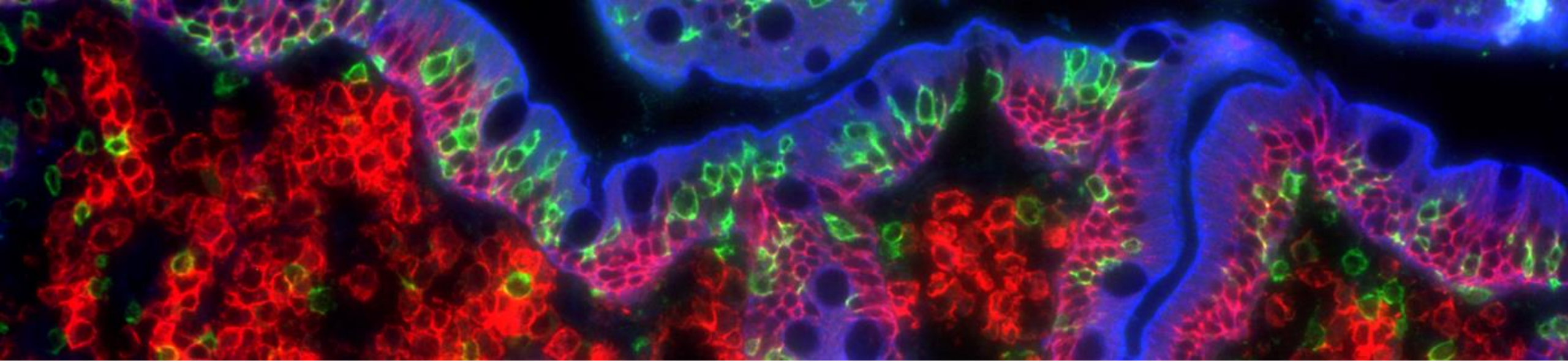

Genetics of celiac disease

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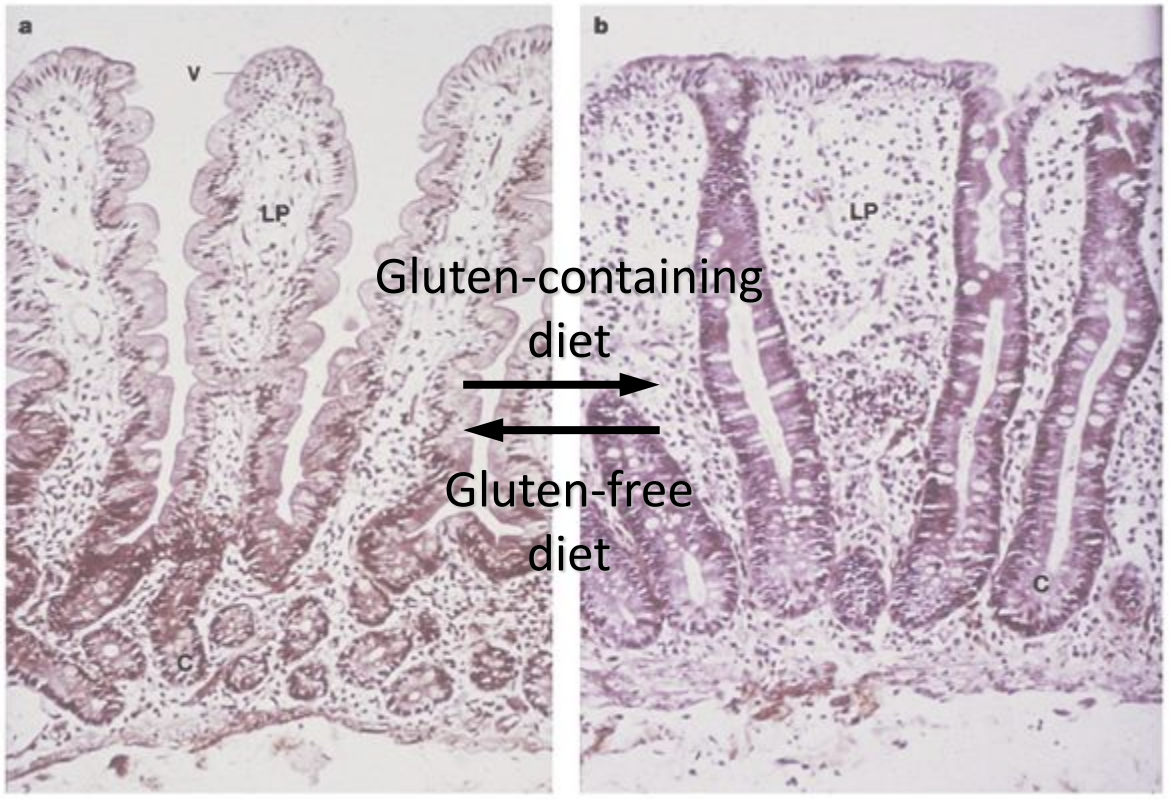
Norwegian Coeliac Disease Research Centre

Oslo University Hospital and University of Oslo

Oslo University Hospital

UiO : University of Oslo

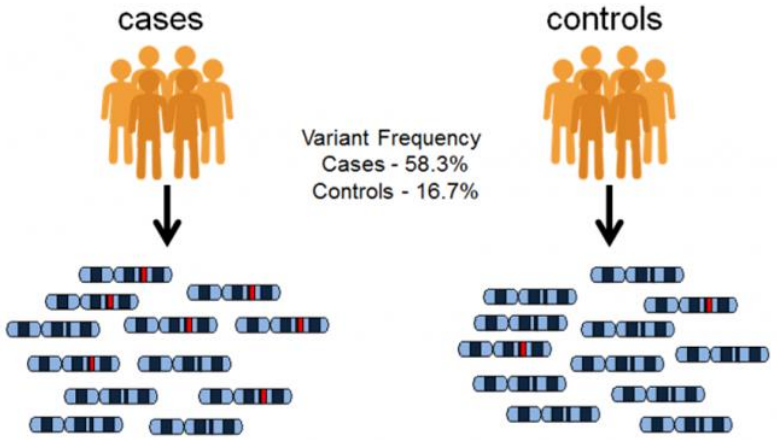
Celiac disease

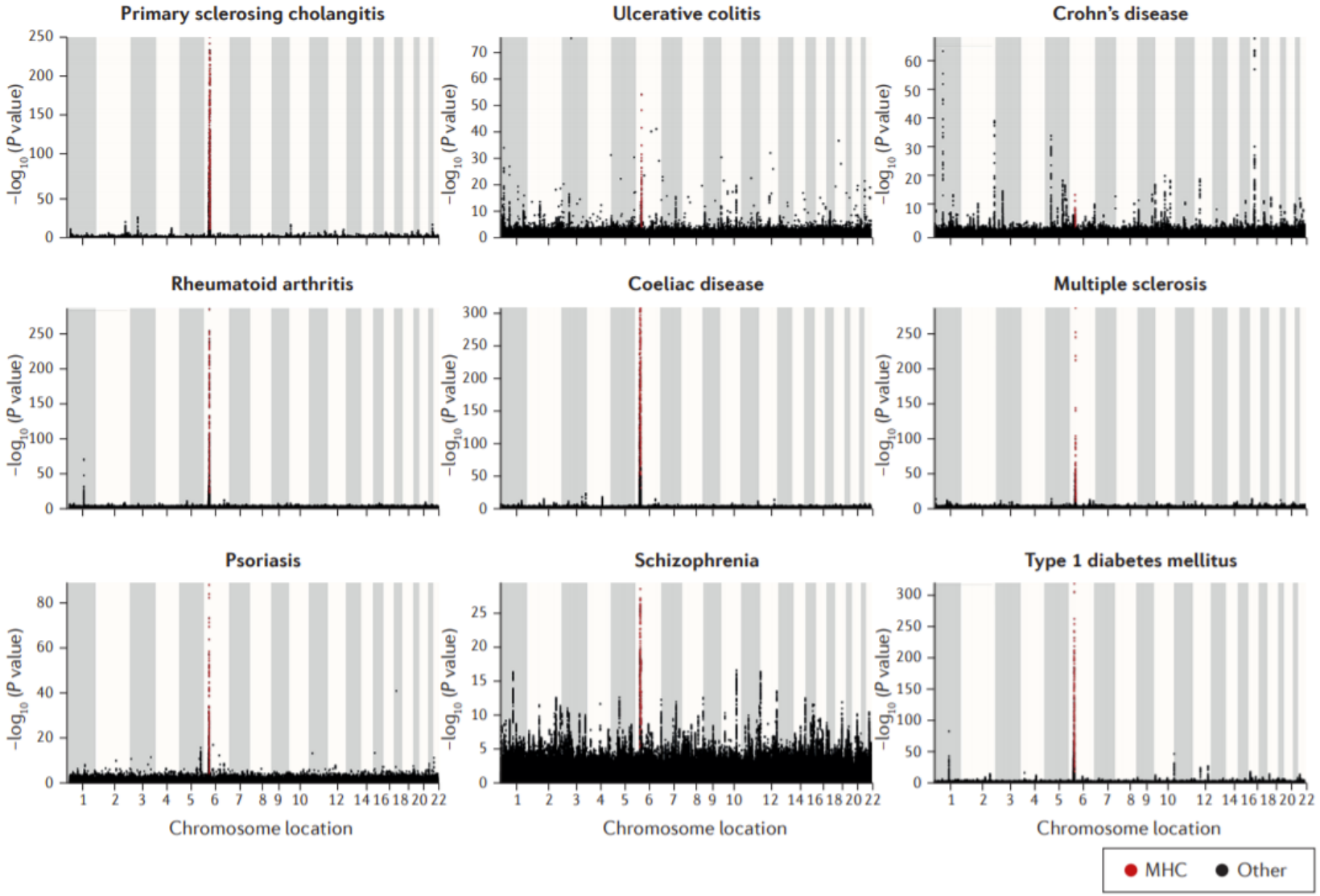


- Inflammation of the small intestine in genetically susceptible individuals.
- Caused by inappropriate immune response against gluten proteins in food.
- Leads to killing of intestinal epithelial cells, villous atrophy, malabsorption.

HLA and autoimmunity

Genome-wide association studies (GWAS)

