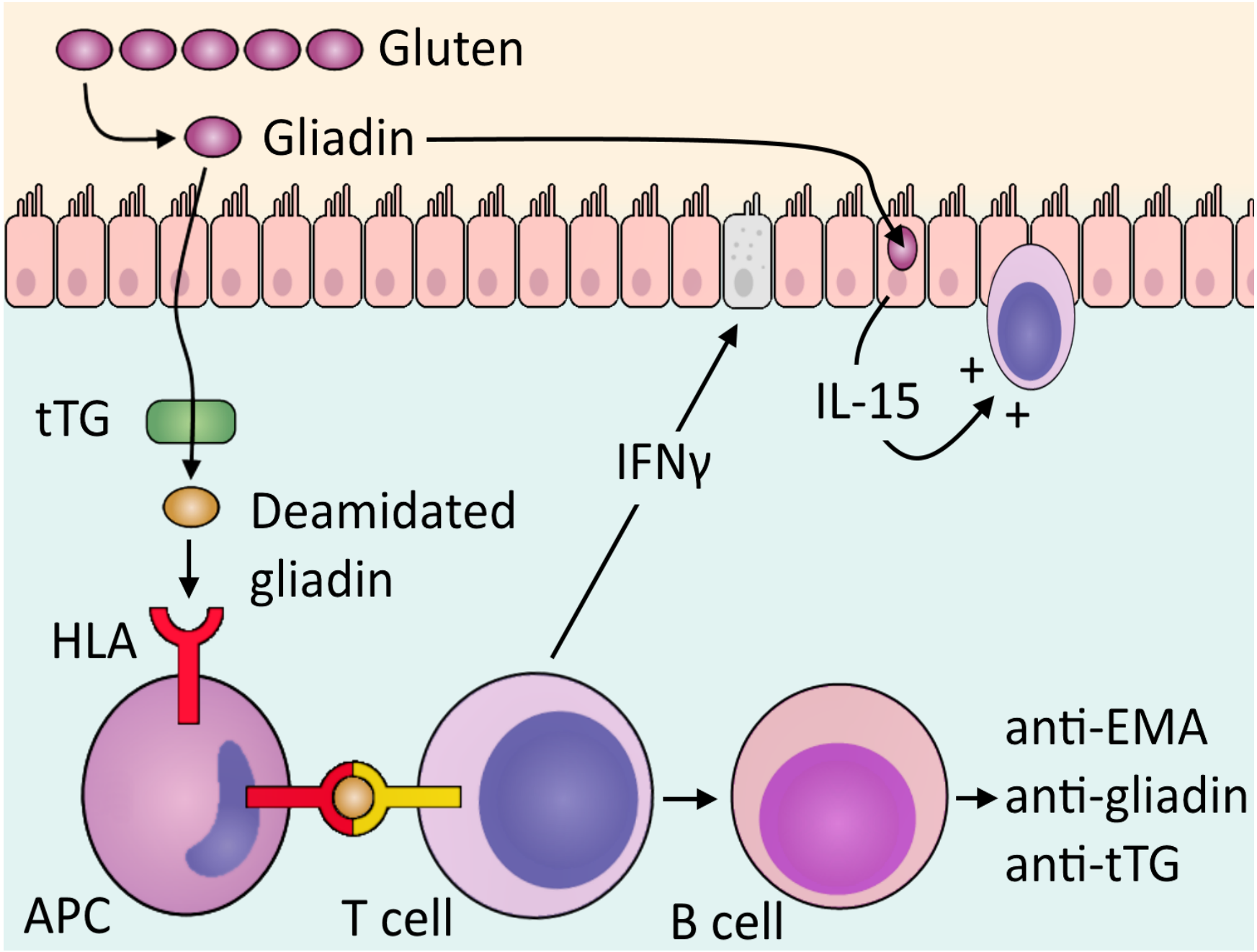



Gluten
Gliadin
tTG
Deamidated
gliadin
HLA
IFNγ
anti-EMA
anti-gliadin
anti-tTG
APC
T cell
B cell

