Grain Intolerances: who should avoid grains for health reasons?



Faculty of Health, Medicine and Life Sciences
NUTRIM- School of Nutrition and Translational Research in Metabolism
The Netherlands

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and are used solely for educational purpose

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Tarwe en gluten zijn de oorzaak van overgewicht en vele chronische ziekten



The question is: "what do the data really tell us?"

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International research Consortium 2017- 2021

WELL ON WHEAT?

- **7 research partners, NL, UK, Spain, DL**
- **20 funding partners: world wide**

http://www.wellonwheat.org

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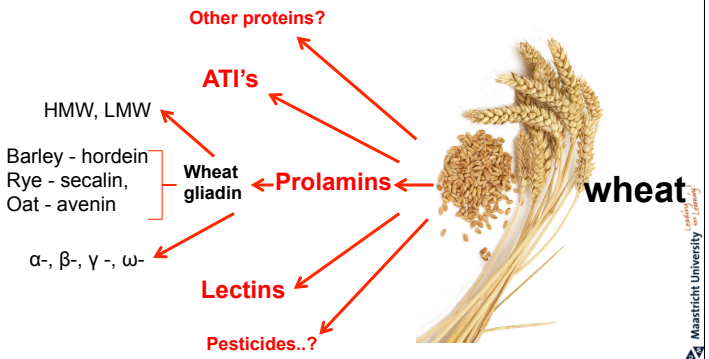
Today's agenda

- Wheat protein:
  - Composition
  - Digestion
  - Components that may trigger intolerance
- Gluten and wheat related disorders:
  - Wheat allergy,
  - Celiac Disease
  - Non Celiac Gluten/Wheat Sensitivity
- ATIs –amylase trypsin inhibitors
- FODMaPs
- Take home messages

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Components that may trigger intolerance

Wheat gluten: storage protein (75-85% of total protein) composed of prolamin (gliadin) and glutenin in a ratio of 2:1*



*Schalk et al PLOS ONE 2017 | DOI:10.1371/journal.pone.0172819

5

Wheat proteins

Albumins & Globulins- 10-20% | **Gluten 80-90%**

14 families of proteins: LTPs, Serpins, Lectins, Purinins, Farinins, ATIs, a.o.

Prolamins family Gliadins Glutenins

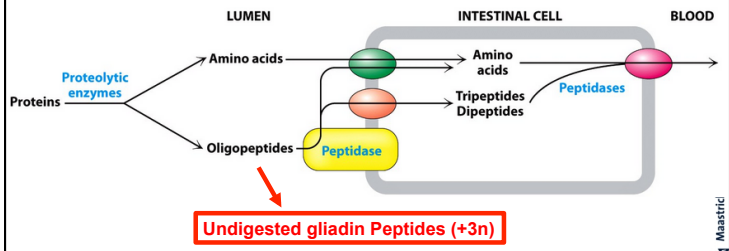
Human small intestinal digestibility of wheat protein* = 90.3 ± 4.3%,

similar to most plant proteins.

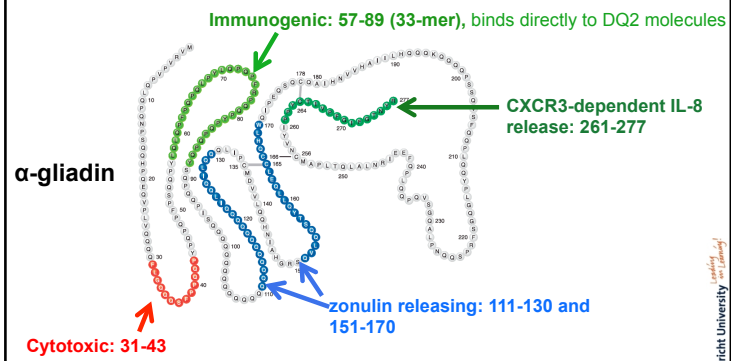
*Bos C. et al Am J Clin Nutr 2005;81:87–94.

Wheat Protein

- **Parts of gluten remain undigested➔ toxic gliadin epitopes**



Indigestible gluten fragments (peptides) involved in CD inflammation and immune activation



Fasano A. Physiol Rev 91: 151–175, 2011;

Wat is gluten?