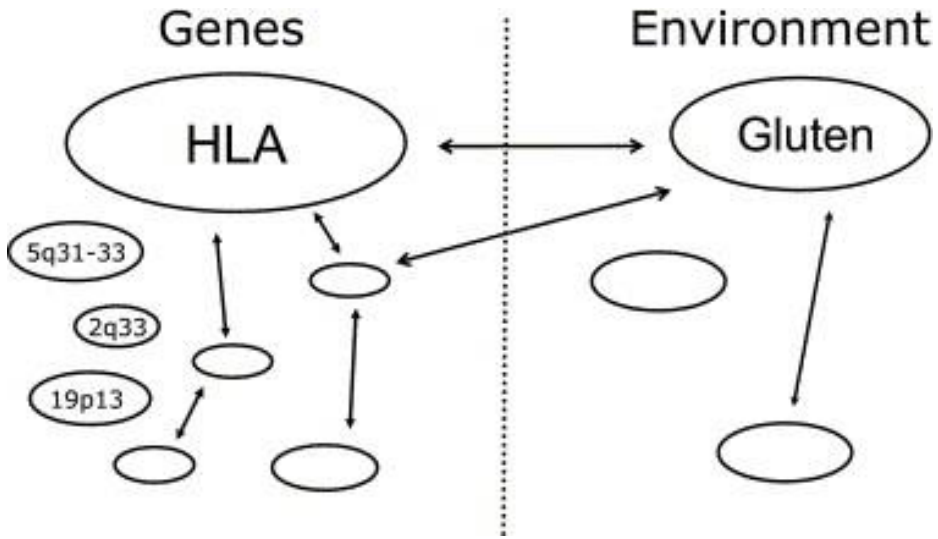




Jiang & Karlsen, Nat Rev Gastroenterol Hepatol, 2017

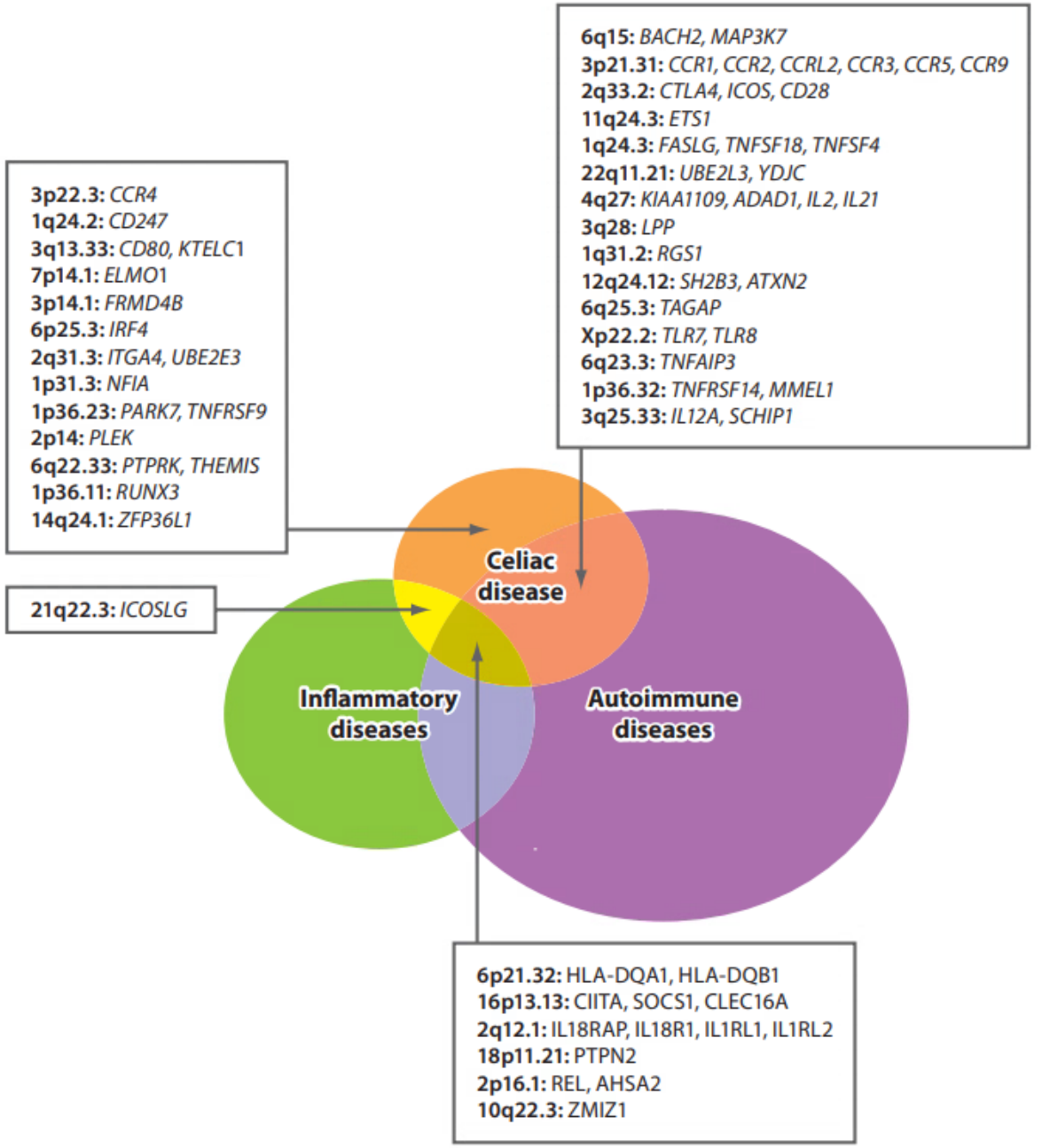
Genetics

- High concordance rate in monozygotic twins, 50-80%.
- Both HLA and non-HLA genes (>40).
- Effect of HLA dominates.
- Missing heritability (~50%).



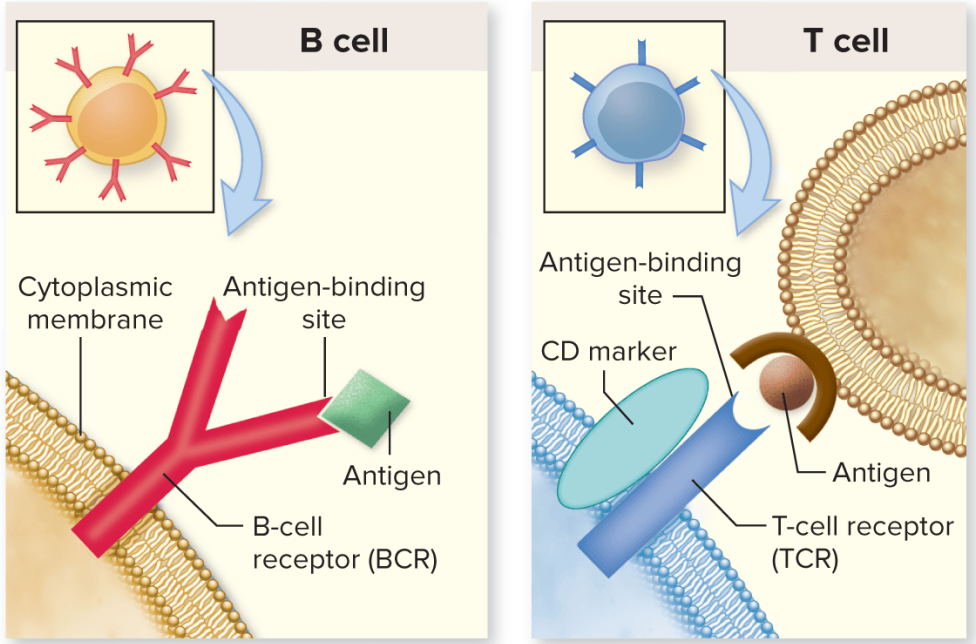
Non-HLA genes

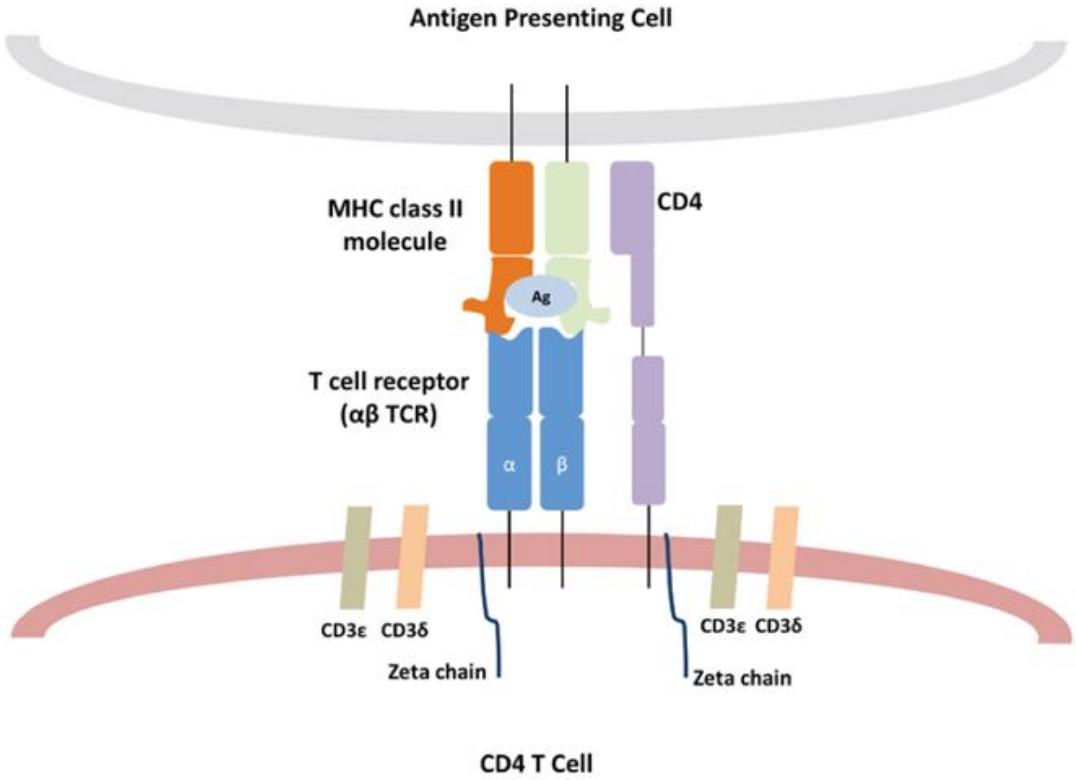
- 95% of SNPs in non-coding regions.
- Genes in associated regions implicated in lymphocyte activation and trafficking.
- Points to an important role of CD4+ T cell activation.



