

# **Seric Zonulin, A Modulator of Tight Junctions Permeability, Is Increased in Different Autoimmune Disorders**

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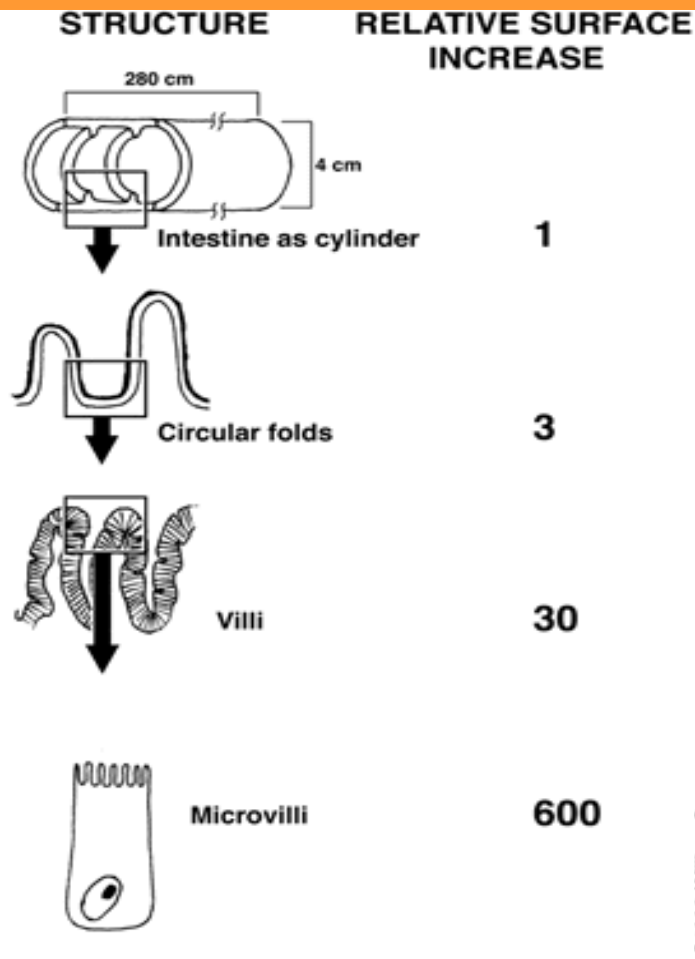
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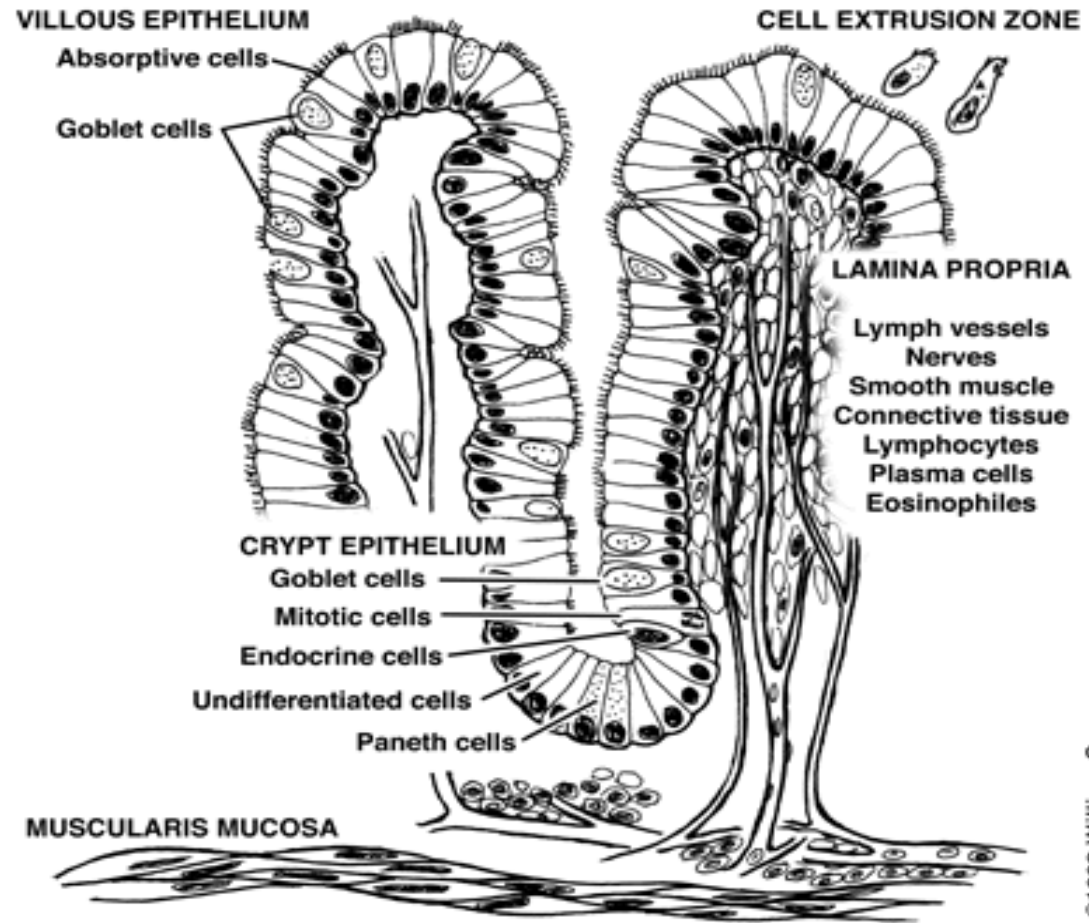
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# The intestinal epithelium is the largest mucosal surface that provides an interface between the external environment and the mammalian host



