

Gluten in coeliac disease and 'non-coeliac gluten sensitivity'

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the «glutenman»**

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 **Oslo
universitetssykehus**



The Oslo definitions for coeliac disease and related terms

Jonas F Ludvigsson,^{1,2} Daniel A Leffler,³ Julio C Bai,⁴ Federico Biagi,⁵ Alessio Fasano,⁶ Peter H R Green,⁷ Marios Hadjivassiliou,⁸ Katri Kaukinen,⁹ Ciaran P Kelly,³ Jonathan N Leonard,¹⁰ Knut Erik Aslaksen Lundin,¹¹ Joseph A Murray,¹² David S Sanders,^{13,14} Marjorie M Walker,¹⁴ Fabiana Zingone,¹⁵ Carolina Ciacci¹⁶

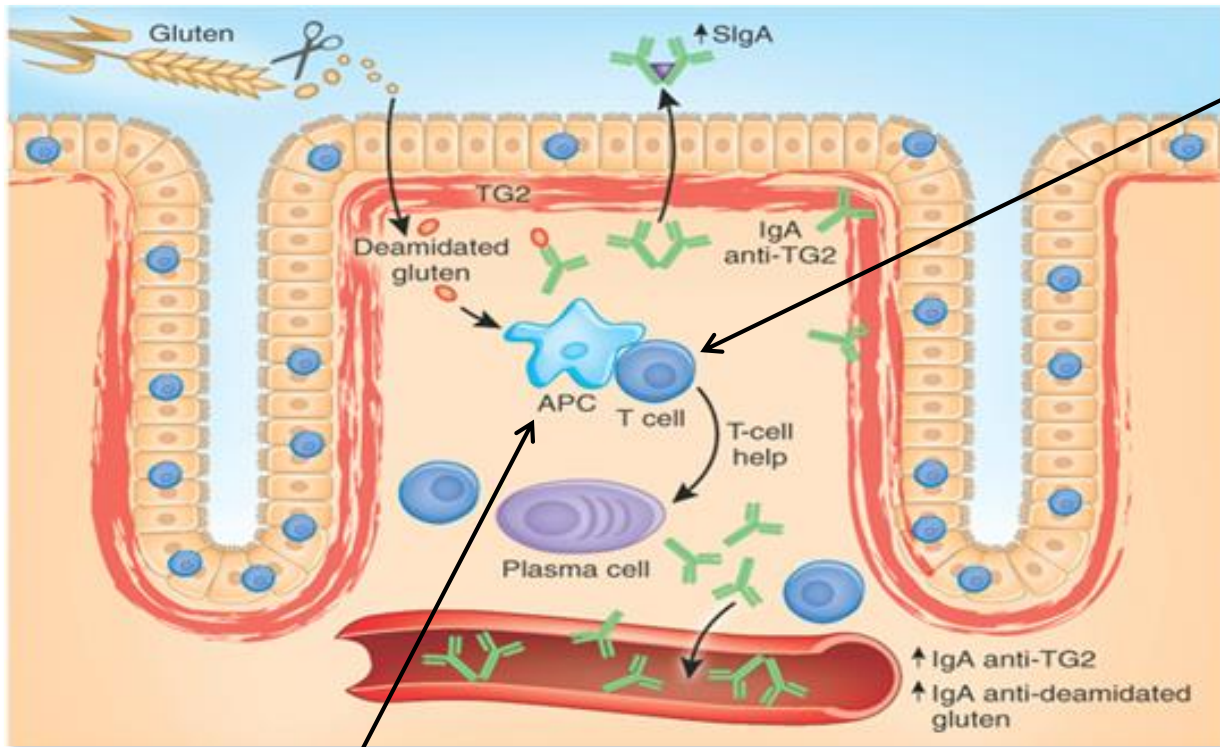
- **Gluten intolerance**

- the broadest term for all aspects of adverse reactions to gluten
- **Coeliac disease**
 - a small intestinal enteropathy, usually also typical serology (IgA-tissue transglutaminase)
- **Wheat allergy** a rapid, allergic response
- **Non-coeliac gluten sensitivity (NCGS)**
 - clinically quite like coeliac disease, but without enteropathy or serology



HLA-DQ2-gliadin tetramers and diagnosis

Modified gluten peptides bound to HLA-DQ2 in antigen presenting cells



Tetramer construct for detection of gluten specific T cells

T cells recognize HLA-DQ2/DQ8-bound gluten peptides



Generation of T-cell epitopes in the gut

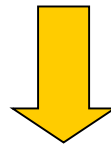
α 2-gliadin (AJ133612)

1 MVRVVPQLQ PQNPSQQQPQ EQVPLVQQQQ FPGQQQPFPP QQPYPQPQPF PSQQPYLQLQ
 61 PFPQPQLPYP QPQLPYPQPQ LPYPQPQPFR PQQPYPQSQP QYSQPQQPIS QQQQQQQQQQ
 121 QKQQQQQQQ QILQQILQQQ LIPCRDVLQ QHSIAYGSSQ VLQQSTYQLV QQLCCQLWQ
 181 IPEQSRCQAI HNVVHAILH QQQQQQQQQQ QPPLSQVSFQ QPQQQYPSGQ GSFQPSQQNP
 241 QAQGSVQPQQ LPQFEEIRNL ALETL PAMCN VYIPPYCTIA PVGIFGTNYR

Transglutaminase (QXP)



digestive enzymes



after transglutaminase treatment

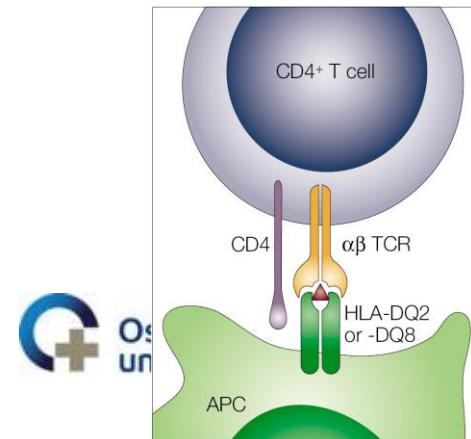
61 PFPQPELPYP QPELPYPQPE LPYPQPQPF

LQLQ

peptide (33 amino acids)