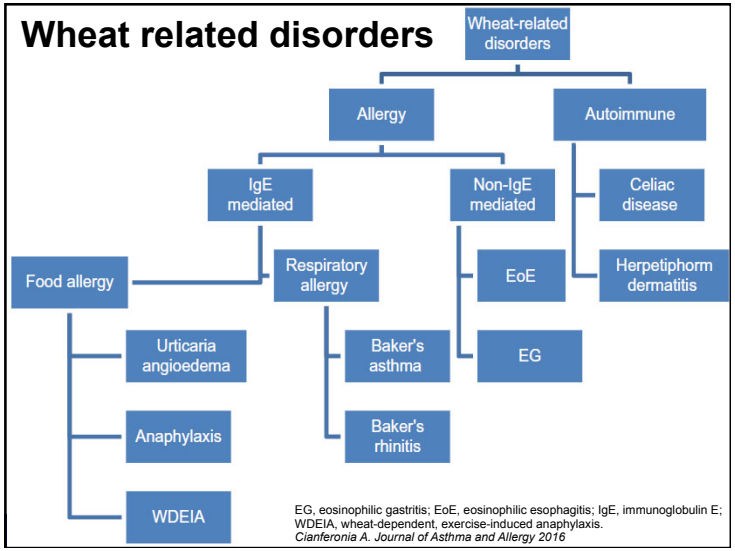
What is gluten?



Gluten elastic network entraps the gas in the dough

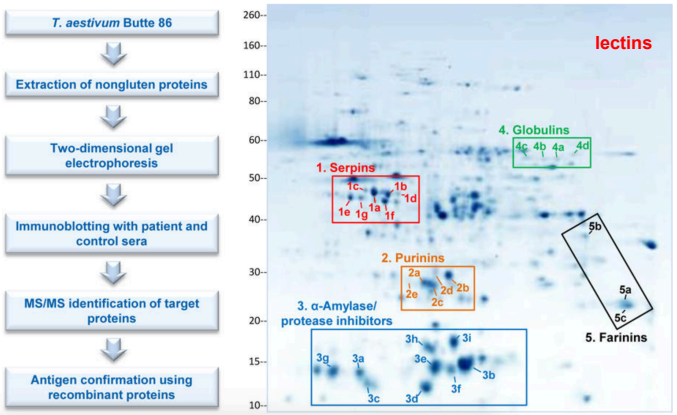


Wheat related disorders



EG, eosinophilic gastritis; EoE, eosinophilic esophagitis; IgE, immunoglobulin E; WDEIA, wheat-dependent, exercise-induced anaphylaxis.
Cianferonia A. Journal of Asthma and Allergy 2016

Non gluten proteins in wheat that may trigger allergy and/or Celiac disease



Huebener 2015, Journal of Proteome Research, 14(1), 503–511.

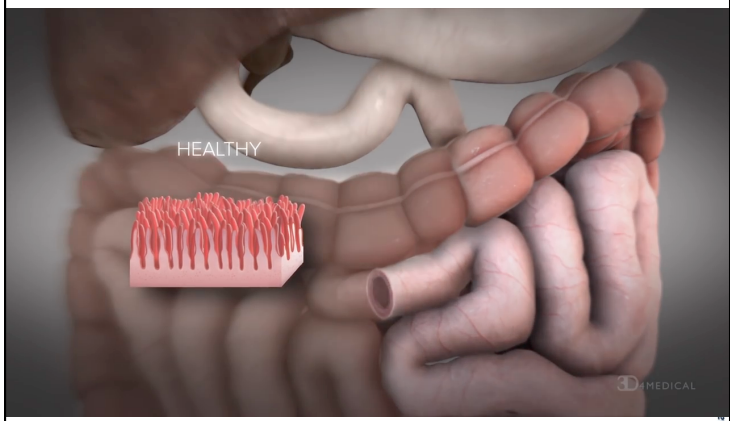
Wheat & Gluten- allergy

- Wheat allergy: 0.5% (0.25- 3%) ←→ many proteins, eg. ATI's

Allergen name	Allergen abbreviation	Molecular weight (kDa)	Reference
α-purothionin	Tri a 37	37	32–34
α-amylase/trypsin inhibitor	Tri a 28 and Tri a 29.01	12–16	5,29
Peroxidase	Tri a Bd36 kd	36	37,38
Thioredoxin	Tri a 25	25	39–41
Lipid protein transfer	Tri a 14	14	29,35,36,128
Serine proteinase inhibitor	Tri a 29	9.9	42,43
Thaumatin-like protein (TLP)		21–26	44
Gliadin	ω-5-gliadin	65	30,31,45
Thiol reductase	Tri a 27	27	128,129
1-cys-peroxiredoxin	Tri a 32		128,130
Serine protease like inhibitor	Tri a 39		128,130