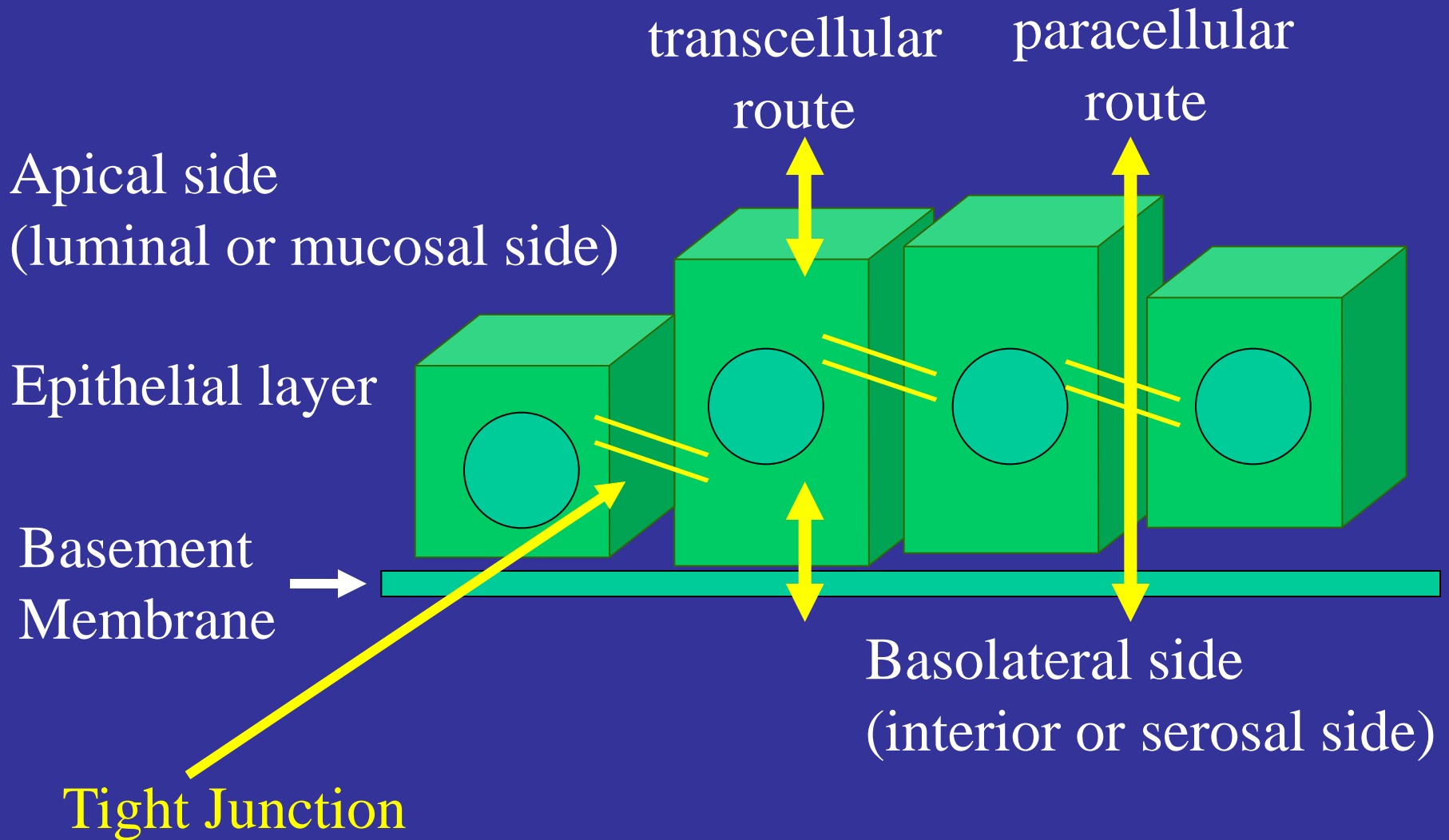
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Under physiological circumstances the intestinal barrier is impermeable to macromolecules