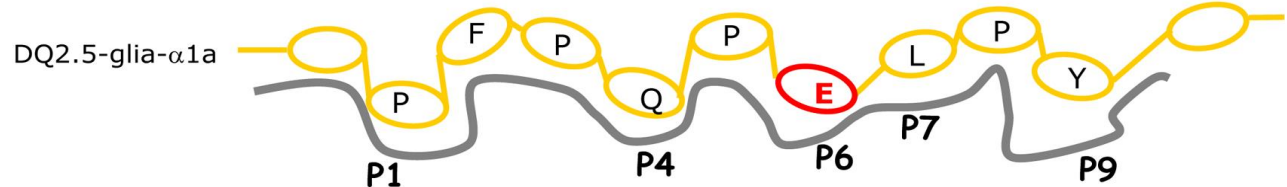
PFPQPELPY
 PFPQPELPY Q
 PYP QPELPY
 P QPELPYPQ
 PYPQPE LPY
 PQPE LPYPQ

6 copies of
 T cell epitopes



HLA-DQ2.5 and HLA-DQ8 restricted gluten T-cell epitopes

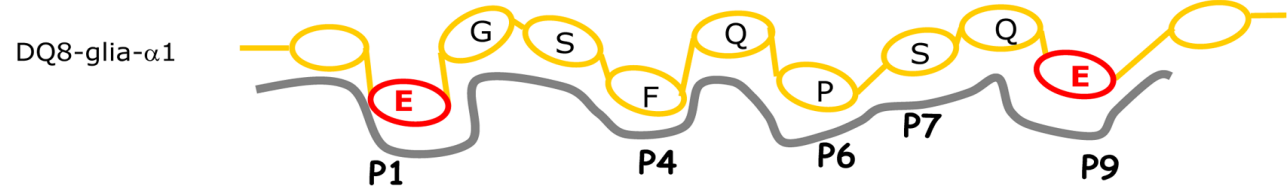
DQ2.5



- DQ2.5-glia-α1a
- DQ2.5-glia-α1b
- DQ2.5-glia-α2
- DQ2.5-glia-α3
- DQ2.5-glia-γ1
- DQ2.5-glia-γ2
- DQ2.5-glia-γ3
- DQ2.5-glia-γ4a
- DQ2.5-glia-γ4b
- DQ2.5-glia-γ4c
- DQ2.5-glia-γ4d
- DQ2.5-glia-γ5
- DQ2.5-glia-ω1
- DQ2.5-glia-ω2
- DQ2.5-glut-L1
- DQ2.5-glut-L2
- DQ2.5-hor-1
- DQ2.5-hor-2
- DQ2.5-hor-3
- DQ2.5-sec-1
- DQ2.5-sec-2
- DQ2.5-ave-1a
- DQ2.5-ave-1b

	P1		P4		P6	P7		P9	
DQ2.5-glia-α1a	P	Y	P	Q	P	E	L	P	Y
DQ2.5-glia-α1b	P	Q	P	E	L	P	Y	P	Q
DQ2.5-glia-α2	F	R	P	E	Q	P	Y	P	Q
DQ2.5-glia-γ1	P	Q	Q	S	F	P	E	Q	Q
DQ2.5-glia-γ2	I	Q	P	E	Q	P	A	Q	L
DQ2.5-glia-γ3	Q	Q	P	E	Q	P	Y	P	Q
DQ2.5-glia-γ4a	S	Q	P	E	Q	P	F	P	Q
DQ2.5-glia-γ4b	P	Q	P	E	Q	P	F	P	Q
DQ2.5-glia-γ4c	Q	Q	P	E	Q	P	F	P	Q
DQ2.5-glia-γ4d	P	Q	P	E	Q	P	F	P	Q
DQ2.5-glia-γ5	Q	Q	P	F	P	E	Q	C	Q
DQ2.5-glia-ω1	P	F	P	Q	P	E	Q	P	F
DQ2.5-glia-ω2	P	Q	P	E	Q	P	F	P	W
DQ2.5-glut-L1	P	F	S	E	Q	P	Q	P	V
DQ2.5-glut-L2	F	S	Q	Q	Q	E	S	P	F
DQ2.5-hor-1	P	F	P	Q	P	E	Q	P	F
DQ2.5-hor-2	P	Q	P	E	Q	P	F	P	Q
DQ2.5-hor-3	P	I	P	E	Q	P	Q	P	Y
DQ2.5-sec-1	P	F	P	Q	P	E	Q	P	F
DQ2.5-sec-2	P	Q	P	E	Q	P	F	P	Q
DQ2.5-ave-1a	P	Y	P	E	Q	E	E	P	F
DQ2.5-ave-1b	P	Y	P	E	Q	E	Q	P	F