IL-15, intraepithelial lymphocytes

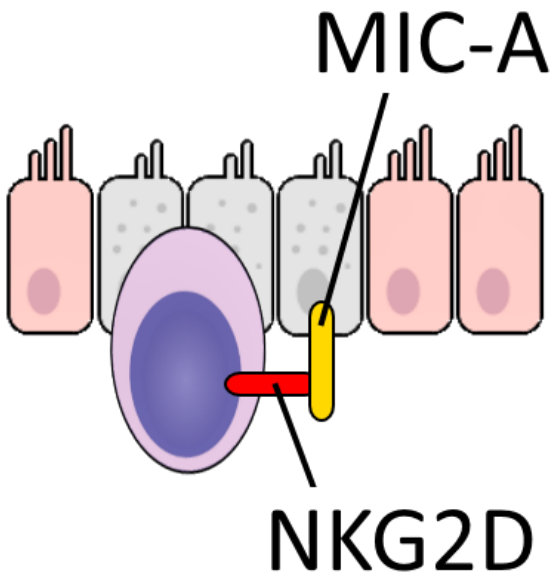
- Gliadin also induces **IL-15** production from enterocytes.
- IL-15 activates and upregulates **intraepithelial CD8 lymphocytes**.

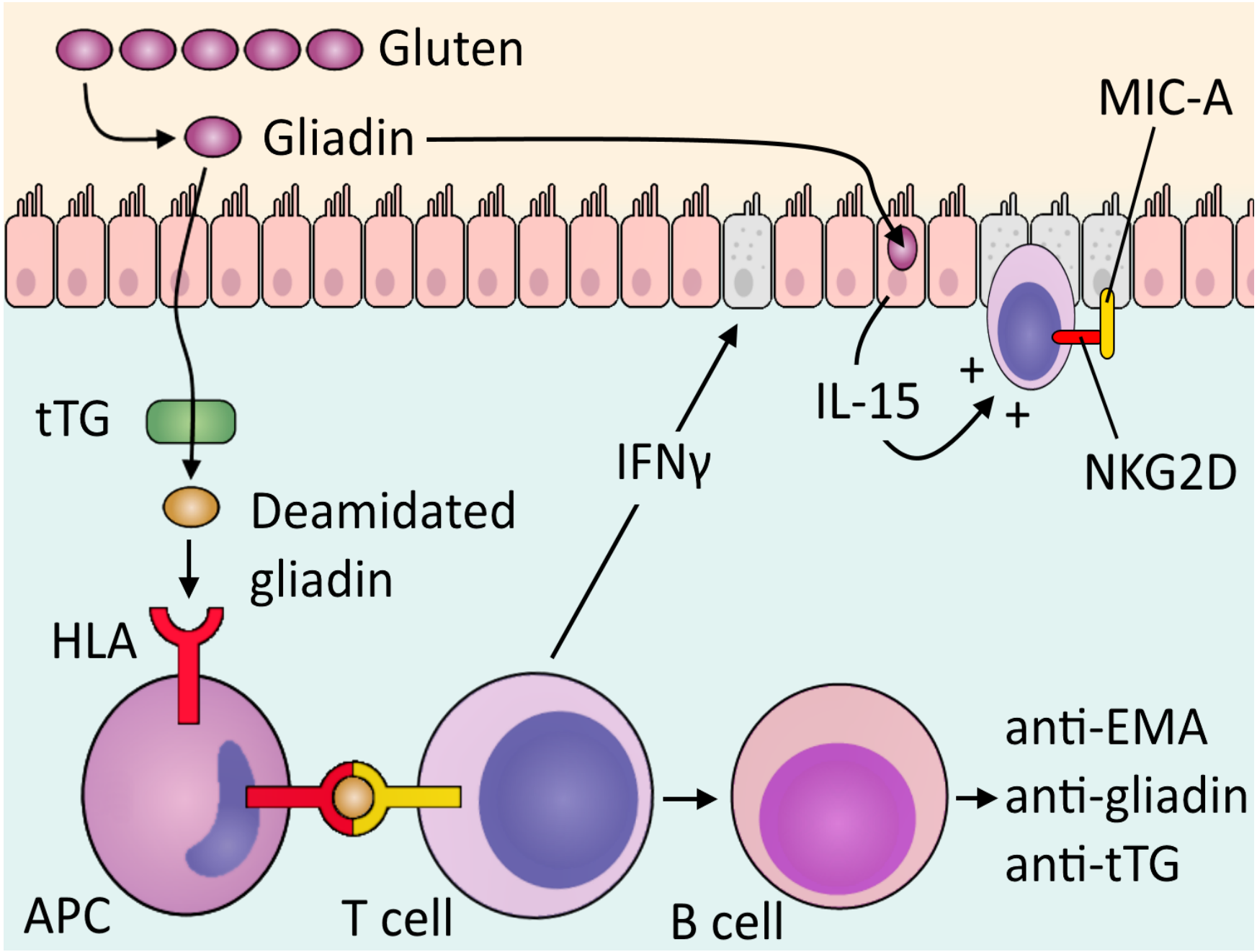



Gluten
Gliadin
tTG
Deamidated
gliadin
HLA
IFNγ
IL-15
+
+
APC
T cell
B cell
anti-EMA
anti-gliadin
anti-tTG