The paracellular route is the dominant pathway for passive solute flow and it is regulated by intercellular tight junctions



## ***BACTERIAL TOXINS***

**Bacteriodes fragilis (metalloprotease toxin)**

**Clostridium difficile (toxins A, B)**

**Clostridium perfringens (enterotoxin)**

**E. coli (cytotoxic necrotizing factor 1)**

**Helicobacter pylori (vacuolating toxin)**

**Listeria monocytogenes (internalin)**

**Vibrio cholerae (zonula occludens toxin)**

## ***INFECTIONS:***

•E.Coli

•Rotavirus

•Salmonella Ty.

•HIV

## ***DRUGS:***

•alcohol

•NSAID

•Tacrolimus

**Tight Junction  
dysfunction**

## ***AUTOIMMUNE DISORDERS:***

**Celiac disease**

**Inflammatory bowel diseases**

**Ankylosing spondylitis**

**Multiple Sclerosis**

**Diabetes Mellitus**

**IgA nephropathy**

# Zonulin, a newly discovered modulator of intestinal permeability, and its expression in celiac disease

*(Fasano A. et al, Lancet 2000)*

- While major progress has been recently made on the composition of tight junctions, limited information were available on the mechanisms of regulation
- The discovery of zonulin, a novel human protein which induces tight junction disassembly, has shed some lights on the physiological regulation of intercellular tight junctions
- Zonulin expression has been found increased in intestinal tissues during the acute phase of celiac disease, a clinical condition in which tight junctions are opened and permeability is increased.
- This up-regulation suggested a possible causal role of zonulin in celiac disease pathogenesis.

# Aims

- To investigate zonulin serum concentration in celiac disease and in a large group of patients with different autoimmune disorders :

	No.
– Celiac Disease	52
– Autoimmune Hepatitis	26
– Primary Biliary Cirrhosis	37
– Insulin-Dependent Diabetes Mellitus	28
– Autoimmune Polyglandular Syndrome Type 1	16
– Multiple Sclerosis	41

# Methods

- Zonulin serum concentration was measured by a quantitative sandwich enzyme-linked immunosorbent assay
- Total serum proteins were measured by Bradford's assay
- Zonulin concentration was expressed as ng/mg of total serum proteins
- HLA typing was performed by amplification of the polymorphic second exon of DRB1, DQA1, DQB1 genes. Amplified DNA was analysed by dot-blot with sequence-specific oligonucleotide probes