DQ8

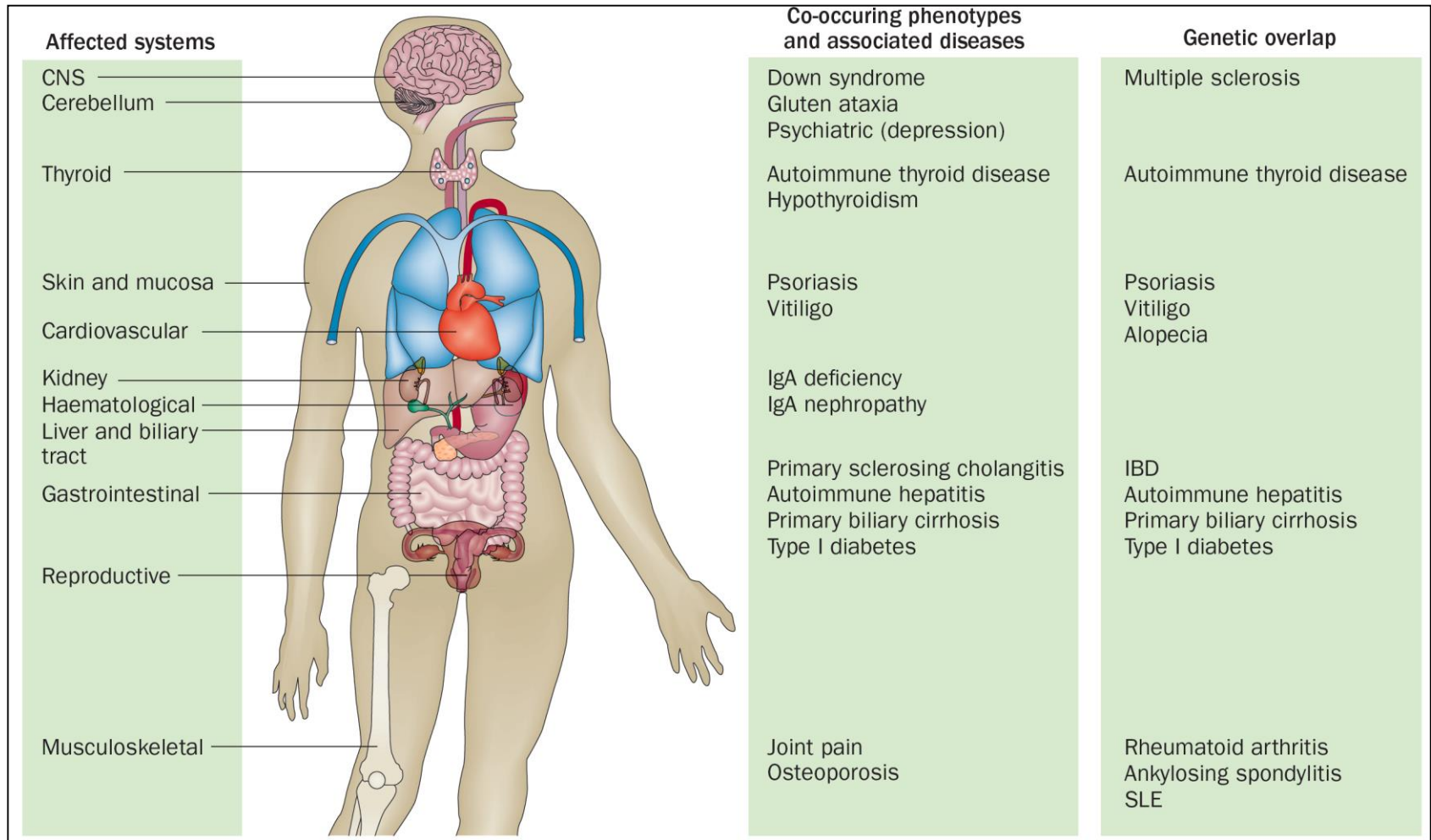


- DQ8-glia-γ1a
- DQ8-glia-γ1b
- DQ8-glut-H1

	P1		P4		P6	P7		P9	
DQ8-glia-γ1a	E	Q	P	Q	Q	P	F	P	Q
DQ8-glia-γ1b	E	Q	P	Q	Q	P	Y	P	E
DQ8-glut-H1	Q	G	Y	Y	P	T	S	P	Q



Genetic and clinical overlap



Coeliac disease

- An adaptive immunology, T cell mediated disease dependent on gluten intake
- Strongly associated to HLA-DQ2 and –DQ8
- Very much is understood
 - Restricted T cell receptor usage, long-lived T cells!
 - Restricted B cell receptor usage
 - Well defined gluten peptides
- But little is known why this develops!

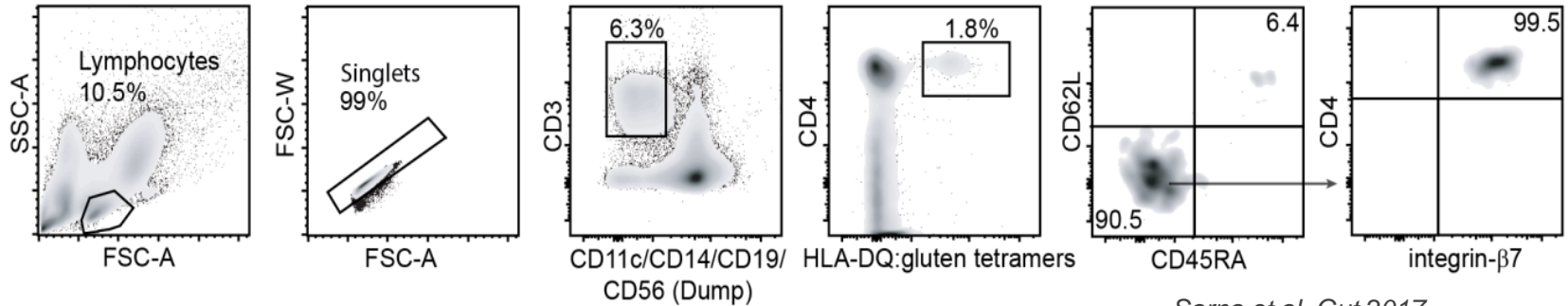


Experimental diagnosis of CD

Flow cytometry based



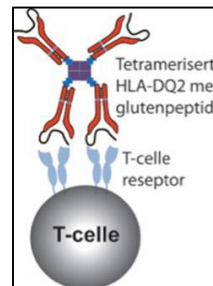
Flow cytometry



Sarna et al. Gut 2017

Exclusion of monocytes, macrophages, granulocytes, NK cells, B cells, dendritic cells