Cianferonia A. Journal of Asthma and Allergy 2016
Gilissen L. et al Journal of Cereal Science Vol. 59, 3, 2014, 337-353

Ceilac Disease



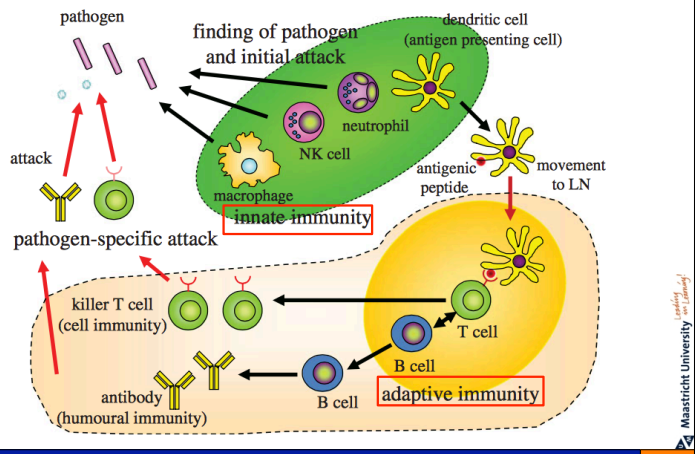
What is Celiac disease? https://www.youtube.com/watch?v=RacnTR4Ceds

Celiac Disease

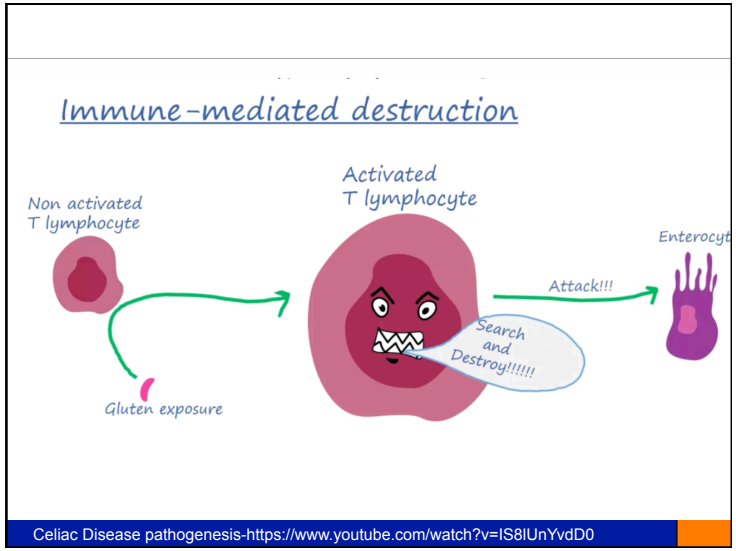
- Predisposition (HLA-DQ2, DQ8 in up to ≈ 40% of the population ➔ of which 2- 3% develops CD
- Global celiac disease: 1% (0.2-5.6%).
- USA 0.2% in 1975 ➔ ≈ 1% today ➔real increase, or better diagnosis, registration?
- Finland-Sweden 2-3% but Germany 0,2%, yet having similar causal factors (consumption, DQ2, DQ8)
- There appears to be a paradoxal distribution of CD and causal factors: area's with high wheat consumption ➔ low CD and area's with low CD yet high DQ2, DQ8 prevalence
- Diagnosis: autoantibodies against tissue transglutaminase 2 (anti-tTG2), endomysium and/or deamidated gliadin peptide

Leonard et al JAMA. 2017;318(7):647-656,

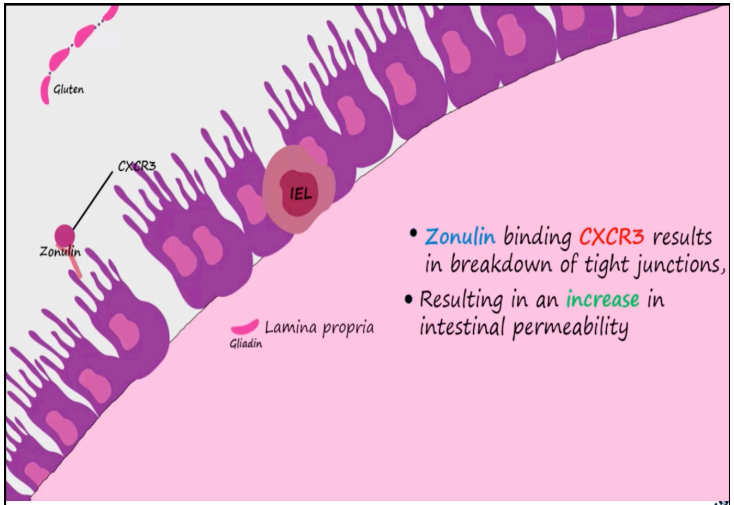
Interactions of innate - adaptive immunity.