# Aims

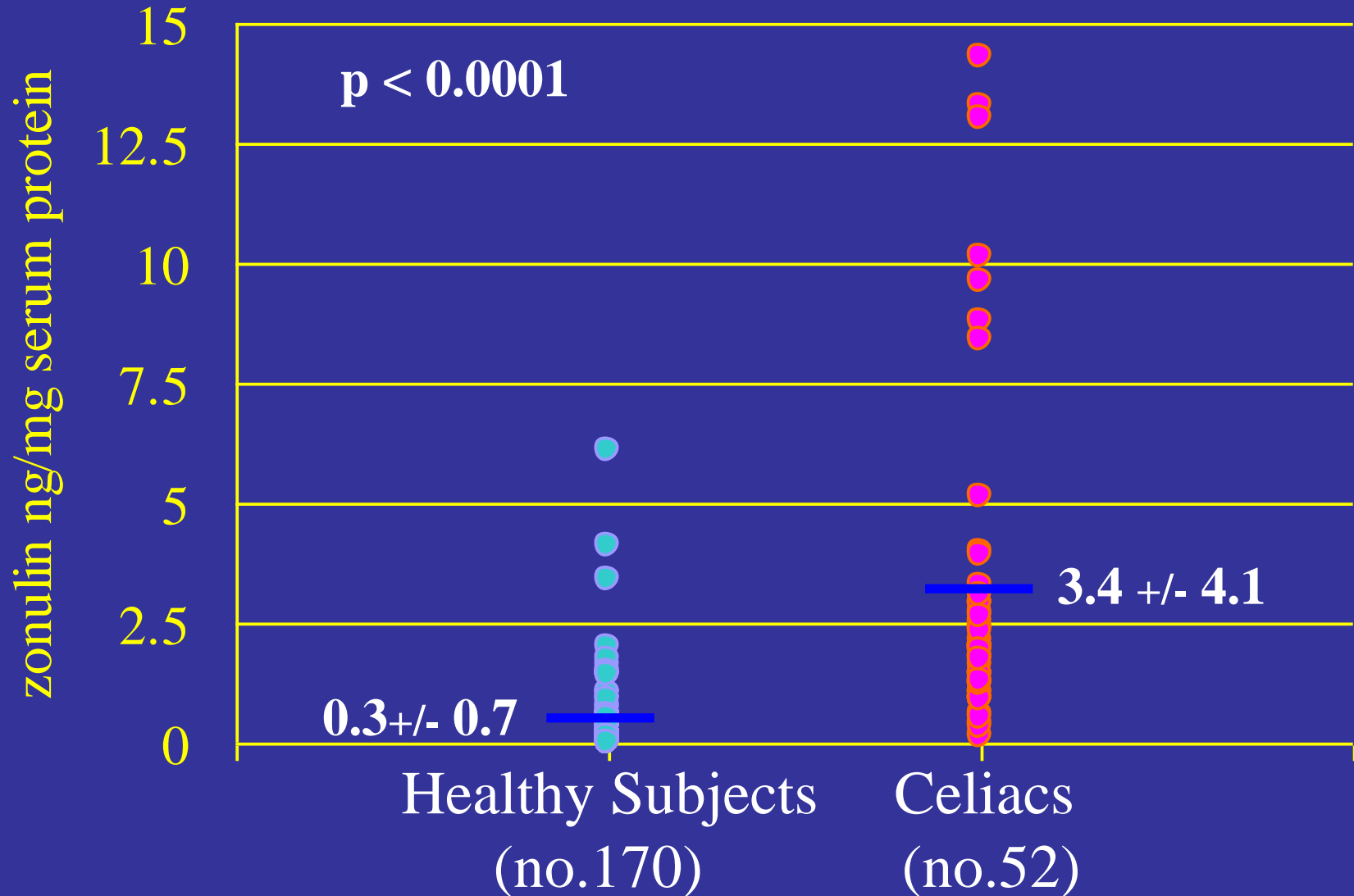
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