Abadie et al., Annu Rev Immunol, 2011

Antigen receptors on B and T cells

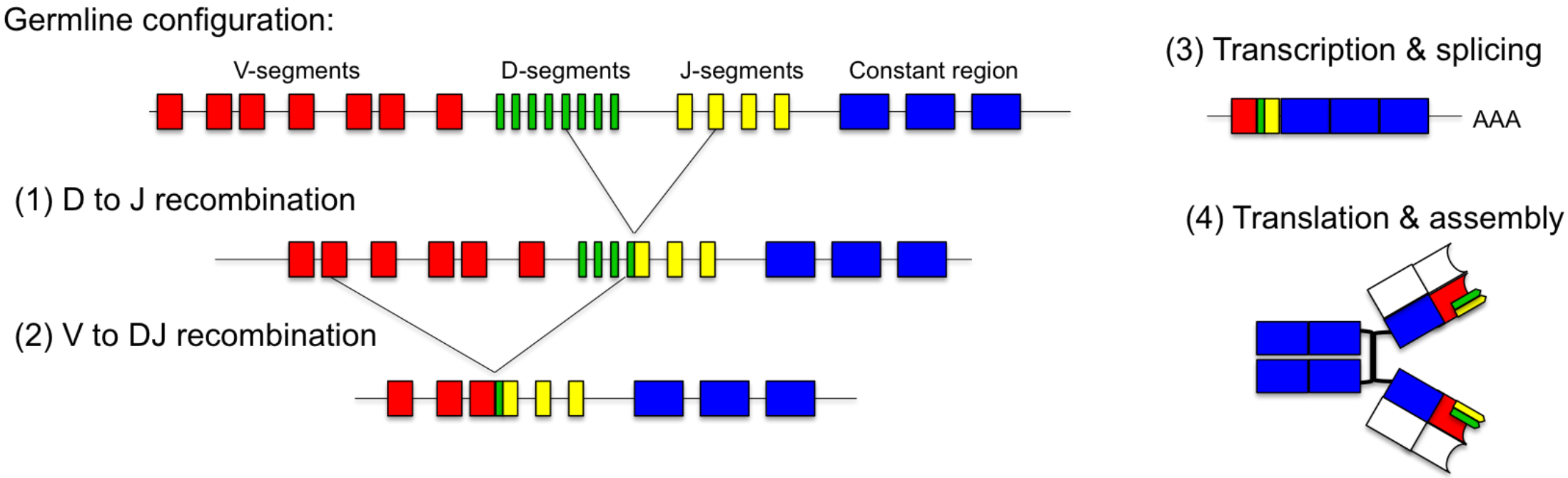




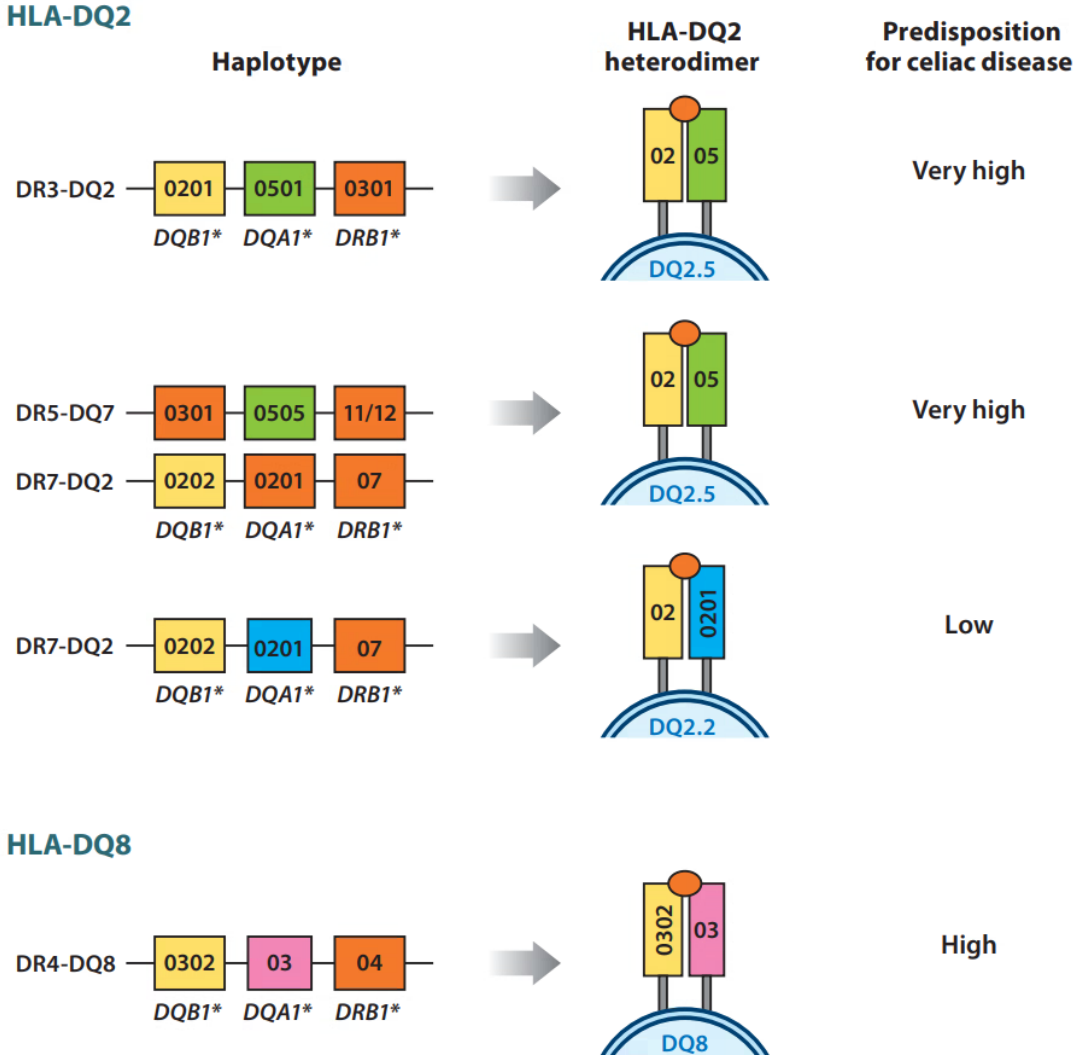
Activation, proliferation

Generation of antigen receptors: V(D)J recombination

- Same mechanism in B and T cells
- Each new cell gets a unique antigen receptor → collection = repertoire
- Theoretically >10^{15} unique receptors



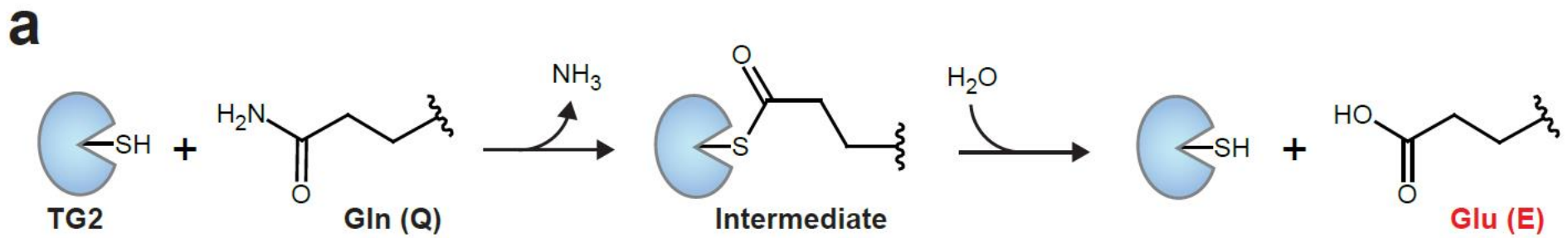
HLA molecules associated with celiac disease

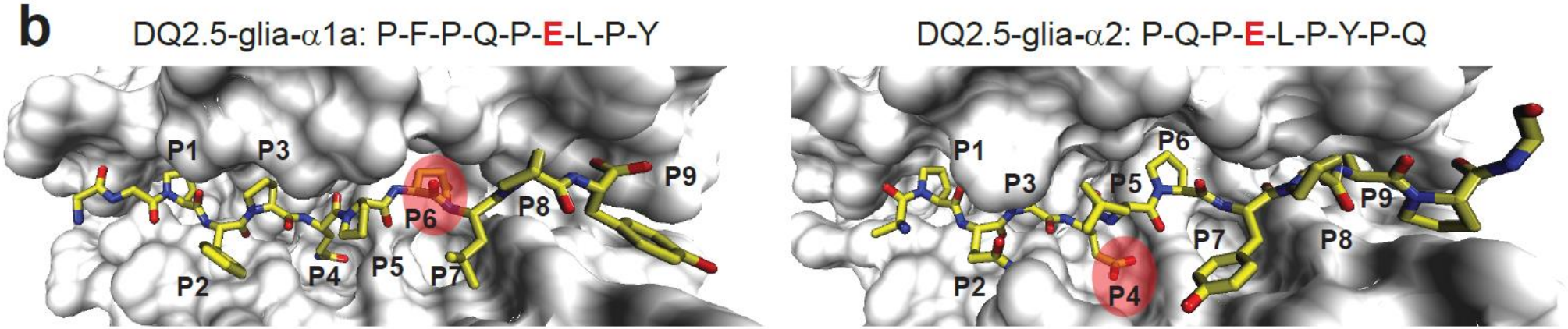


Epitope*	Previous names	Peptide-binding register† 1	2	3	4	5	6	7	8	9
DQ2.5 restricted epitopes										
DQ2.5-glia-α1a	DQ2-α-I, α9	P	F	P	Q	P	**E**	L	P	Y††
DQ2.5-glia-α1b	DQ2-α-III	P	Y	P	Q	P	**E**	L	P	Y
DQ2.5-glia-α2	DQ2-α-II, α2	P	Q	P	**E**	L	P	Y	P	Q
DQ2.5-glia-α3	glia-α20	F	R	P	**E**	Q	P	Y	P	Q
DQ2.5-glia-γ1	DQ2-γ-I	P	Q	Q	S	F	P	**E**	Q	Q
DQ2.5-glia-γ2	DQ2-γ-II, γ30	I	Q	P	**E**	Q	P	A	Q	L
DQ2.5-glia-γ3	DQ2-γ-III	Q	Q	P	**E**	Q	P	Y	P	Q
DQ2.5-glia-γ4a	DQ2-γ-IV	S	Q	P	**E**	Q	**E**	F	P	Q
DQ2.5-glia-γ4b	DQ2-γ-VIIc	P	Q	P	**E**	Q	**E**	F	P	Q
DQ2.5-glia-γ4c	DQ2-γ-VIIa	Q	Q	P	**E**	Q	P	F	P	Q
DQ2.5-glia-γ4d	DQ2-γ-VIIb	P	Q	P	**E**	Q	P	F	C	Q
DQ2.5-glia-γ4e§		L	Q	P	**E**	Q	P	F	P	Q
DQ2.5-glia-γ5	DQ2-γ-VI	Q	Q	P	F	P	**E**	Q	P	Q
DQ2.5-glia-ω1	DQ2-ω-I	P	F	P	Q	P	**E**	Q	P	F
DQ2.5-glia-ω2	DQ2-ω-II	P	Q	P	**E**	Q	P	F	P	W

Molecular basis for HLA association

- Preference for negatively charged peptides.
- Gluten deamidation mediated by transglutaminase 2 (TG2).

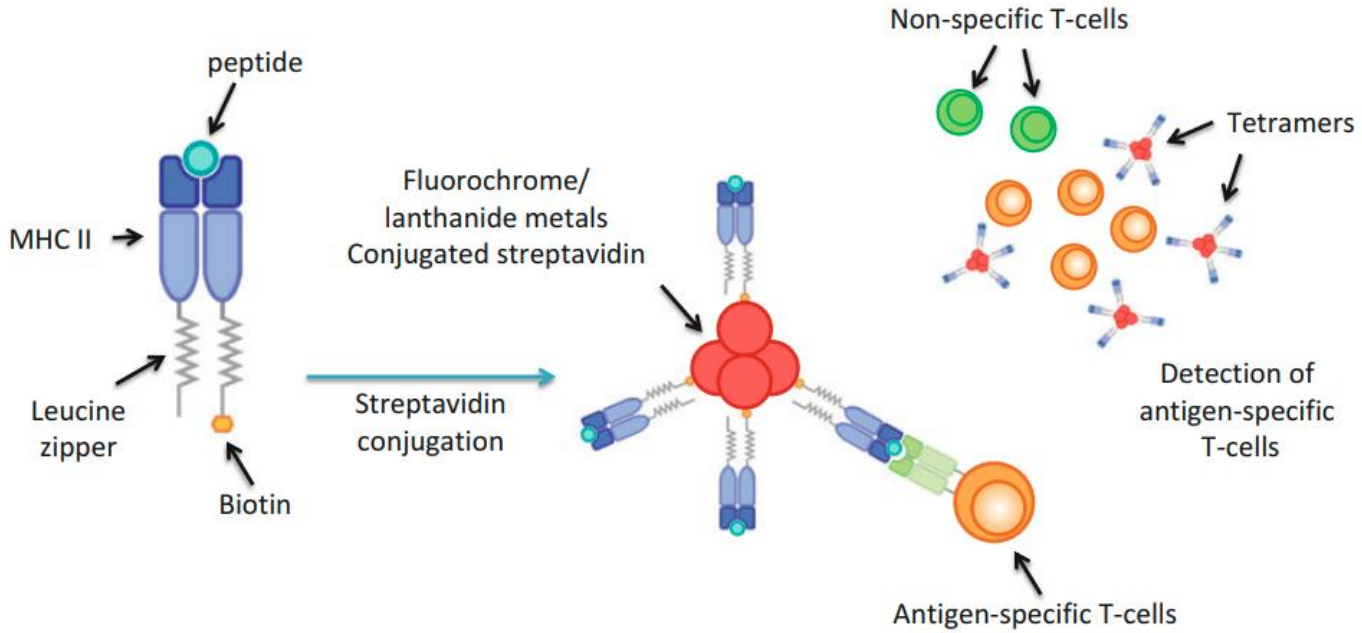


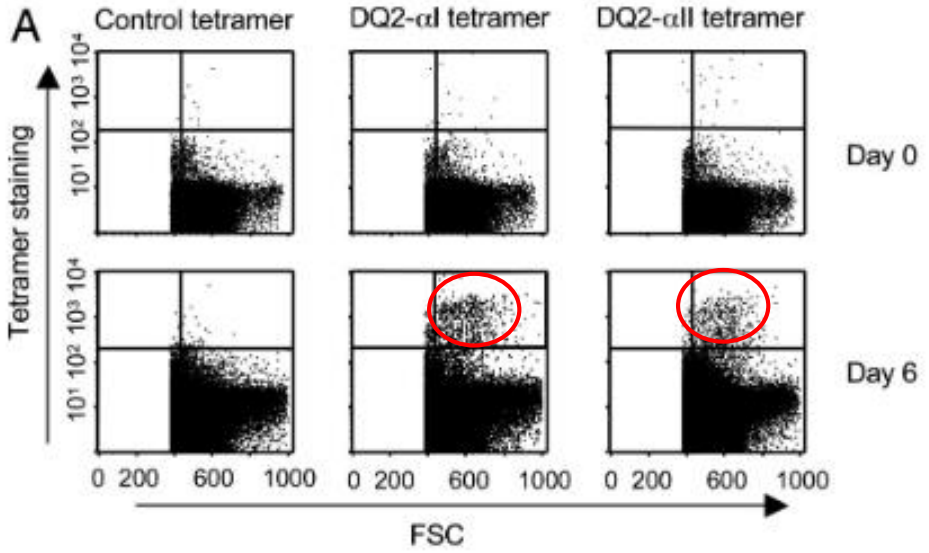


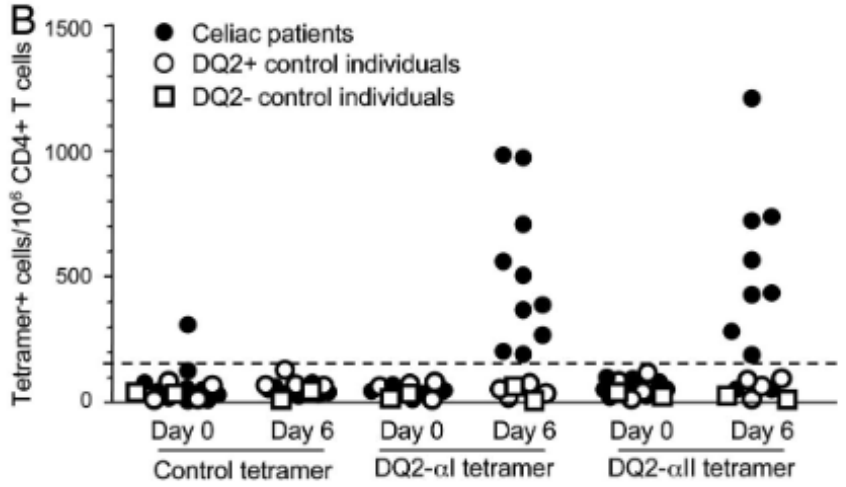
Detection of gluten-specific T cells

Advantages of studying celiac disease:

- Well-defined antigens.
- Good access to the disease lesion.
- Response can be turned on/off.