MIC-A, NKG2D

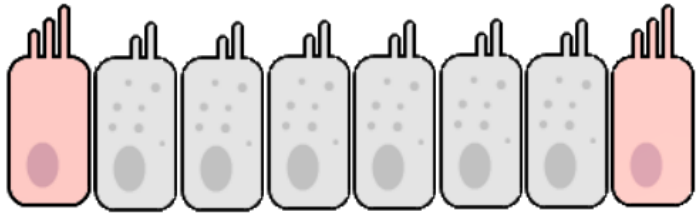
- Various stressors causes **MIC-A** to be expressed on enterocytes.
- Intraepithelial lymphocytes receive MIC-A via **NKG2D** in a **cytotoxic interaction**, killing enterocytes.

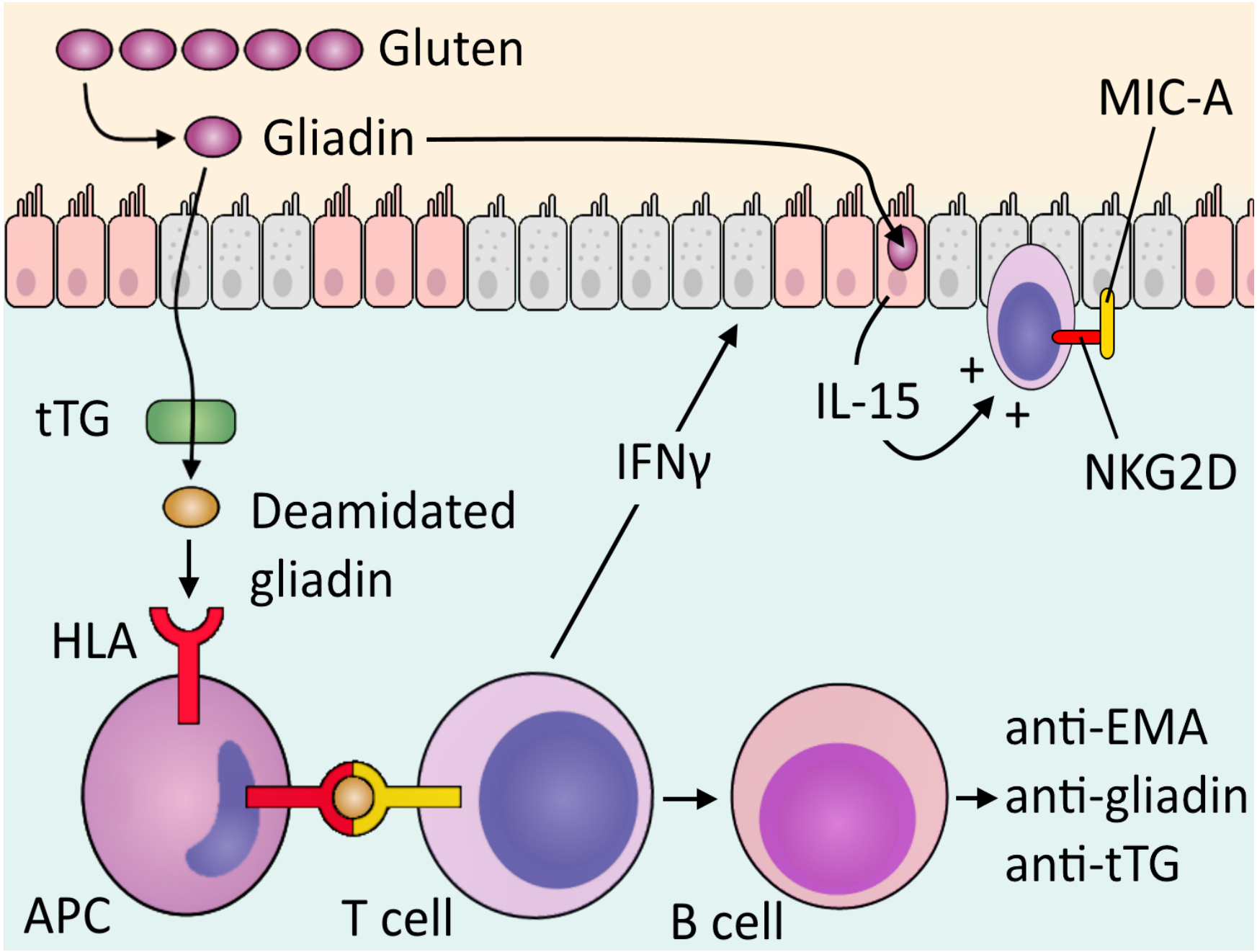



Gluten
Gliadin
MIC-A
tTG
IFNγ
IL-15
+
+
NKG2D
Deamidated
gliadin
HLA
anti-EMA
anti-gliadin
anti-tTG
APC
T cell
B cell

Progression

- Tissue damage progresses with **villous atrophy** and **loss of surface area**.
- Damage allows increased movement of gliadin across the epithelium, amplifying disease.