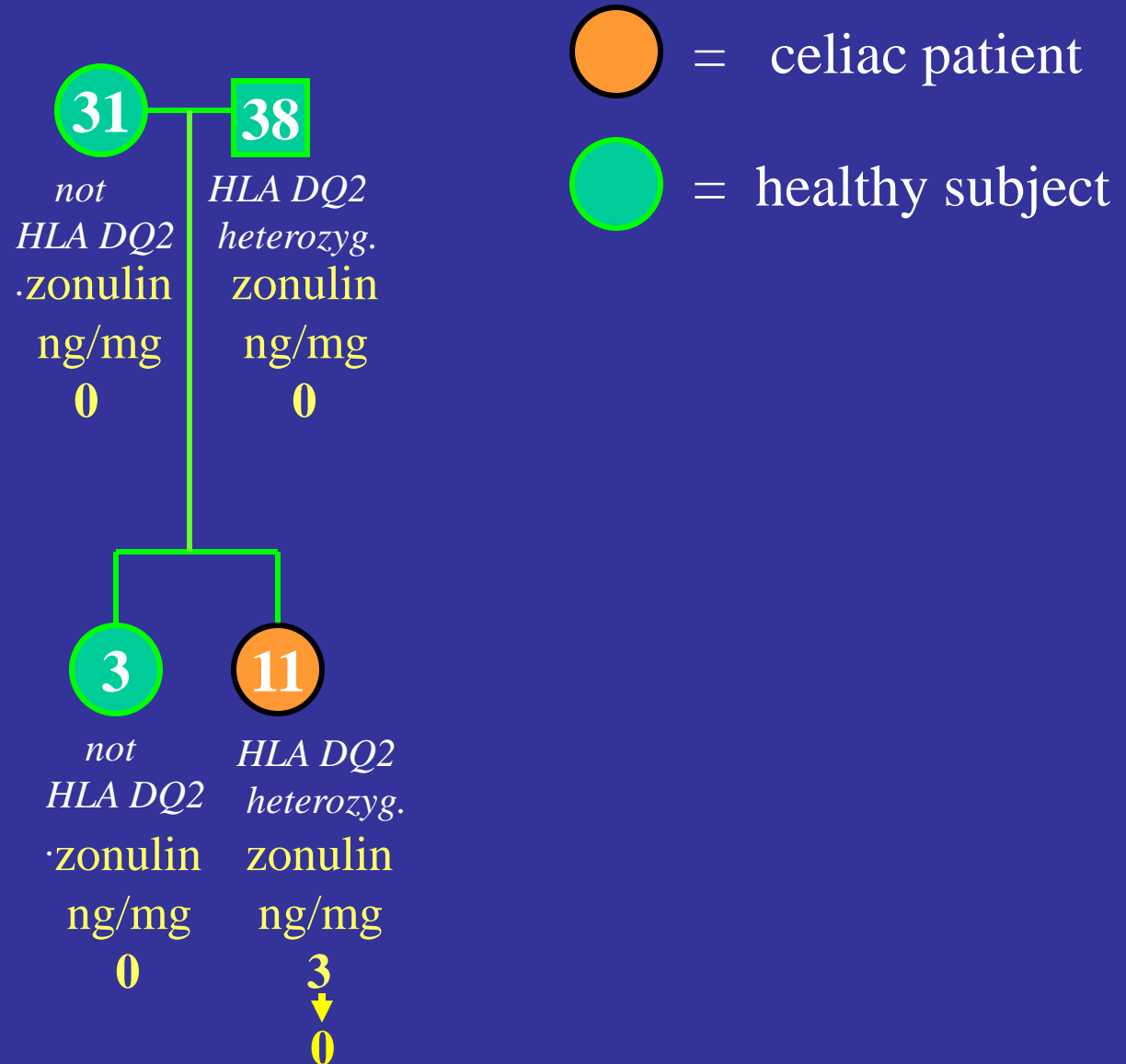
# Results