Differentiation of T_{naive} , T_{EM} , T_{CM} cells



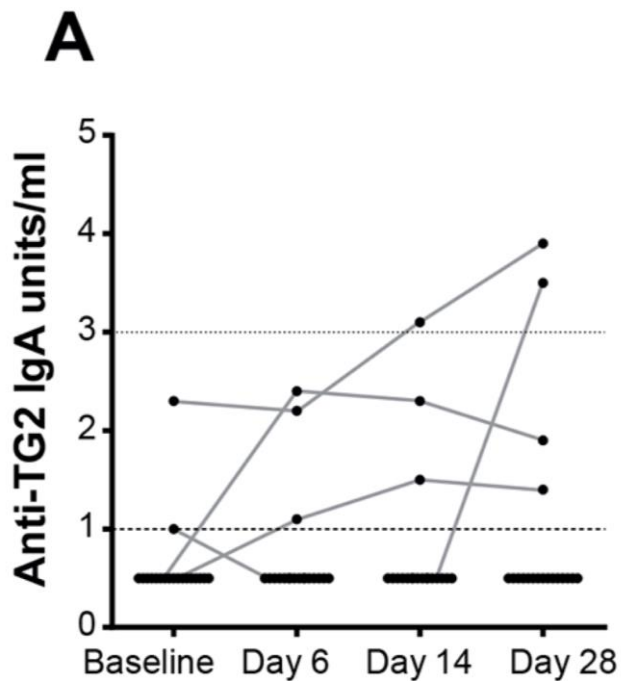
Sarna et al. Gastroenterologen 2015



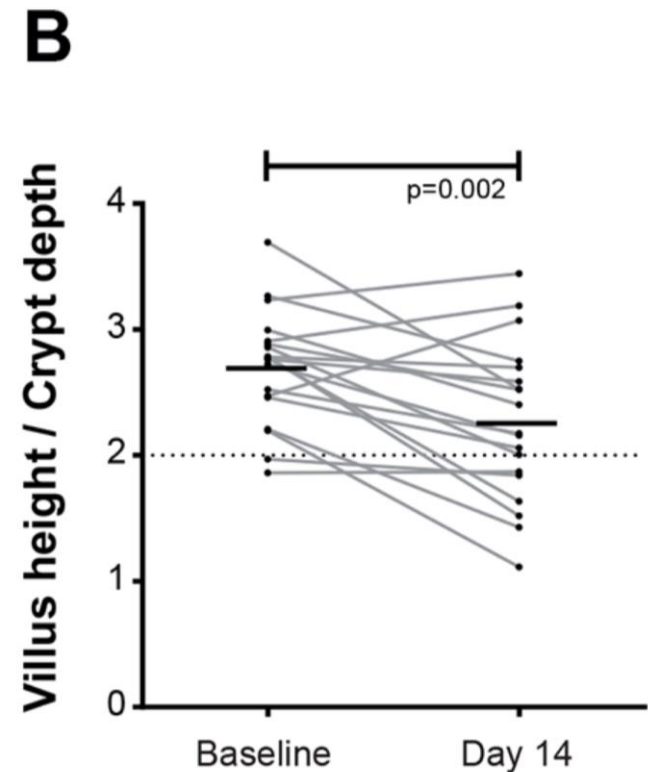
HLA-DQ:gluten tetramer test in blood gives better detection of coeliac patients than biopsy after 14-day gluten challenge

Gut 2017

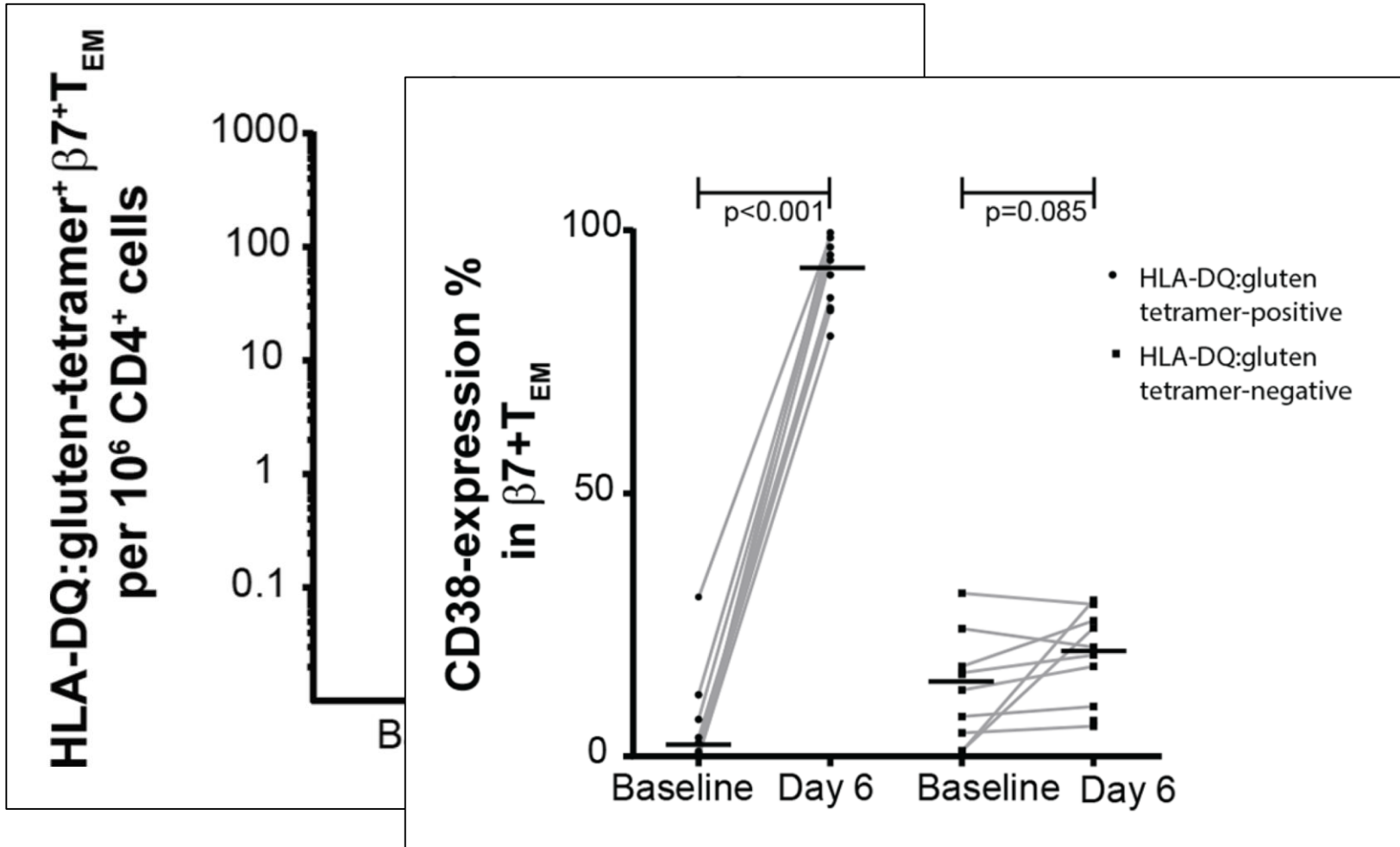
Vikas K Sarna,^{1,2} Gry I Skodje,^{2,3} Henrik M Reims,⁴ Louise F Risnes,^{1,5}
Shiva Dahal-Koirala,^{1,5} Ludvig M Sollid,^{1,2,5} Knut E A Lundin^{2,5,6}



Weak antibody responses in serum until day 28



Experimental read-out of gluten challenge



Tetramer-visualized gluten-specific CD4⁺ T cells in blood as a potential diagnostic marker for coeliac disease without oral gluten challenge