- An **increased rate of mitosis** is seen with **reduced enterocyte differentiation and function**.
- Tissue damage, loss of surface area, and reduced function result in **malabsorption**.



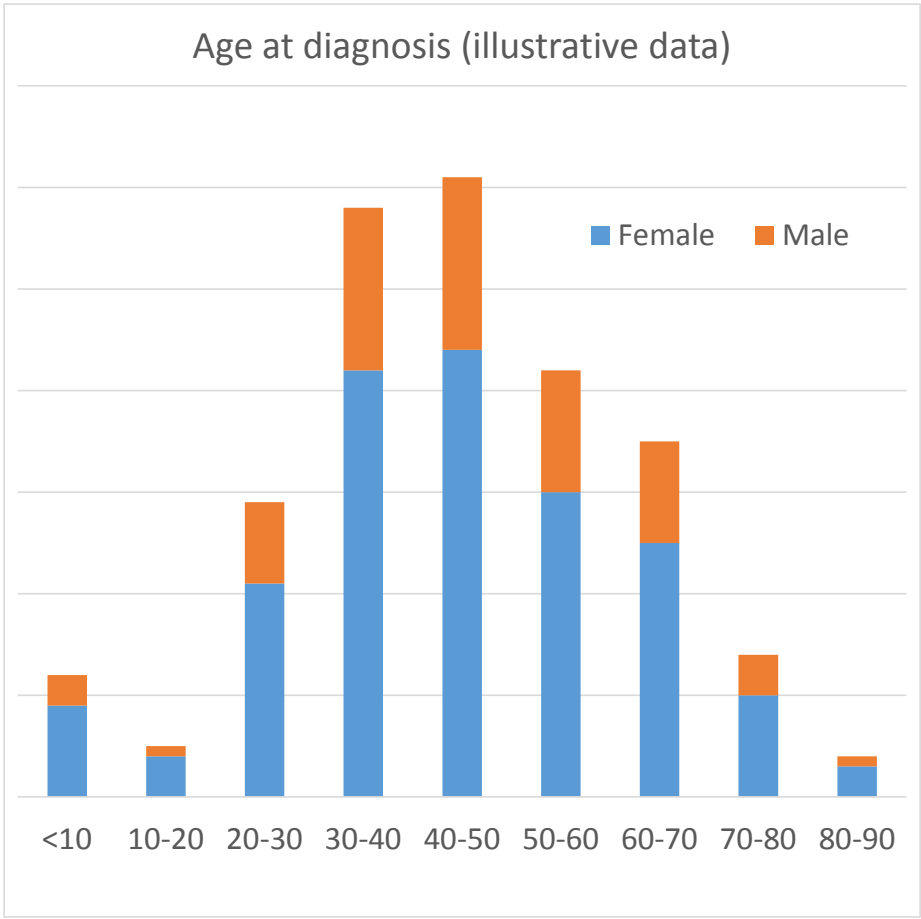

Gluten
Gliadin
MIC-A
tTG
IFNγ
IL-15
+
+
NKG2D
Deamidated
gliadin
HLA
anti-EMA
anti-gliadin
anti-tTG
APC
T cell
B cell

Clinical features

- Many **atypical presentations**, often an **incidental finding**

- Presentations most commonly **30-60y, but any age**
- Peaks in **infancy** and **50s**