Serum zonulin concentration in healthy subjects and celiacs



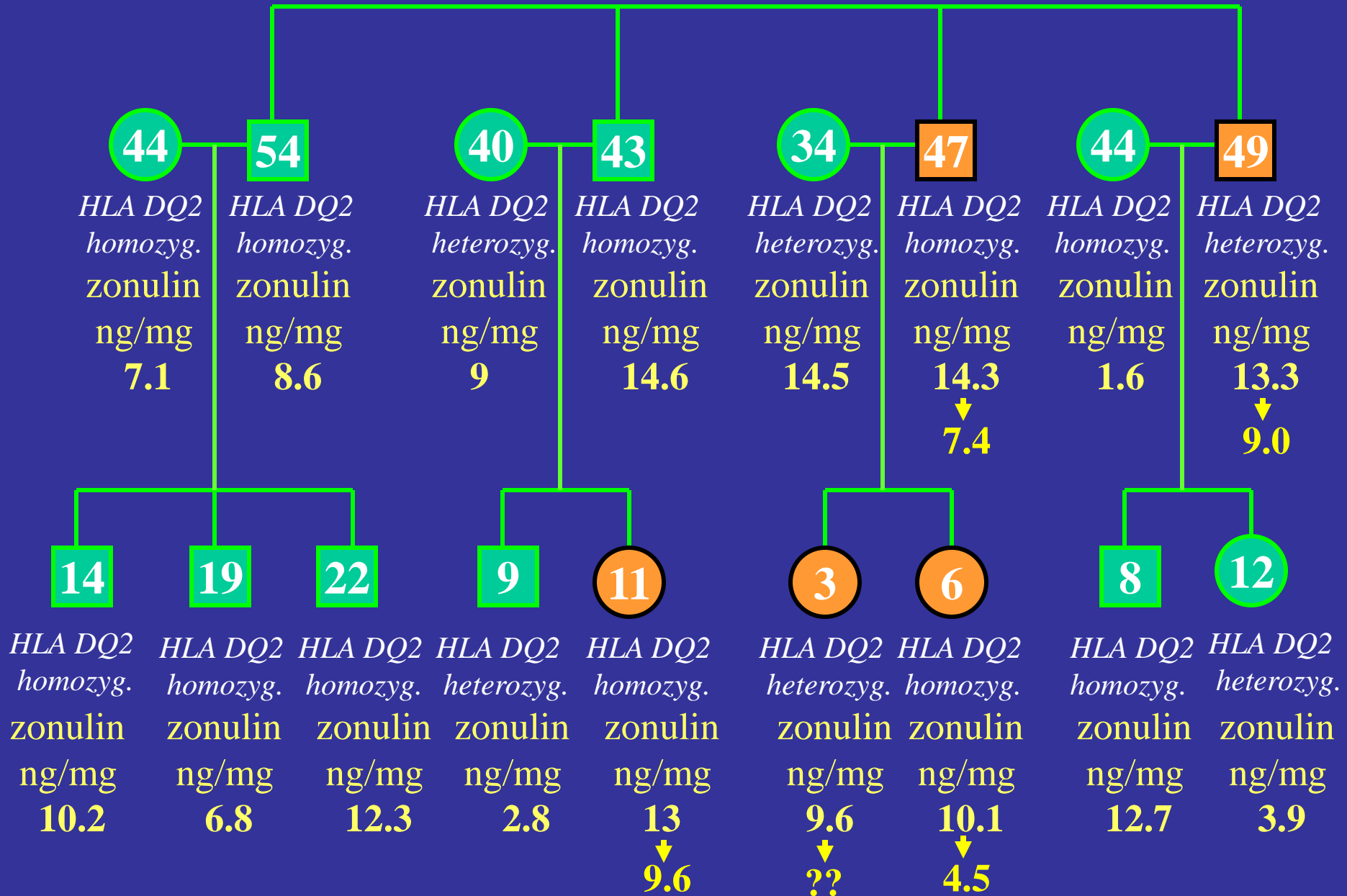
# Results

## zonulin expression in 1<sup>st</sup> degree CD family members



# Results

zonulin expression in 1<sup>st</sup> degree CD family members