Asbjørn Christophersen¹, Melinda Ráki¹, Elin Bergseng¹, Knut EA Lundin^{1,2}, Jørgen Jahnsen³, Ludvig M Sollid¹ and Shuo-Wang Qiao¹

United European Gastroenterology Journal
0(0) 1-11

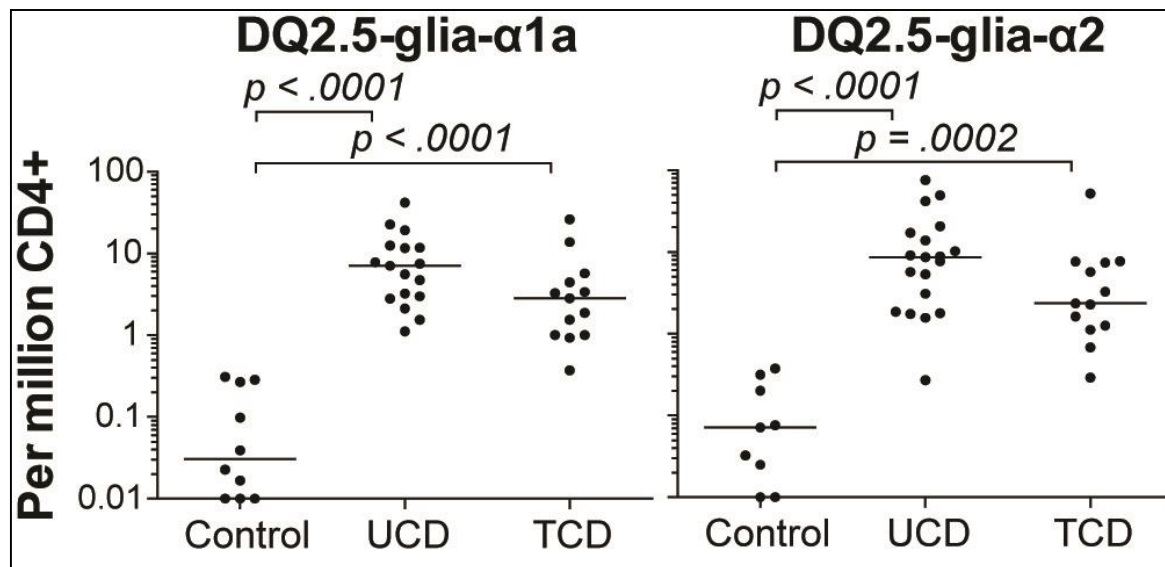
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DOI: 10.1177/2050640614540154

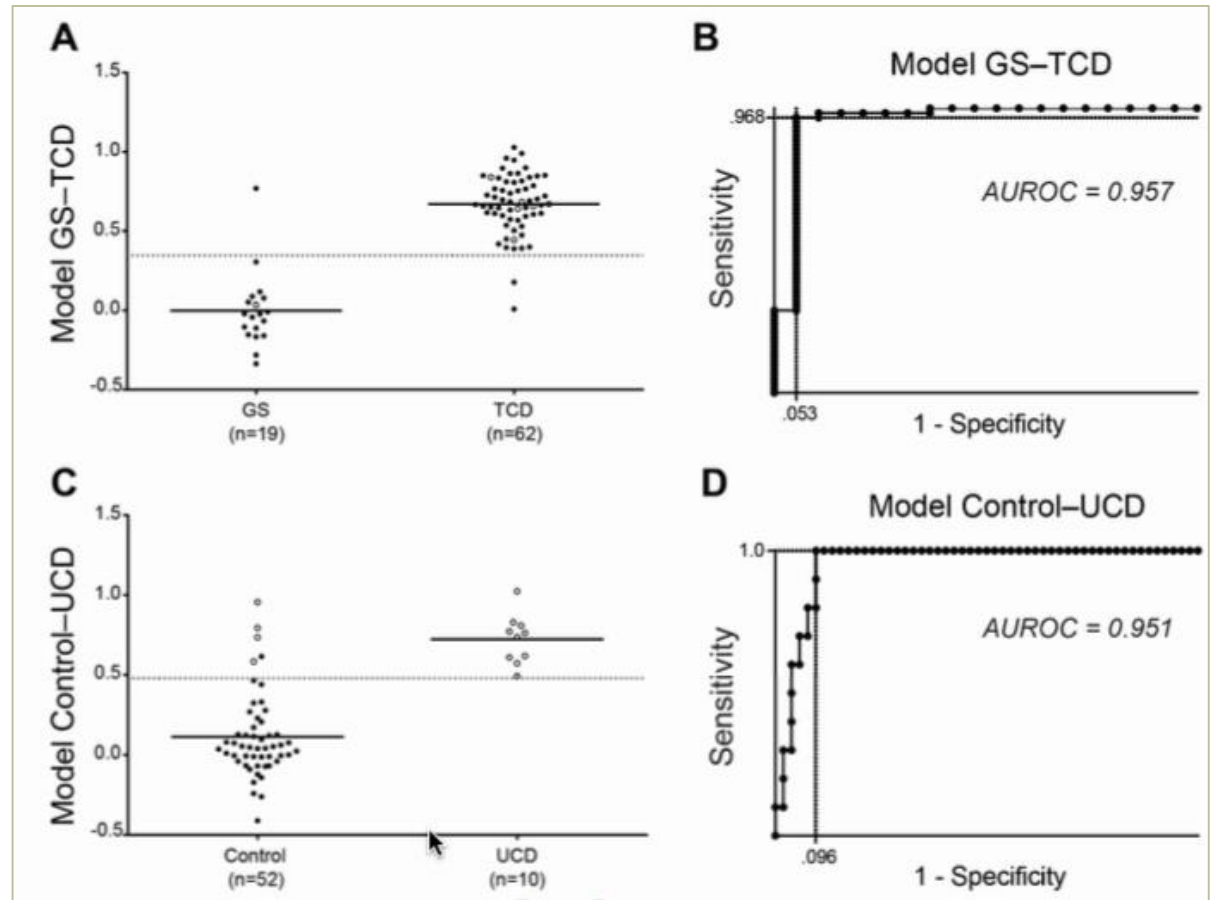
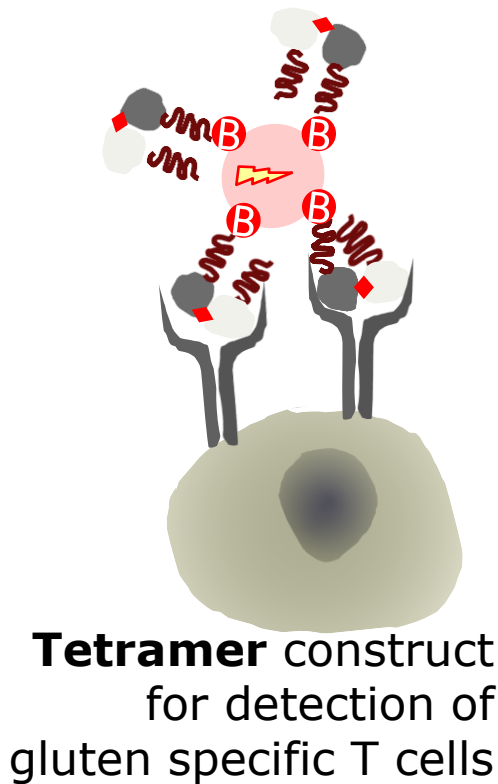
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UCD Untreated
celiac disease