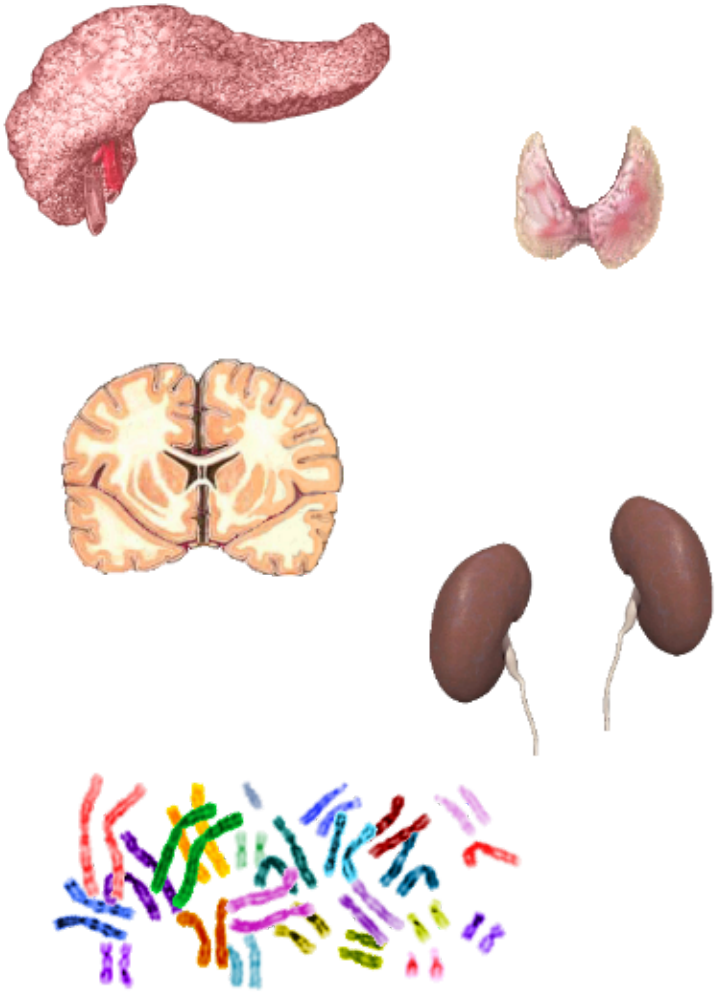
- No gender difference, but **2-3x more women detected**
  - menstrual blood loss potentiates anaemia