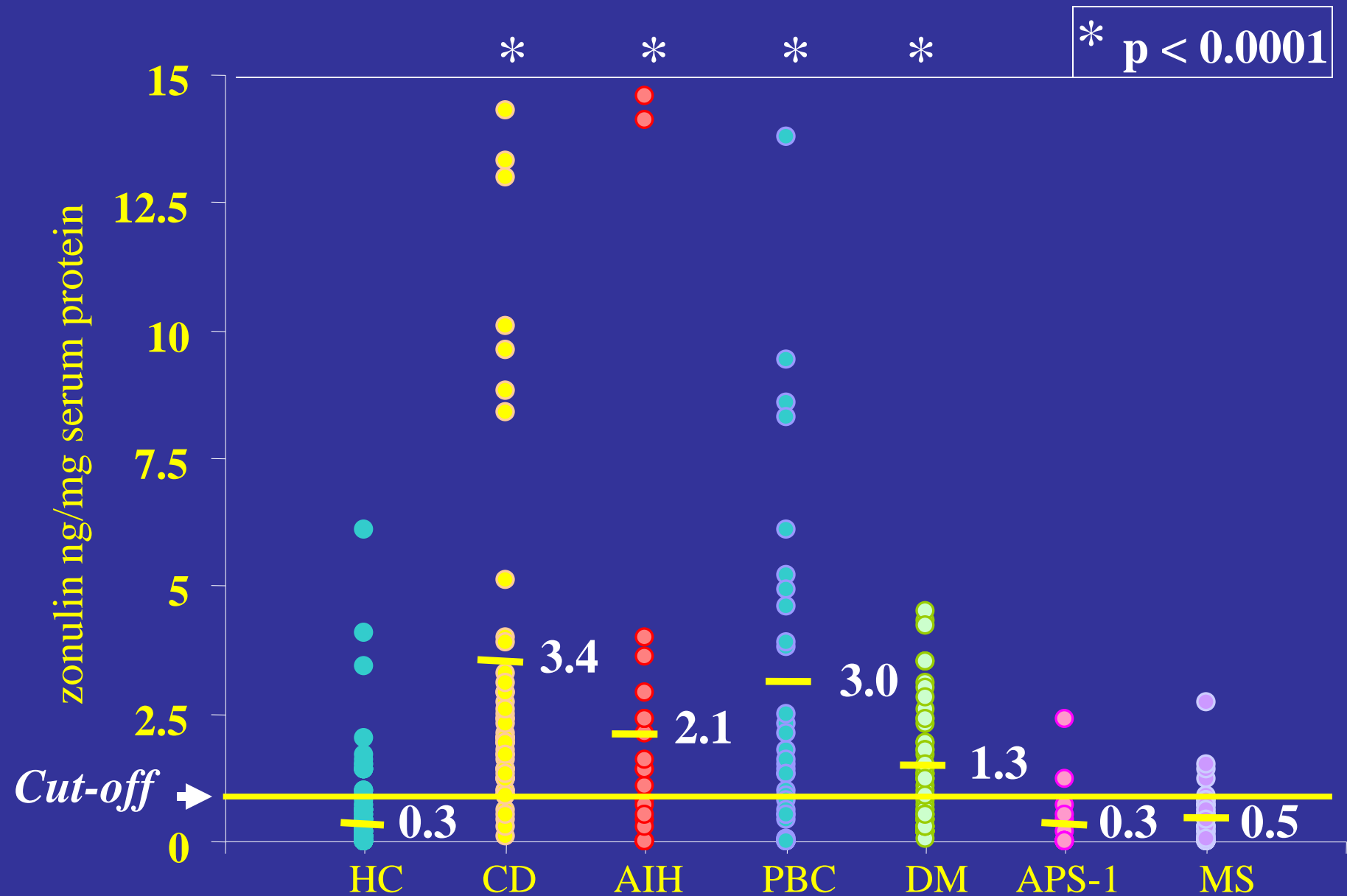
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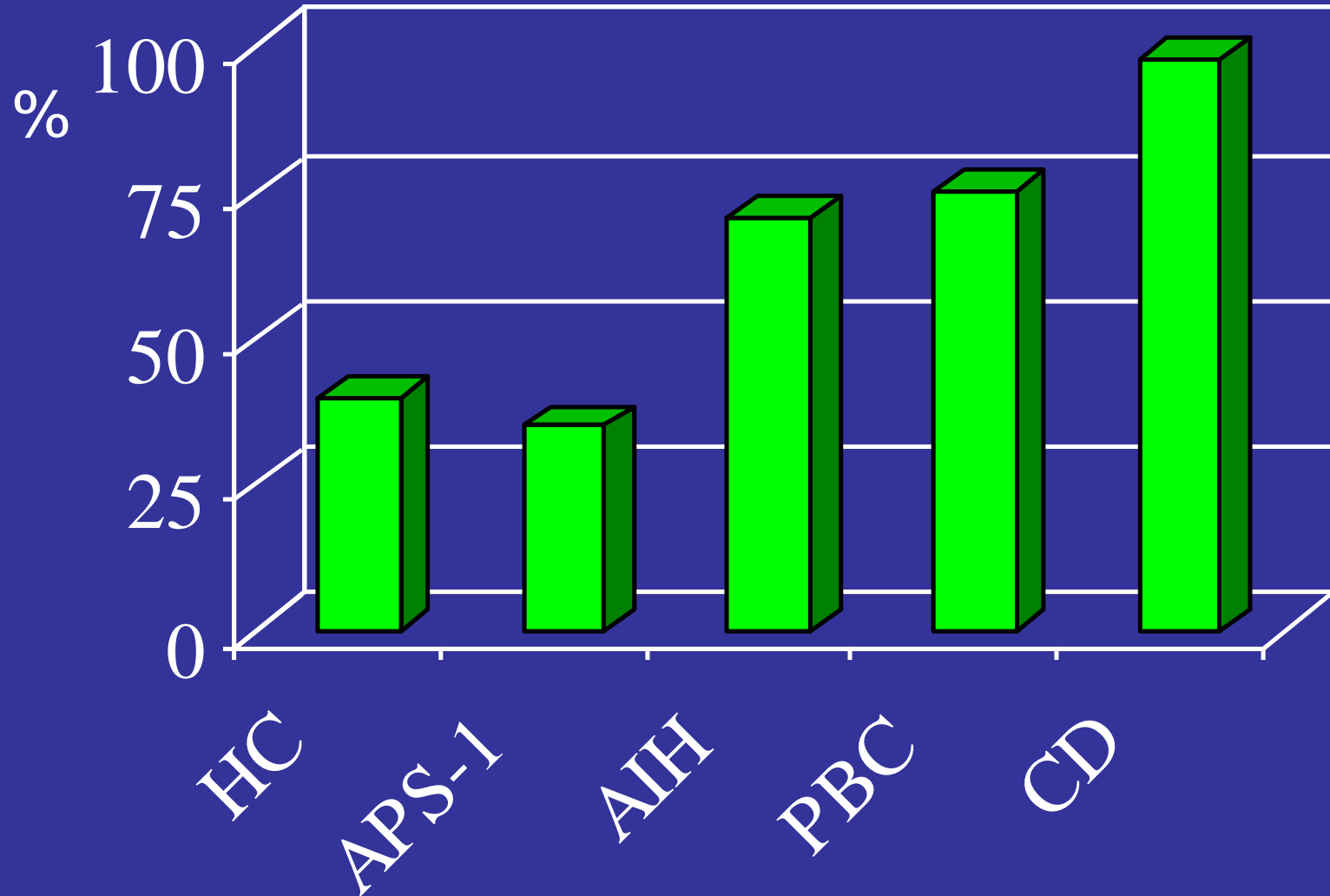
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## Serum zonulin concentration in different autoimmune disorders