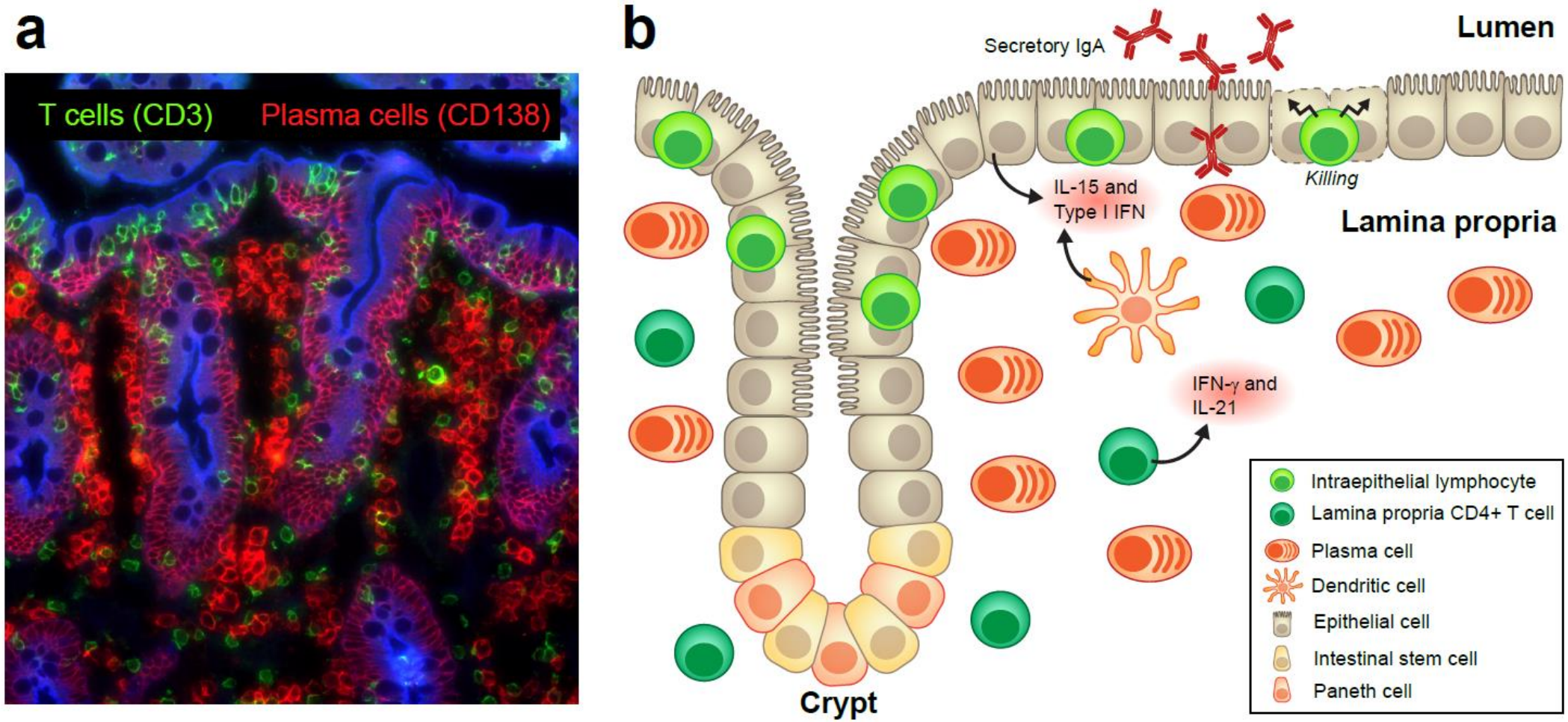






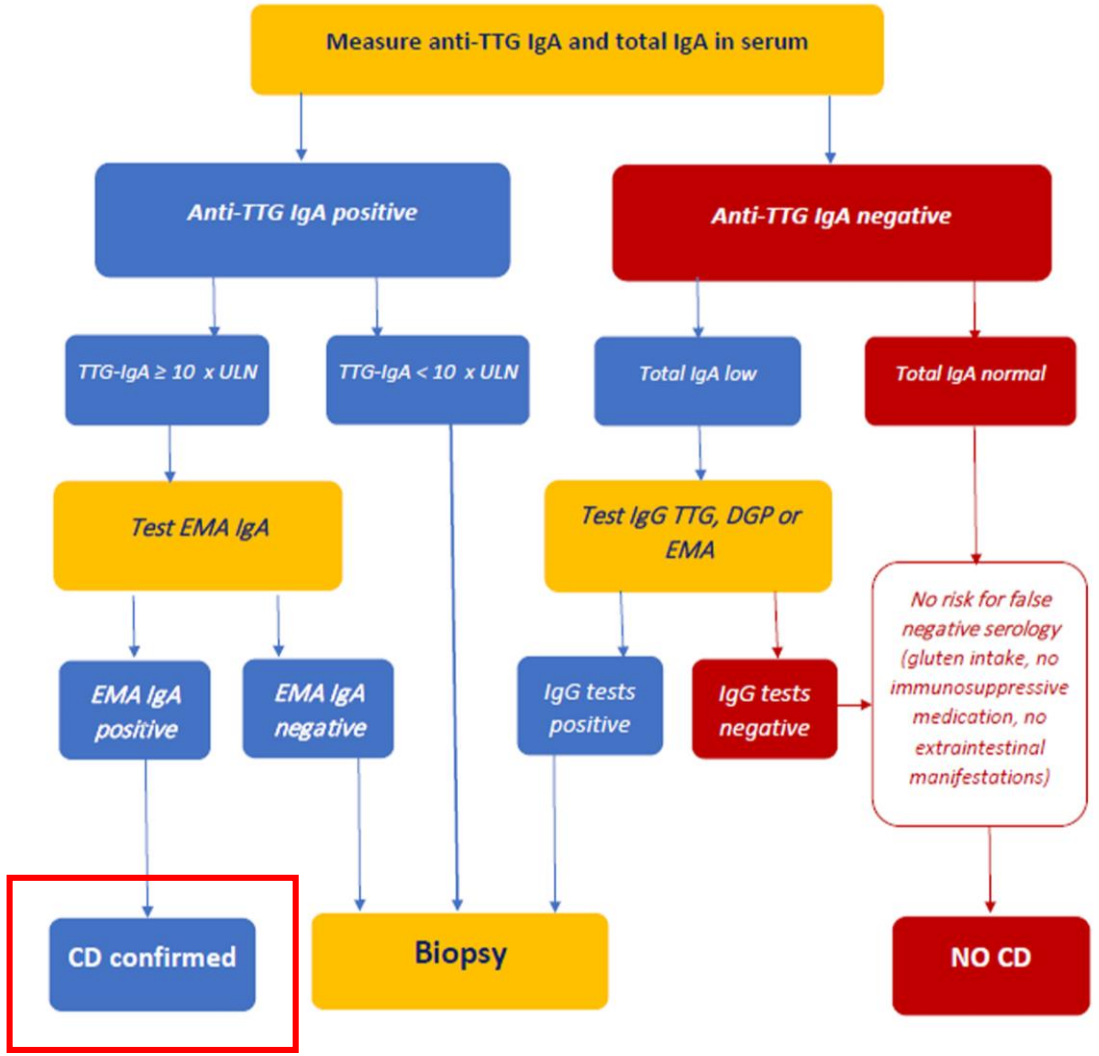
Raki et al., PNAS, 2006

Immune cell infiltration in the gut



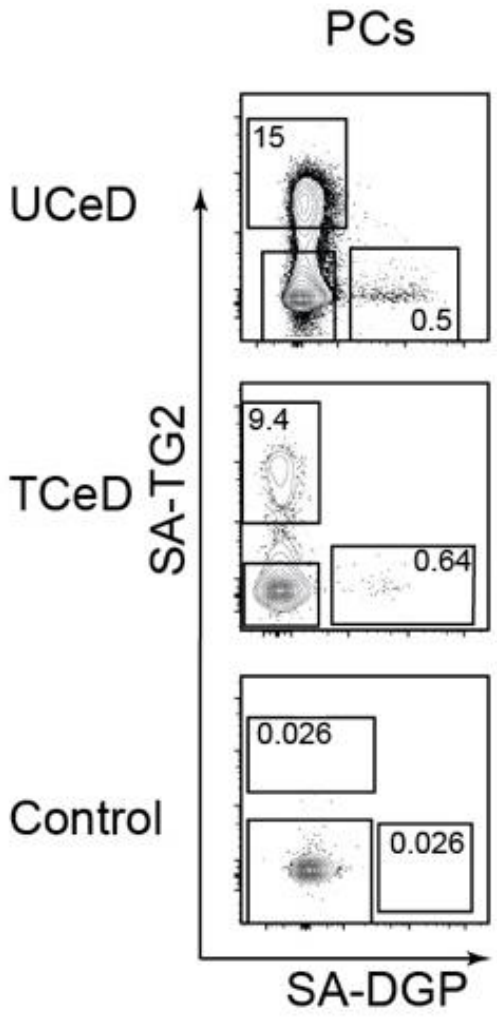
Serum antibodies in celiac disease

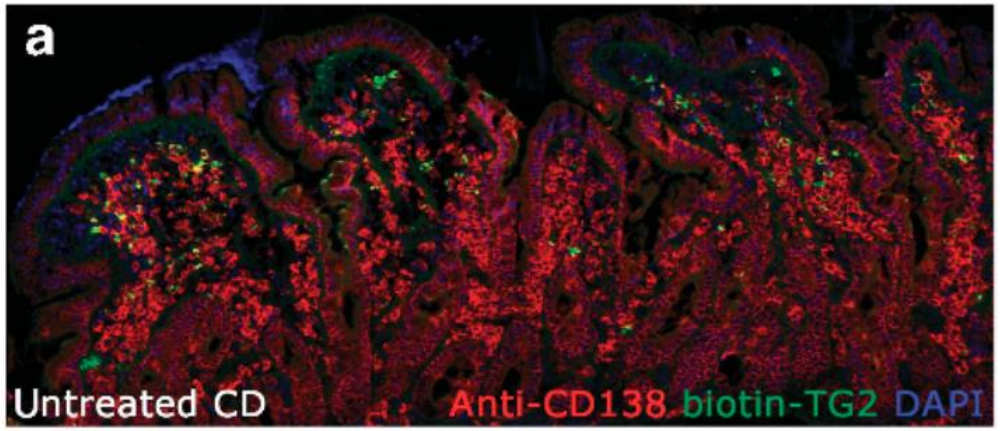
- Anti-deamidated gluten peptide (DGP) antibodies (IgG > IgA)
- Anti-tissue transglutaminase (TTG or TG2) antibodies (IgA > IgG)
- Detection with recombinant TG2 or tissue sections – endomysial antibodies (EMA)