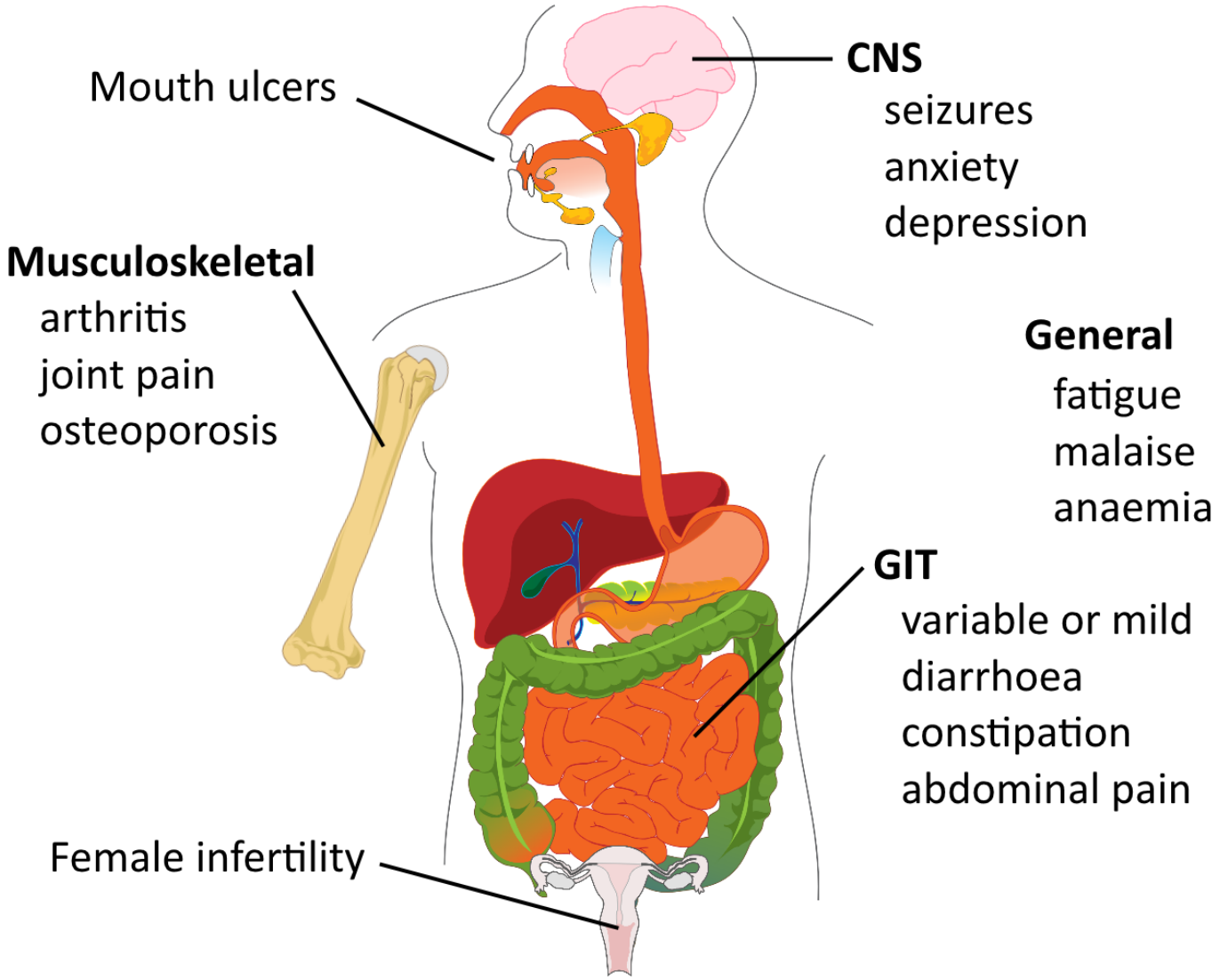
Disease associations

- **Immune diseases** and **atopy**:
  - Diabetes mellitus type 1
  - Thyroiditis
  - Sjögren syndrome

- Other diseases:
  - Epilepsy
  - IgA nephropathy
  - Down syndrome
  - Turner syndrome



Symptoms


Mouth ulcers
CNS
seizures
anxiety
depression
Musculoskeletal
arthritis
joint pain
osteoporosis
General
fatigue
malaise
anaemia
GIT
variable or mild
diarrhoea
constipation
abdominal pain
Female infertility

Malabsorption-related symptoms

Manifestation	Malabsorbed nutrient
Steatorrhoea	Fats
Diarrhoea	Fats, carbohydrates

Manifestation	Deficiency
Weight loss, wasting	Fats, proteins, carbs
Anaemia	Iron, vit B12, folic acid
Paraesthesia, tetany	Calcium, vit D
Osteoporosis, arthritis	Calcium, vit D
Bleeding, bruising	Vit K
Oedema	Protein

Dermatitis herpetiformis

- **10%** of patients
- Similar appearance to herpes
- Itchy papulovesicular rash

Paediatric

- **Classical:**
  - **6-24 months**
  - Irritability
  - Abdominal distension, diarrhoea
  - Anorexia, weight loss, failure to thrive
  - Muscle wasting

- **Non-classical:**
  - **Older** ages
  - Abdominal pain, nausea, vomiting
  - Bloating, constipation