TCD Treated
celiac disease

A blood test to sort out coeliac disease without gluten exposure!



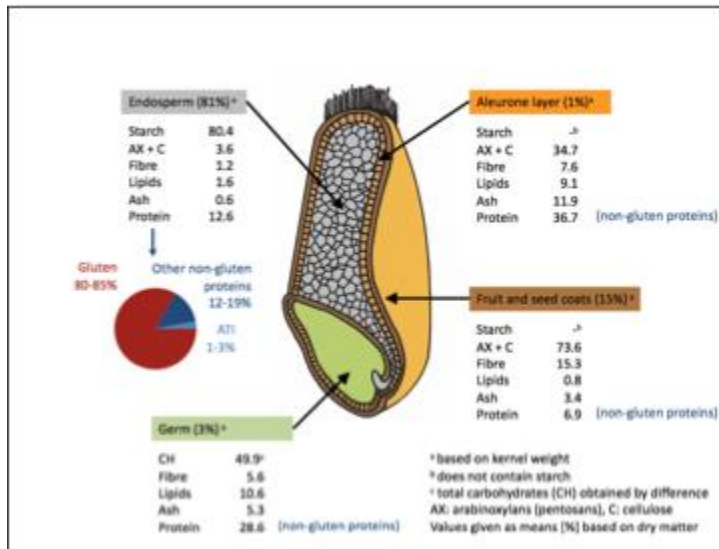
Then what about ‘non-celiac
gluten sensitivity?’



Opposing views

- NCGS is caused by a specific, innate immune reaction to proteins in “gluten”

- NCGS is caused by a reaction to “fermentable oligo-, di-, monosaccharides and polyols” (FODMAP)
- Fructan is one of several FODMAPS
- Bread is rich in fructan



NCGS – why bother?

- NCGS aka as
 - NCWS (Non-coeliac wheat sensitivity)
 - PWAG (People who avoid gluten)
- Mostly self instituted gluten free diet
- These people come to the health care
 - Do I have coeliac disease?
 - Do I have to stay on a gluten free diet? (they mostly answer themselves)
 - Can I have reimbursement?



Oslo work on NCGS – PhD Margit Brottveit

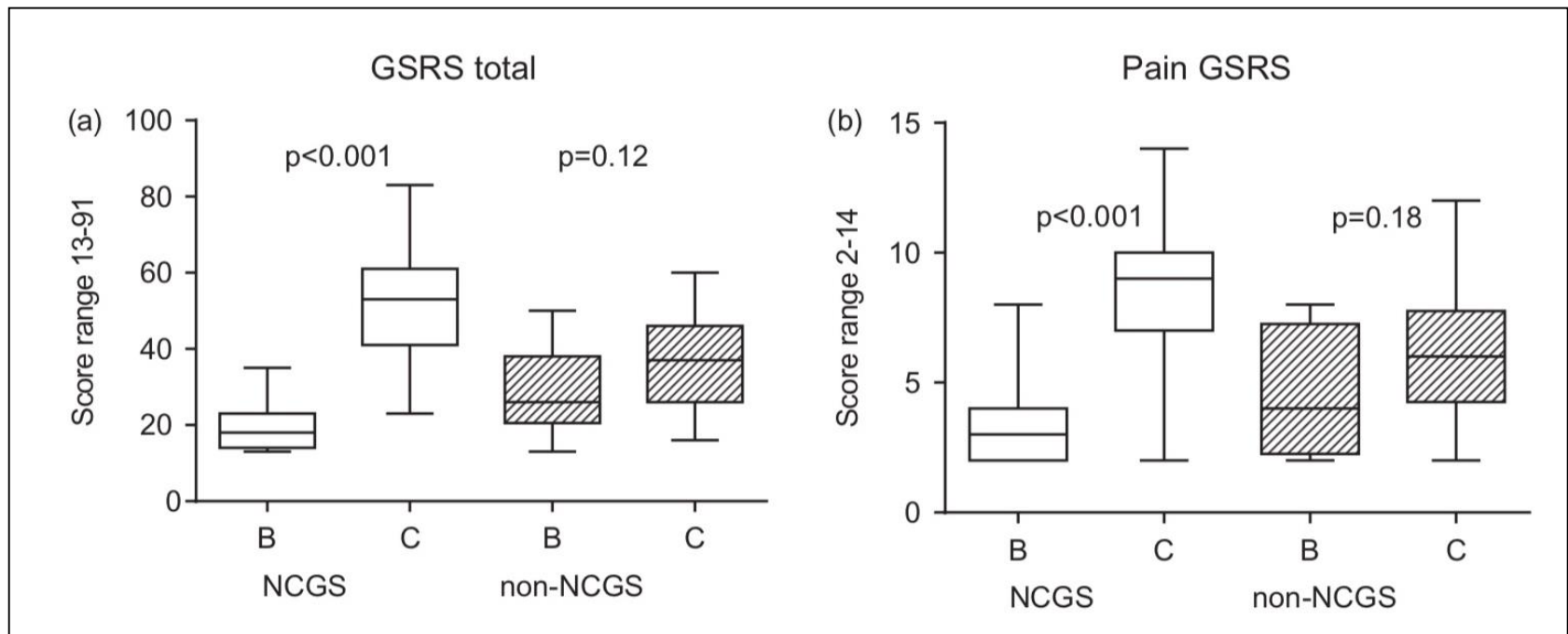
- Coeliac disease rare among NCGS “individuals” from general population
 - 130 responders, 35 were DQ2+, 3 with CD
 - Gastroscopy and “HLA-DQ2:gliadin peptide tetramer test”
 - Brottveit et al Am J Gastro 2011
- No signs of psychosomatic disorder
 - Three days challenge with bread
 - Brottveit et al Scand J Gastro 2012
- NCGS intestines with signs of immune activation
 - Increased levels of IEL, activation of IFN- γ after bread challenge
 - Brottveit et al Am J Gastro 2013