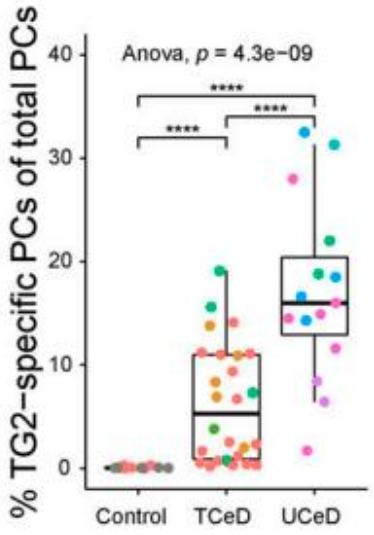


Antibody-secreting plasma cells in the gut

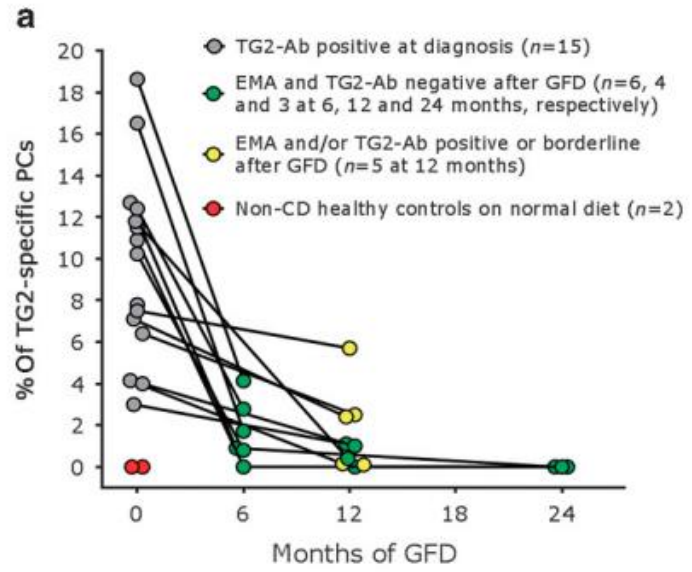
- 10-20% TG2-specific.
- <1% DGP-specific.
- Dependent on gluten in the diet.







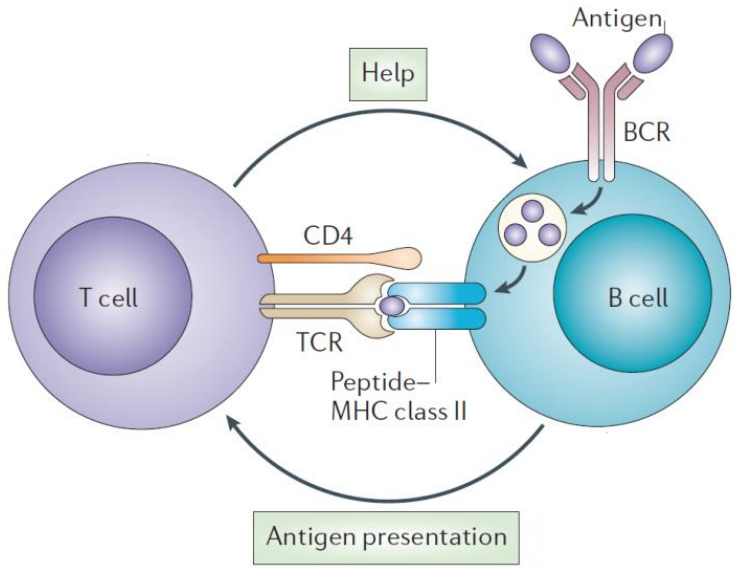
Lindeman et al., J Exp Med, 2021

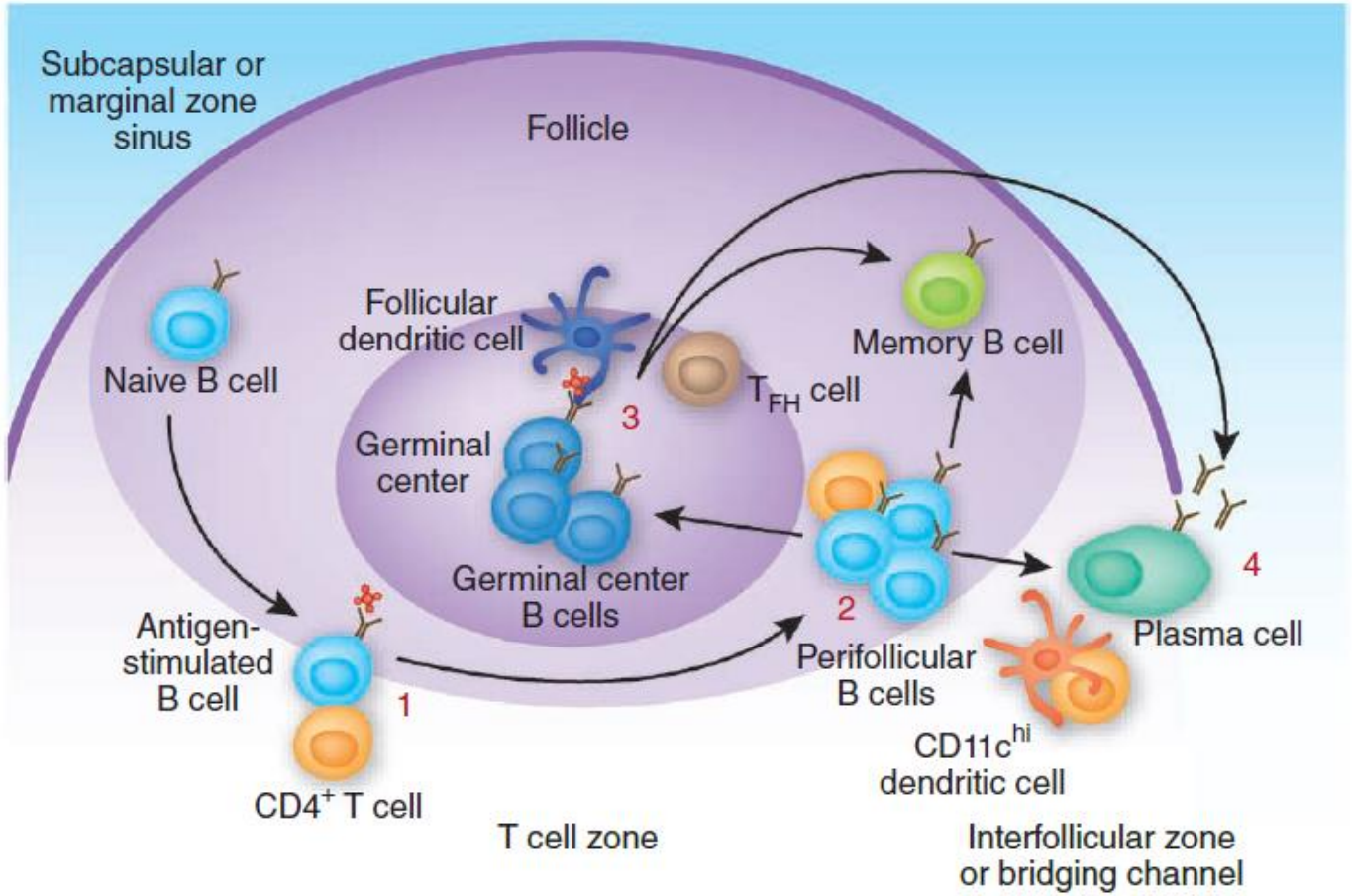


Di Niro et al., Mucosal Immunol, 2016

B-cell activation

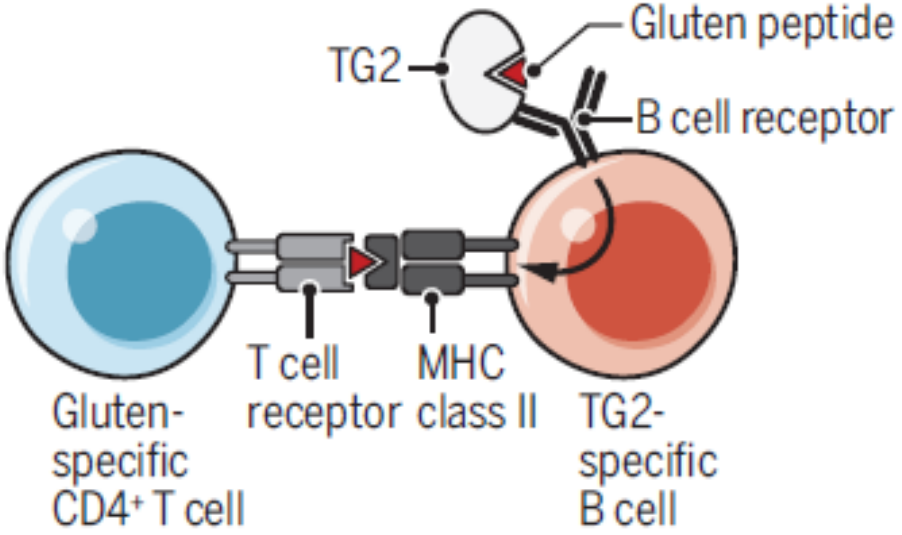
- Antigen binding → BCR signaling.
- Antigen uptake → interaction with cognate CD4+ T cells.
- Proliferation, differentiation to memory cells and plasma cells (antibody production).

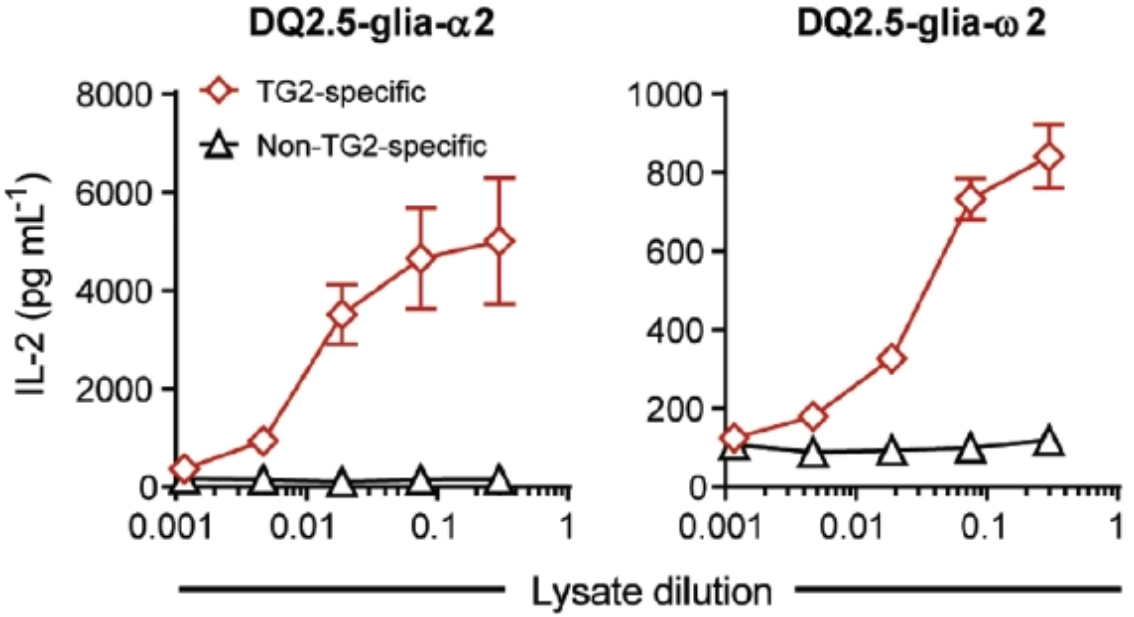




What is the role of TG2-specific B cells / antibodies?