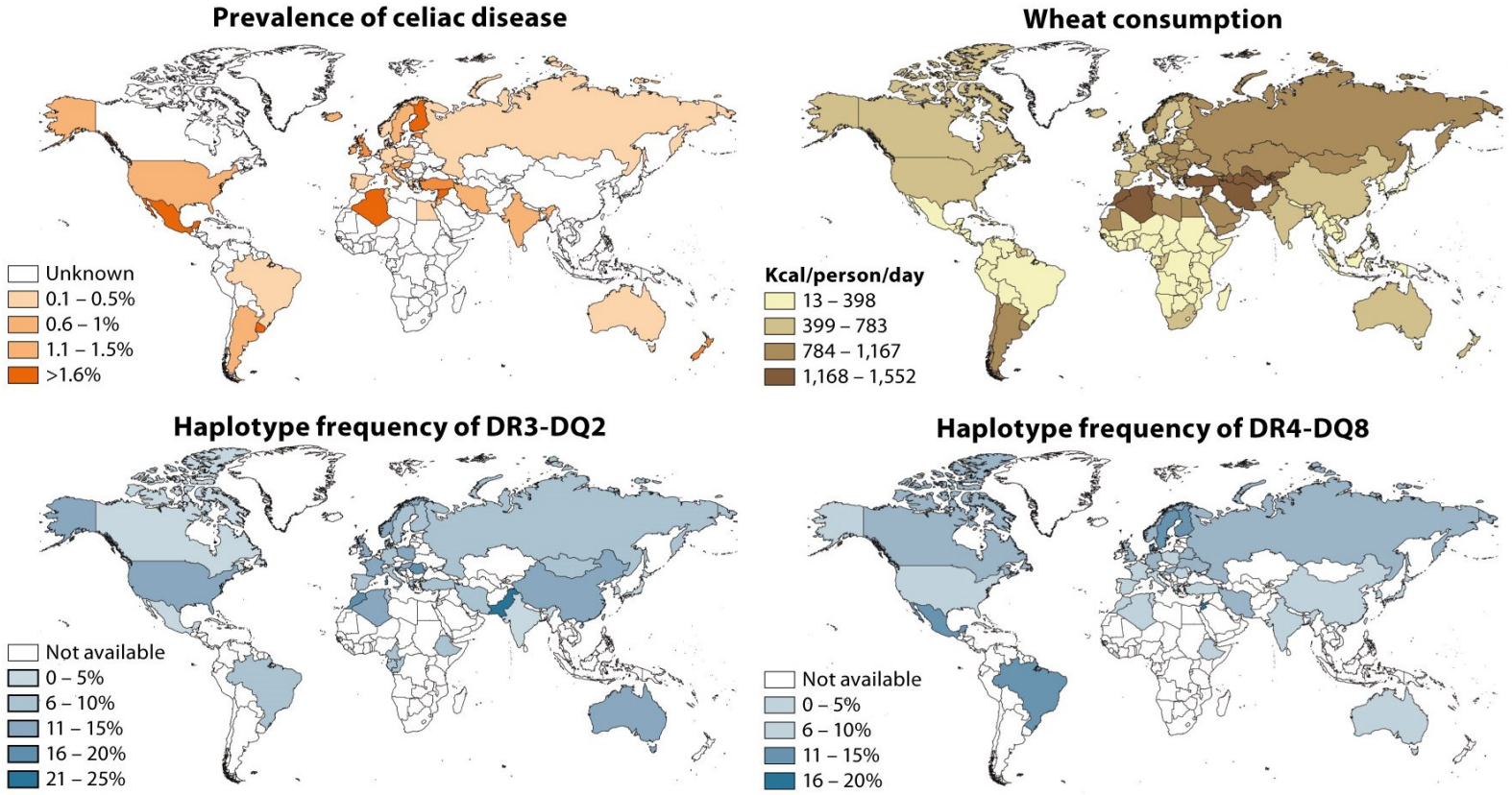
Signs

- Few and non-specific

- **Anaemia**
  - tachycardia
  - pallor
- **Bruising** (vit K deficiency)
- Hyperactive **bowel sounds**
- **Neurological** signs
- **Oedema (severe cases)**

HLA DQ2, HLA DQ8

- **95% of patients** have at least one
- accounts for 50% of genetic component



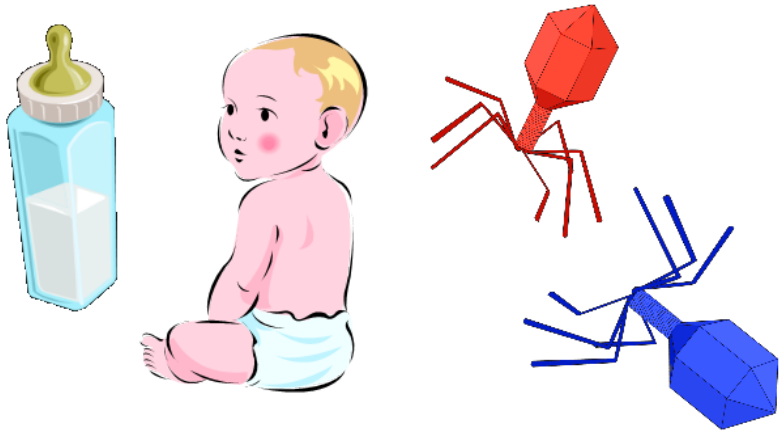
Abadie, V. et al., 2011

Other risk factors

- Other **immune system polymorphisms**:
  - e.g. IL-2, IL-21

- Other ill-defined genetic components:
  - 10-15% of 1st degree relatives (may be clinically silent)
  - 70% monozygotic twin concordance