ORIGINAL ARTICLE

Wheat challenge in self-reported gluten sensitivity: a comparison of scoring methods

Gry I. Skodje^a, Christine Henriksen^b, Trude Salte^c, Thea Drivenes^c, Ieva Toleikyte^a, Astrid M. Lovik^a, Marit B. Veierød^{b,d} and Knut E.A. Lundin^{e,f,g}



Open challenge with regular bread
(gluten and FODMAP)

Challenge – the placebo problem



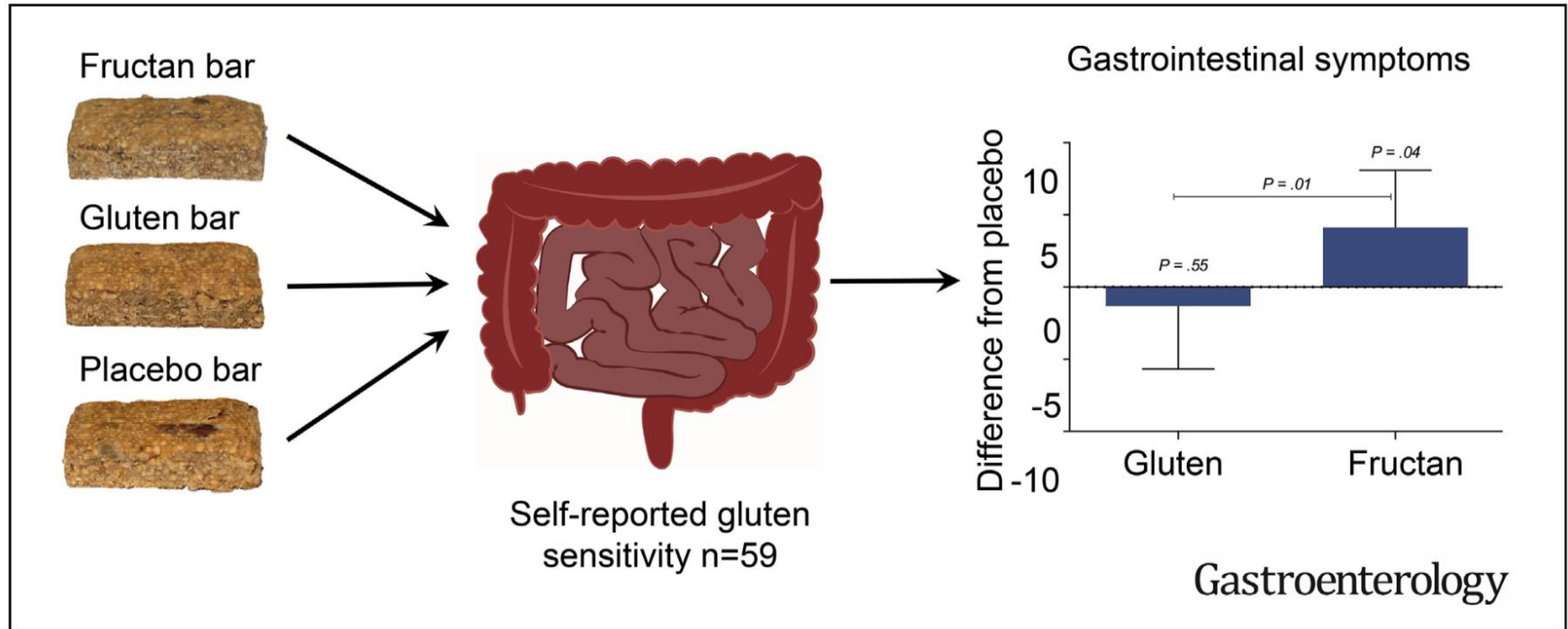
- Supply all food?
- Traditional placebo
 - Capsules flour or placebo
 - Research tool
 - Lundin and Alaedini 2012
 - Catassi et al 2016
- Quinoa based müsli bars with and without “clean” gluten and FODMAP



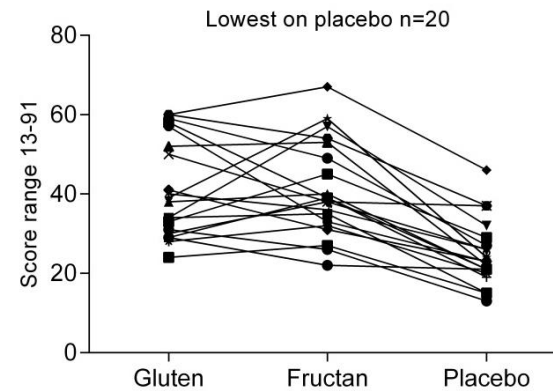
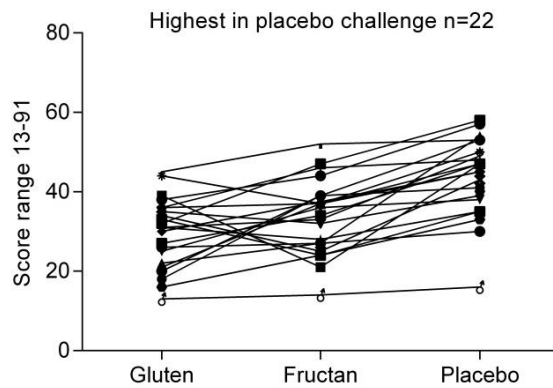
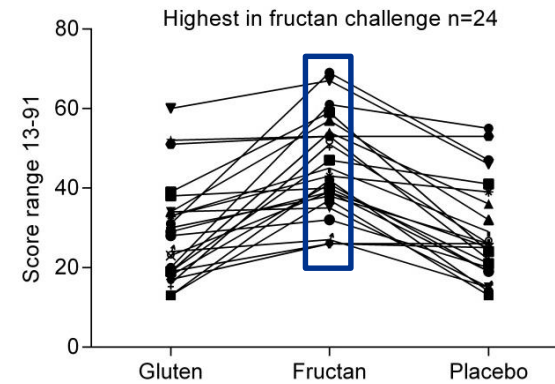
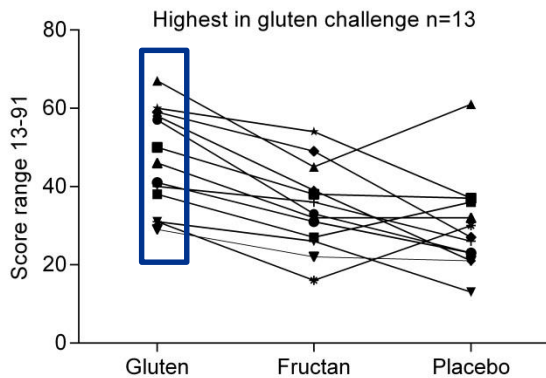