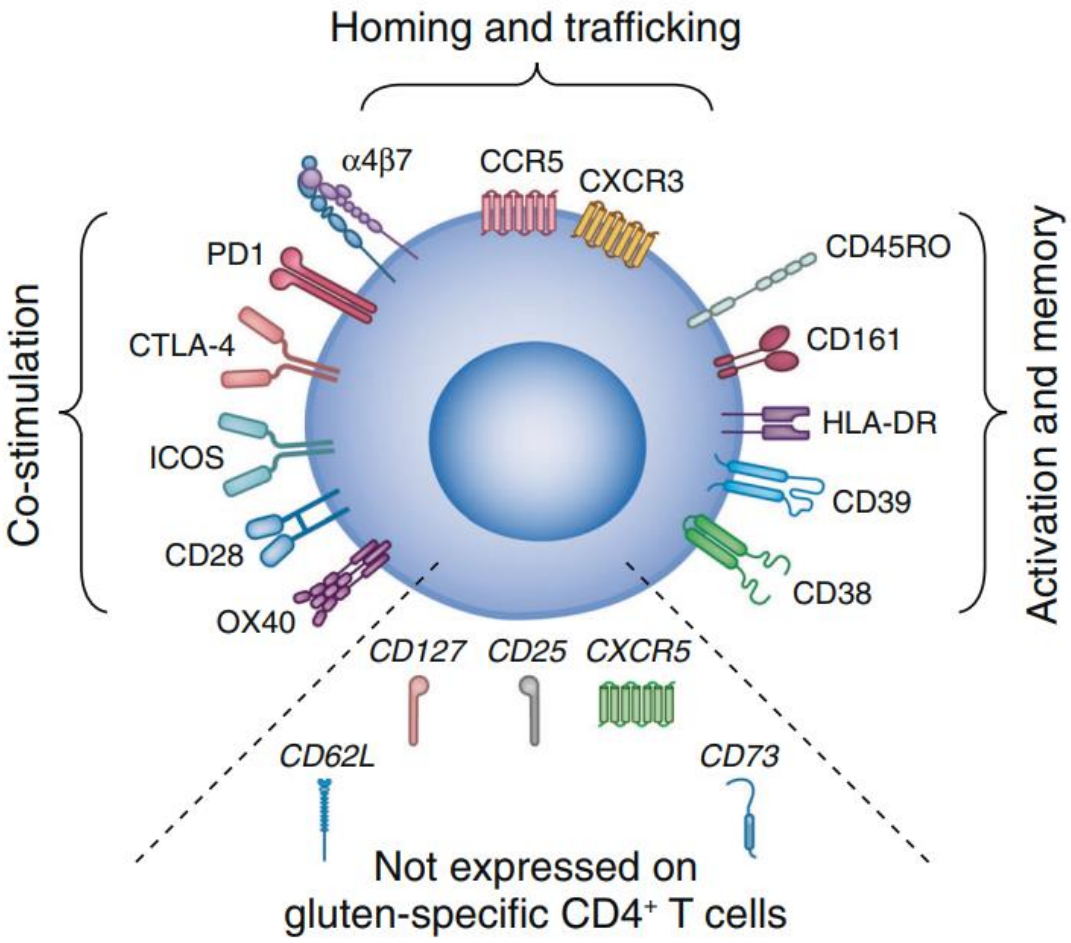
- Soluble TG2-specific antibodies do not have a clear pathogenic effect.
- B cells with TG2-specific BCR can present antigen to gluten-specific T cells.
- TG2-specific B cells main antingen-presenting cell for gluten-specific CD4+ T cells.





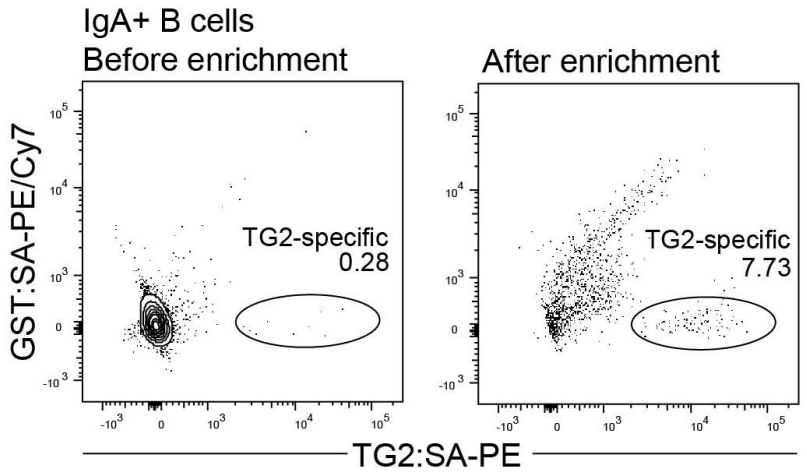
Iversen, Amundsen et al., Gastroenterology, 2020

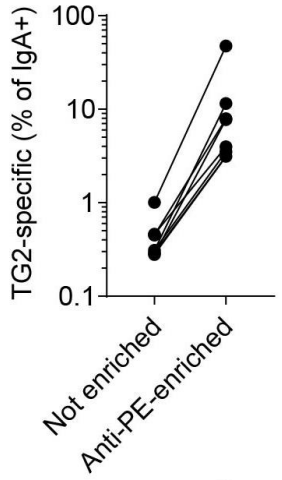
T-cell phenotype

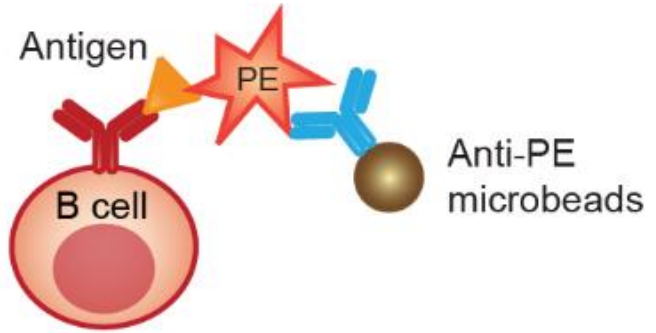


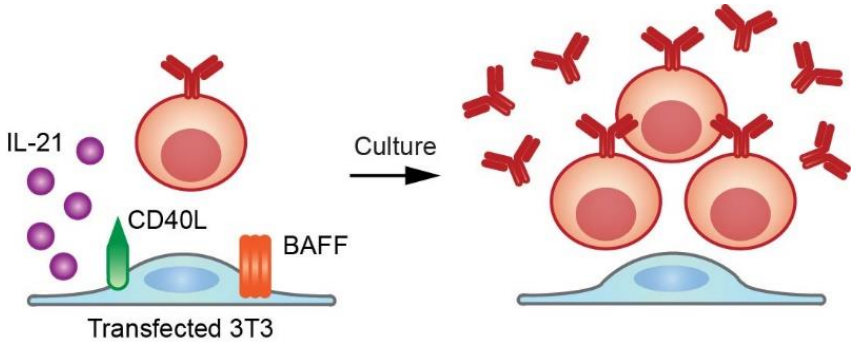
- Characterization by mass cytometry and single-cell RNA sequencing.
- Surface markers indicating activation and gut-homing.
- Secretion of B-helper cytokines IL-21 and CXCL13.
- Similar to previously described “T peripheral helper cells” (Tph).

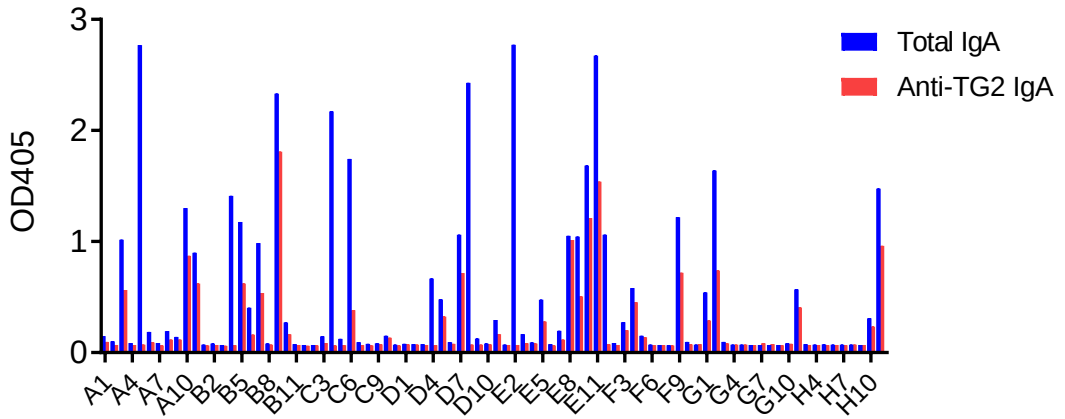
Identifying TG2-specific B cells in blood