- **Breast feeding** and **gluten introduction ages** significant
- Infant **rotavirus** infection



Serology

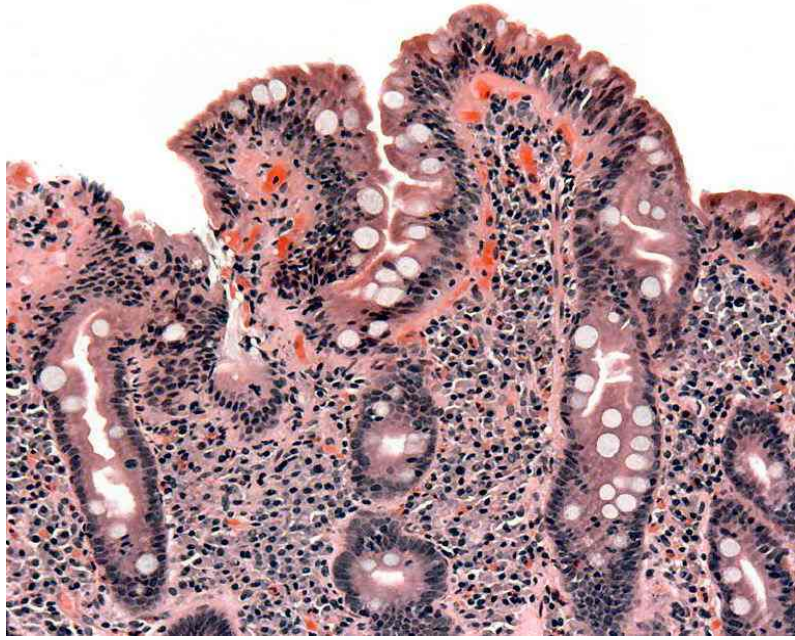
- Conduct **non-invasive** serology **before biopsy**
- Also for **dietary compliance monitoring**
- 2.5% of coeliac patients have **IgA deficiency**
  - Verify normal levels
  - Investigate IgG if IgA deficient

IgA anti-tTG	+ sensitive
IgA or IgG anti-demanidated gliadin	+ sensitive
Anti-EMA	++ specific, - sensitive
HLA DQ2/DQ8	cannot confirm diagnosis helps exclude diagnosis if negative

Biopsy

- Small bowel **endoscopic biopsy**
- 'Gold standard', but not always necessary in clear-cut cases with serology
- **Not specific**, other causes, need serology also

- Histology:
  - Sub-total **villous atrophy**
  - Increase in **lamina propria, lymphocytes, plasma cells, mast cells and eosinophils**



Acute complications

- Mostly rare
- Anecdotal intestinal obstructions and perforations

- **Coeliac crisis**
  - acute, fulminant worsening of symptoms
  - often with a gluten challenge
  - hypoproteinaemia, oedema
  - severe diarrhoea
  - dehydration, electrolyte imbalance
  - metabolic acidosis
  - hospitalisation, fluid replacement, corticosteroids

Chronic complications

- **Refractory coeliac disease** (RCD)
  - improvement with diet, then **loss of response**
  - increased **complications** (malignancy), poor prognosis

- **Malignancy** risk
  - Enteropathy-assoc. T cell lymphoma
  - Small intestinal adenocarcinoma

Chronic complications

- Ulcerative jejunitis
- Anaemia
- Female infertility
- Osteoporosis (even when on strict diet)
- Malnutrition, cachexia
- Paraesthesia, ataxia, muscle weakness
- Splenic atrophy
  - need pneumococcal vaccinations

Treated

- Initial **supplementation** of **mineral** and **vitamin** body stores

- **Gluten-free diet**
  - Improvement in symptoms within days/weeks
  - Improvement in morphology after months
  - **Long-term survival**, unrelated mortality
  - **Challenging** and **costly** to maintain

- **Long-term risk** of small intestinal and oesophageal **malignancy**

Untreated

- **Poor compliance** relatively common

- Elaboration of **malabsorption features**
- Severe **diarrhoea**
  - dehydration, electrolyte imbalances
- **Osteoporosis**
- **Malignancy**
- **Neurological**, **psychiatric** complications

- Children
  - growth retardation
  - short stature
- Pregnancy
  - miscarriage
  - congenital malformations