Fructan, Rather Than Gluten, Induces Symptoms in Patients With Self-Reported Non-Celiac Gluten Sensitivity

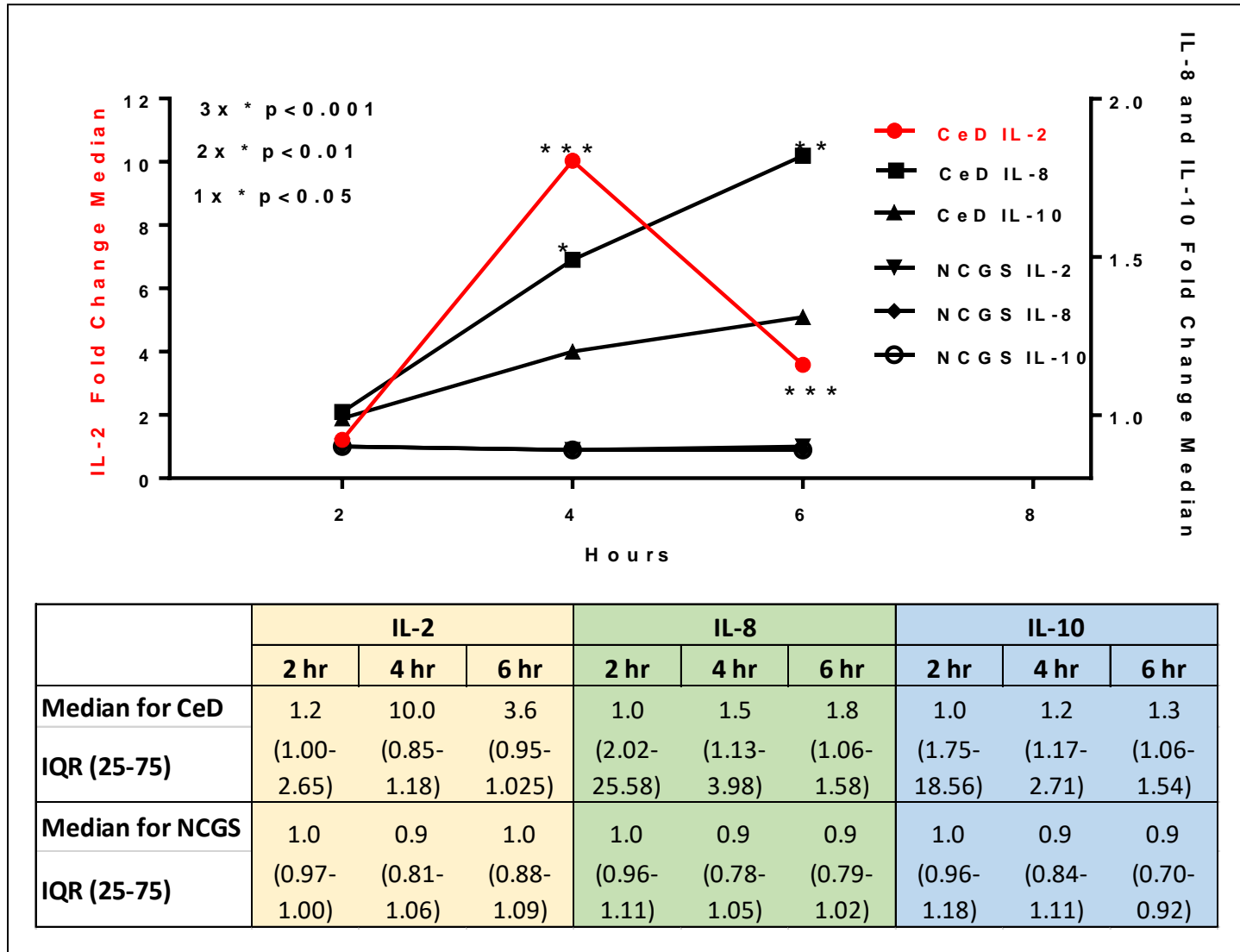
Gry I. Skodje,^{1,2,4} Vikas K. Sarna,^{2,3} Ingunn H. Minelle,⁴ Kjersti L. Rolfsen,⁴ Jane G. Muir,⁵ Peter R. Gibson,⁵ Marit B. Veierød,^{4,6} Christine Henriksen,^{2,4} and Knut E. A. Lundin^{2,3,7,8}



Individual courses



4-hour test distinguishes CD and NCGS!



Wrap up

- 14 d gluten challenge in CD
 - Symptoms, slow serological response, but mucosal response and immune response
 - Efflux of IL-2, IL-8, IL-10 within 4 hours
- 7 d gluten challenge in NCGS
 - None of the above
 - Symptoms of FODMAP challenge
 - (But the participants are still on a GFD...)
- Where did the innate response to gluten go?



Thanks!

- UiO/OUS
 - Gry Skodje
 - Vikas Sarna
 - Christine Henriksen
 - Marit Veierød
 - Margit Brottveit
 - Ludvig M. Sollid
- Monash University
 - Jane Muir
 - Peter Gibson
- ImmusanT
 - Bob Anderson
 - Leslie Williams
 - John Dzuris
 - Gautam Goel
- Exstrafoundation
- Helse Sør-Øst
- All the participants!