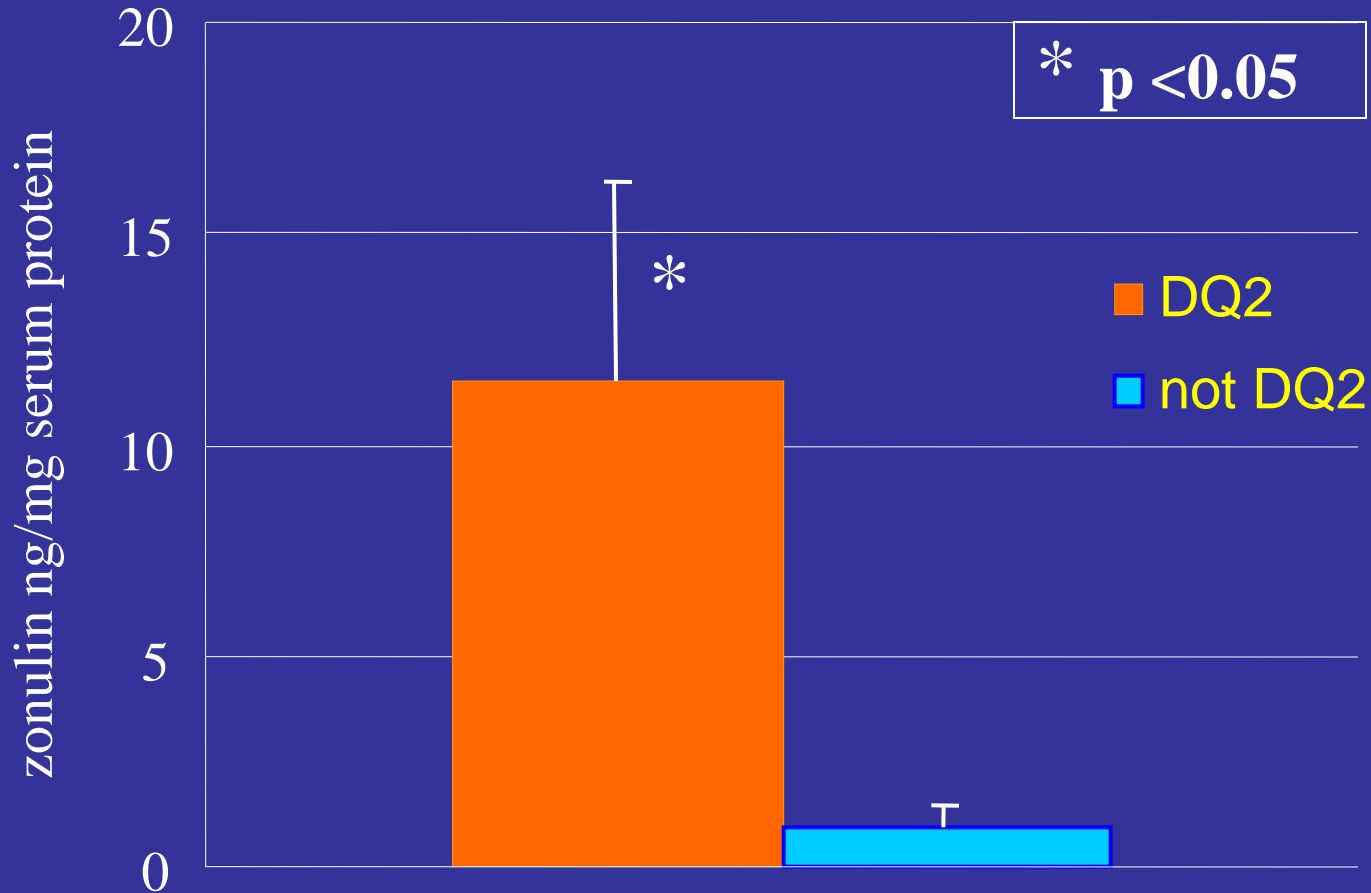


## Results

Percent of HLA DQ2 carriers among Sardinian healthy and autoimmune disease groups



# Zonulin serum concentration in HLA DQ2-positive and HLA DQ2-negative patients



# CONCLUSIONS

- Zonulin expression was:
  - significantly higher in celiac patients than healthy controls
  - very high also in the 1<sup>st</sup> degree family healthy members, suggesting that its up-regulation is a necessary but not sufficient predisposing condition for autoimmune diseases;
  - significantly higher in patients affected by other autoimmune disorders, such as:
    - Insulin-Dependent Diabetes Mellitus
    - Primary Biliary Cirrhosis
    - Autoimmune Hepatitis
  - significantly associated with the HLA DQ2 heterodimer.



# CONCLUSIONS

- High values of zonulin might cause increased intestinal permeability with abnormal antigen delivery across the intestinal mucosa, triggering specific autoimmune reactions in genetically predisposed subjects.
- A dysregulation of zonulin expression might represent a common predisposing state for many autoimmune diseases in which increased intestinal permeability has been described.