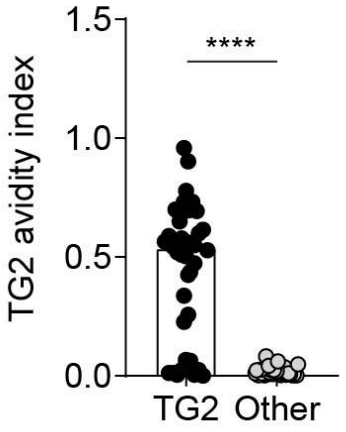






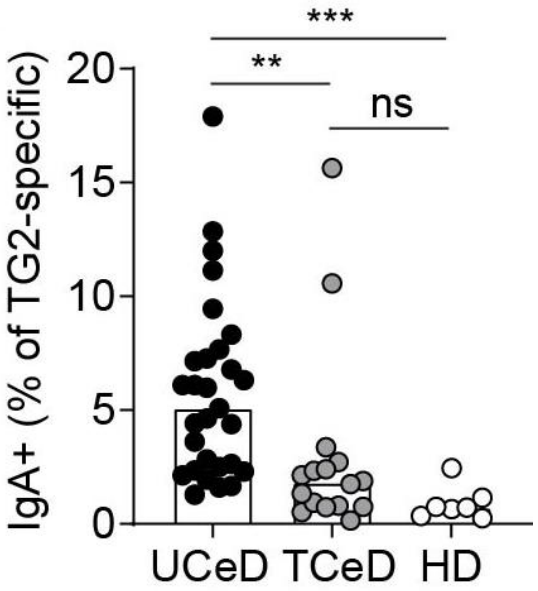


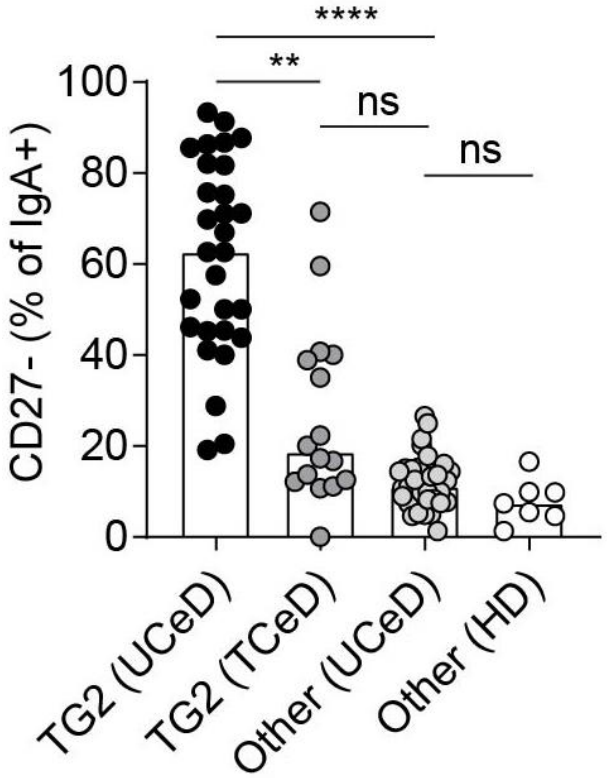




TG2-specific IgA+ B cells

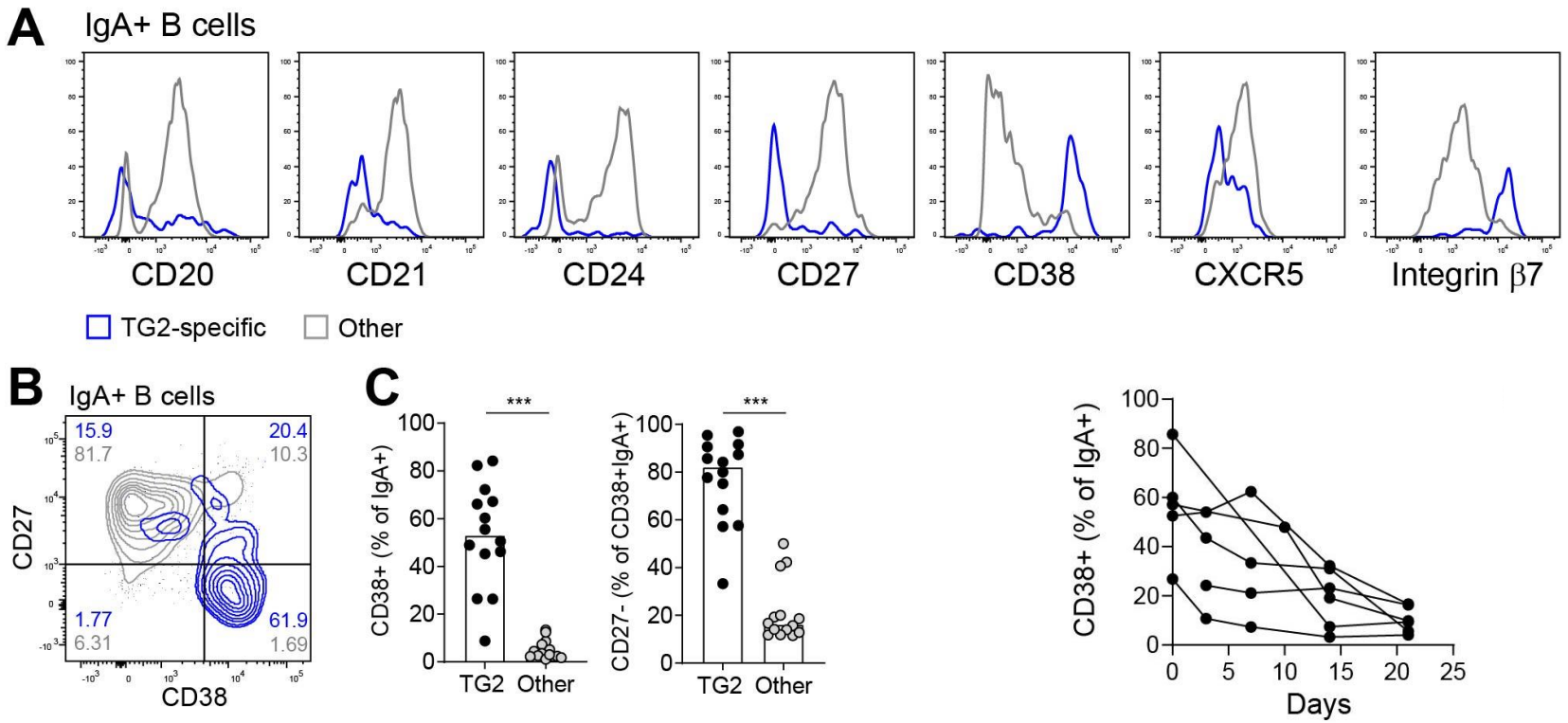
- Present in untreated patients.
- Negative for the classical memory marker CD27.





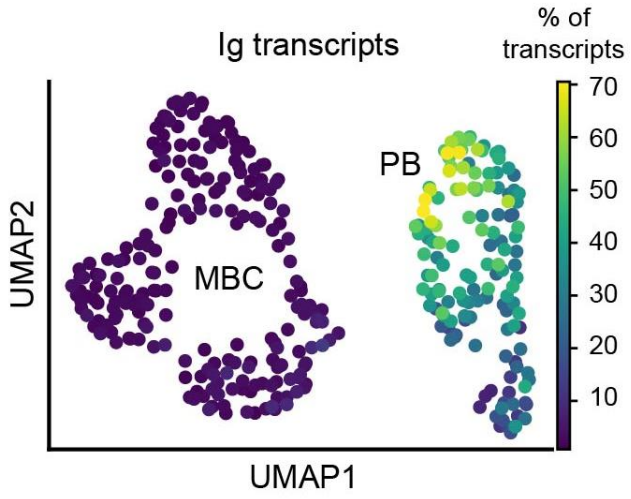
B-cell phenotype – flow cytometry

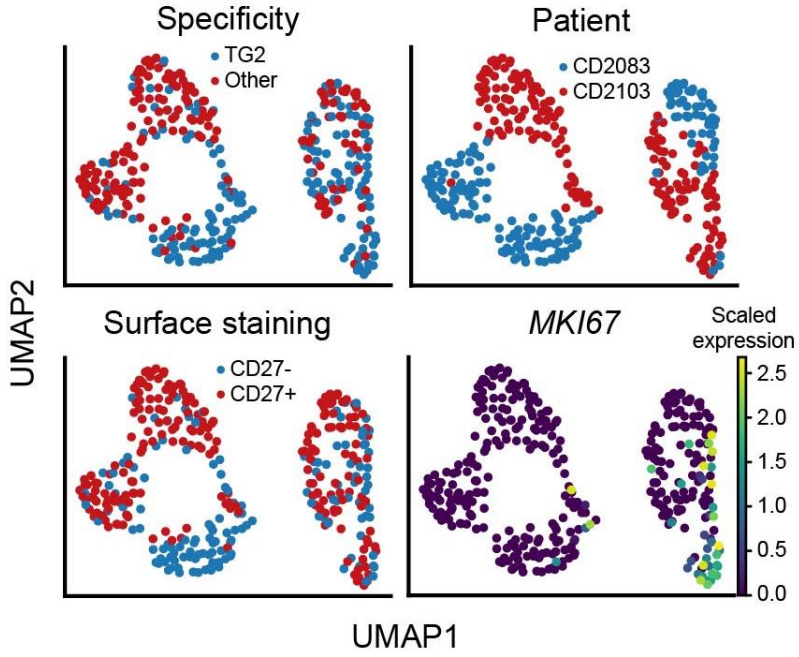
- Surface markers indicating activated, gut homing memory B cells / plasmablasts.
- Activated cells disappear rapidly on gluten-free diet.

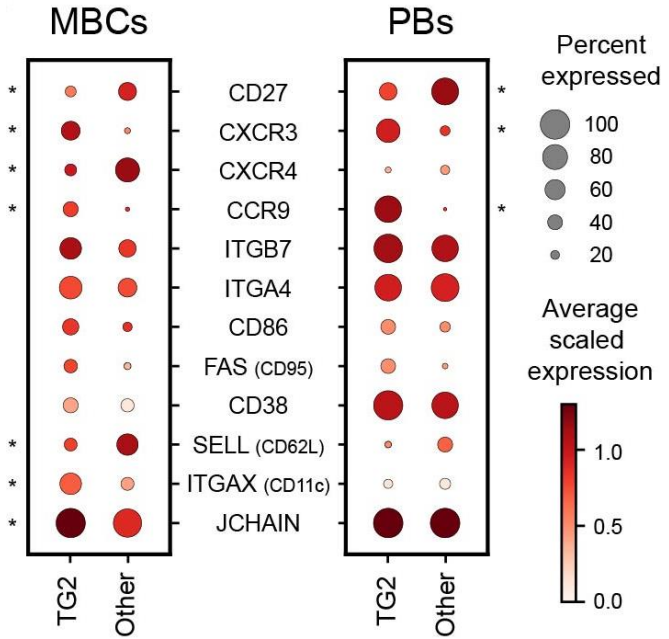


Single-cell RNAseq

- Two main clusters: memory B cells and plasmablasts.
- CD27 negative, activation, gut-homing.

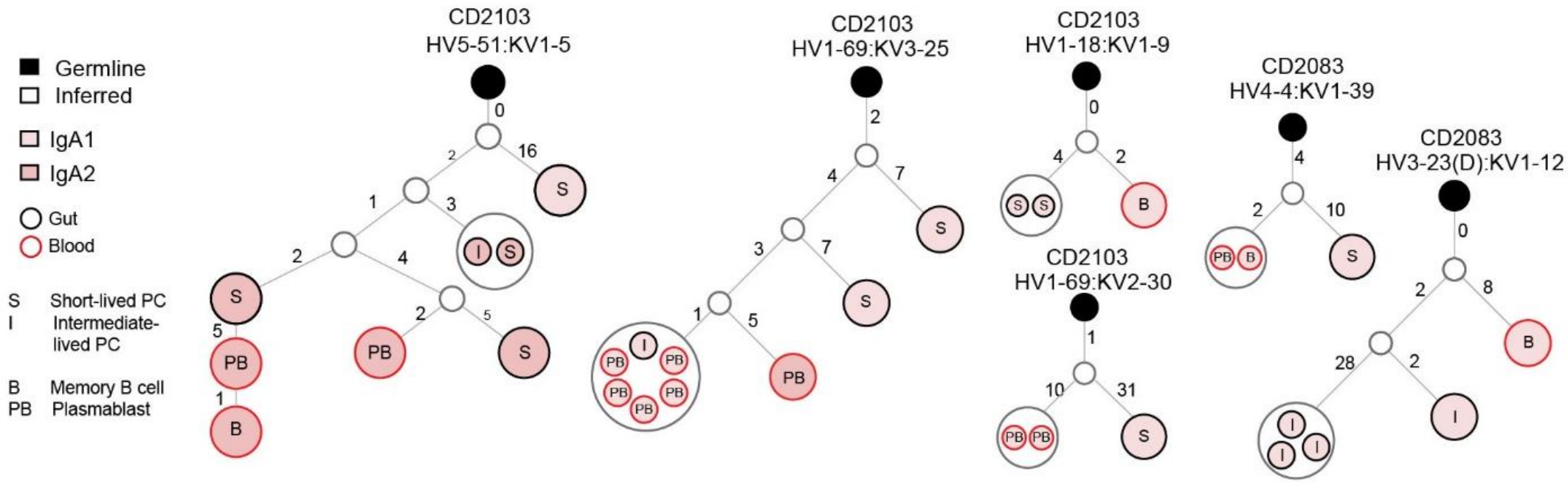




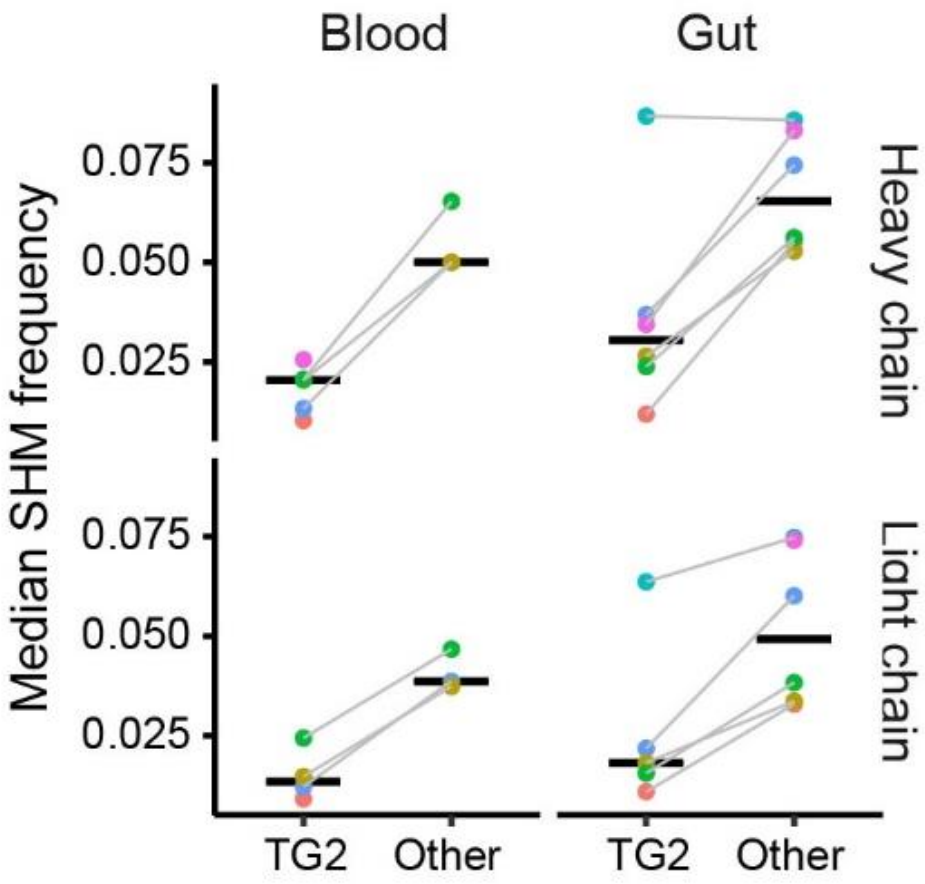


V(D)J sequences

- Clonal overlap between TG2-specific cells in blood and gut (same ancestral B cells).
- Cells in blood are precursors of gut plasma cells.

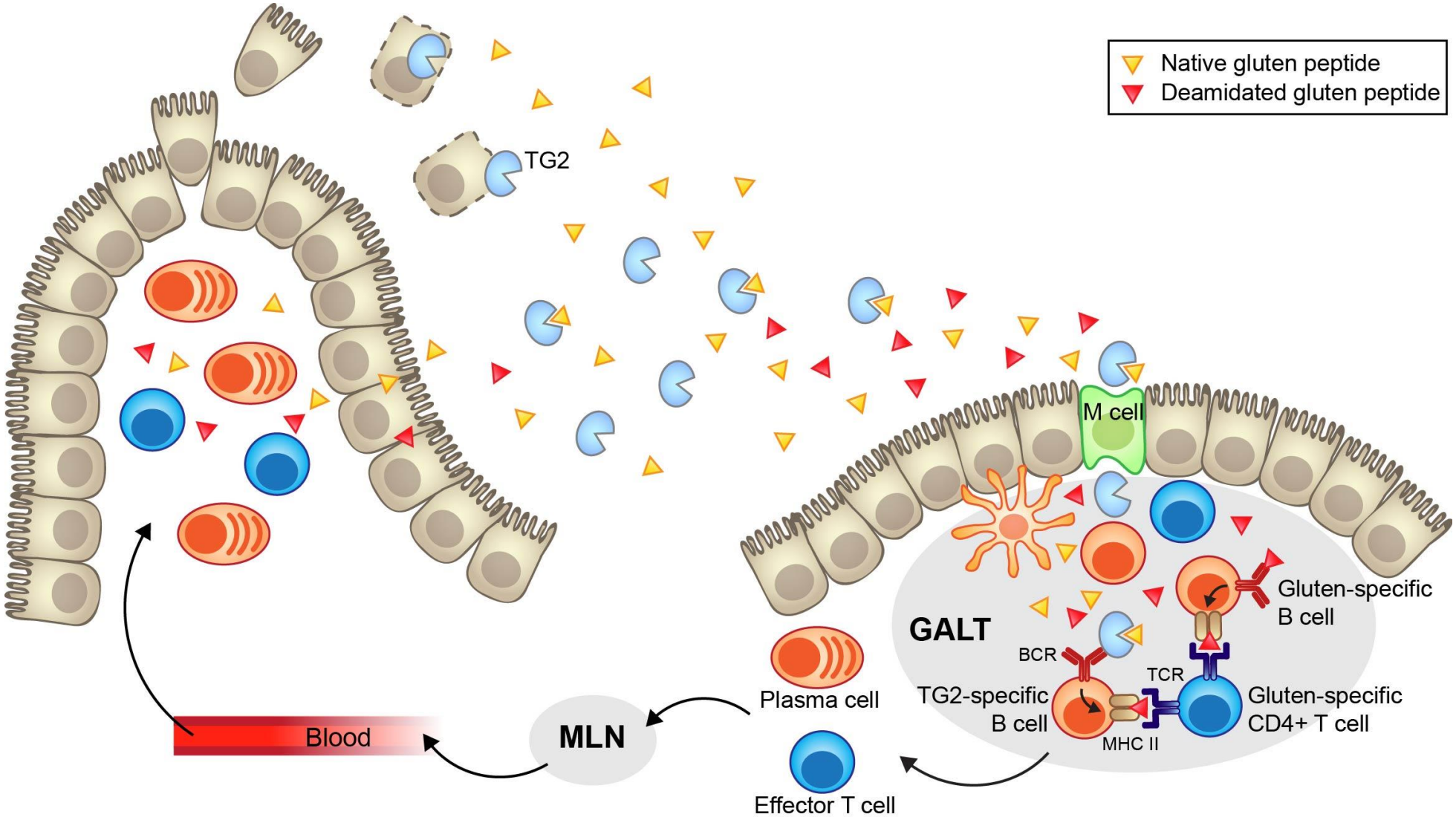


BCR mutations



- TG2-specific cells have fewer mutations than other B cells/plasma cells.
- SHM mainly happens in germinal centers.
- CD27 is expressed in germinal centers.
- Lack of CD27 and SHM could indicate extrafollicular origin.
- Supported by phenotype of gluten-specific T cells (Tph).

A model for celiac disease pathogenesis



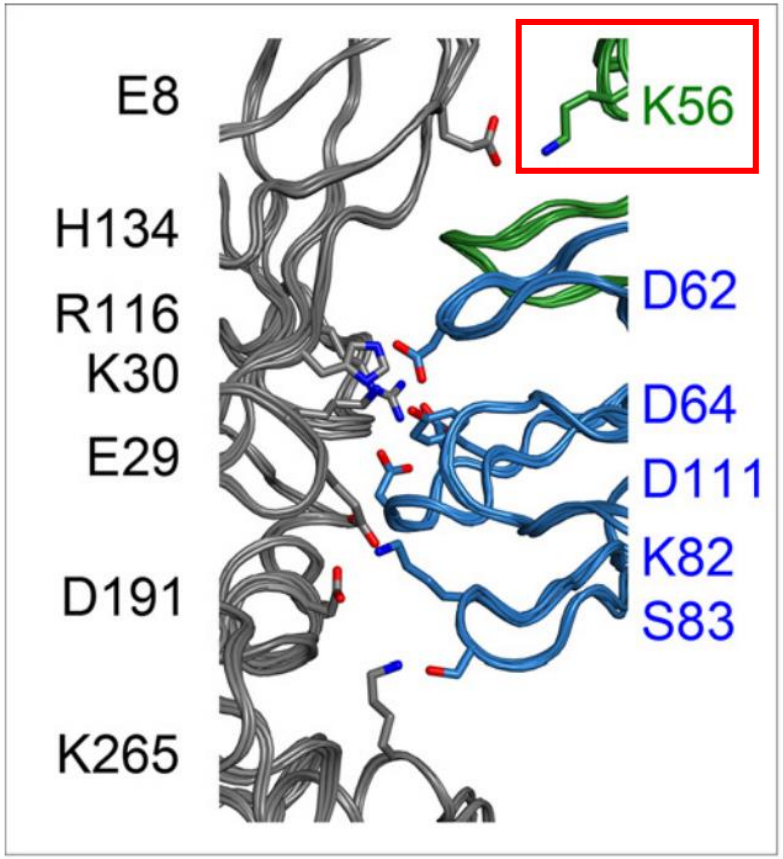
Could BCR and TCR be disease susceptibility genes?

Preference for certain V-genes observed for:

- TG2-specific B cells/plasma cells
- DGP-specific plasma cells
- Gluten-specific T cells

Most common heavy/light chain combination for TG2-specific cells: *IGHV5-51:IGKV1-5*

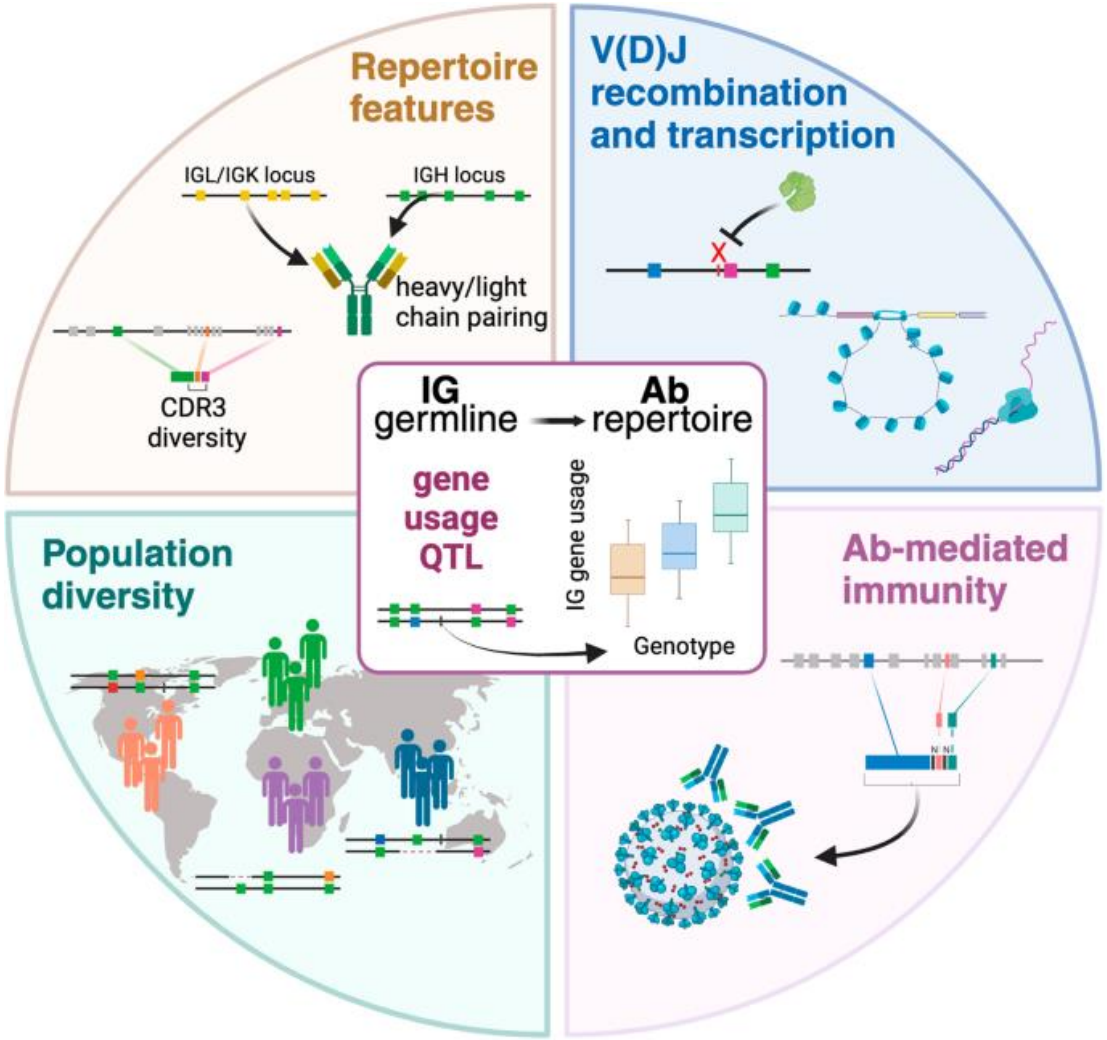
IGKV1-5 mutation K56D
→ 200 fold reduction in affinity



Chen et al., J Biol Chem, 2015

Genetic diversity in BCR and TCR genes

- Bigger diversity than previously appreciated
- Both in coding and non-coding regions
- Can affect repertoire composition
- Implications for precursor frequencies
- BCR and TCR regions not covered in GWAS



Watson et al., Genes Immun, 2024

Conclusions

- HLA dominates genetic predisposition for celiac disease
- Both HLA and non-HLA genes point to T-cell activation as key pathogenic event
- B cells likely act as main antigen-presenting cells for gluten-specific T cells
- TG2-specific B cells internalize enzyme-substrate complexes of TG2 and gluten
- Directly links antigen uptake and deamidation
- Phenotype of both T cells and B cells suggests extrafollicular interactions at induction sites
- Importance of TCR and BCR specificity implicates them as potential susceptibility genes

Acknowledgements

Iversen lab

- Filipa Vaz
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- Louise Risnes

Oslo University Hospital

- Knut Lundin

Akershus University Hospital

- Jørgen Jahnsen

And all the patients!!!

HELSE SØR-ØST

UiO : University of Oslo