Akira Phil. Trans. R. Soc. B (2011) 366, 2748–2755

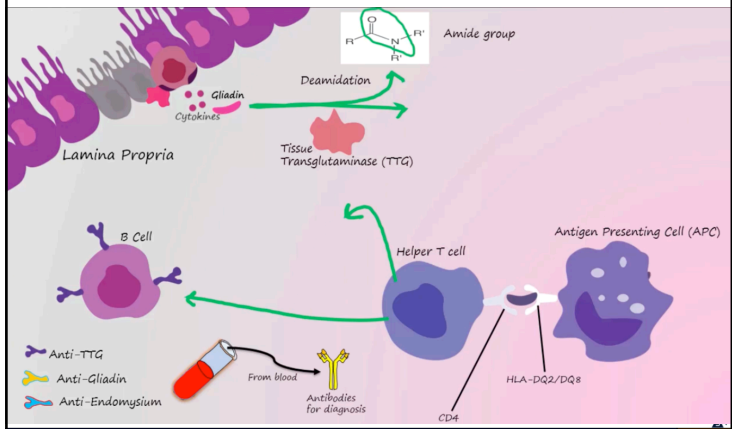


Celiac Disease pathogenesis-https://www.youtube.com/watch?v=IS8lUnYvdD0

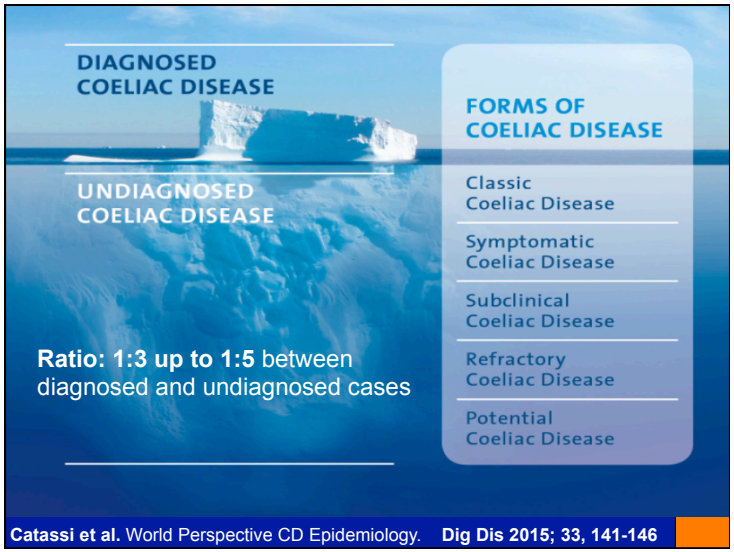


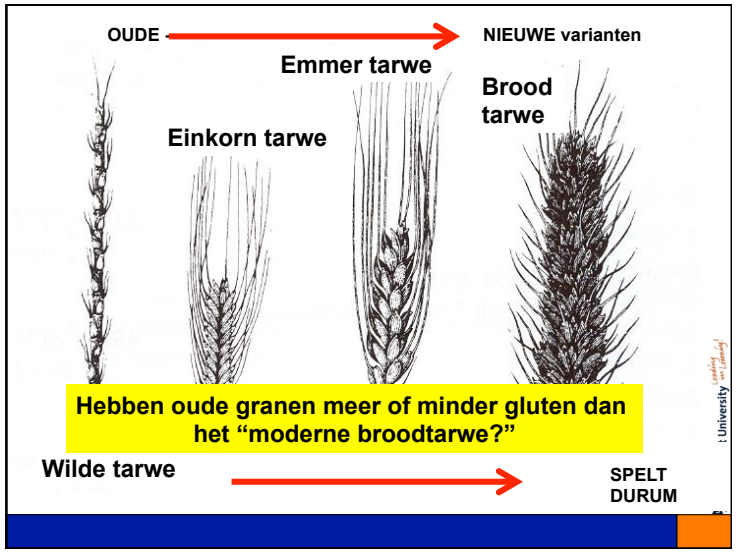
Celiac Disease pathogenesis-https://www.youtube.com/watch?v=IS8lUnYvdD0

In genetically predisposed individuals immune response and inflammation may result in CD



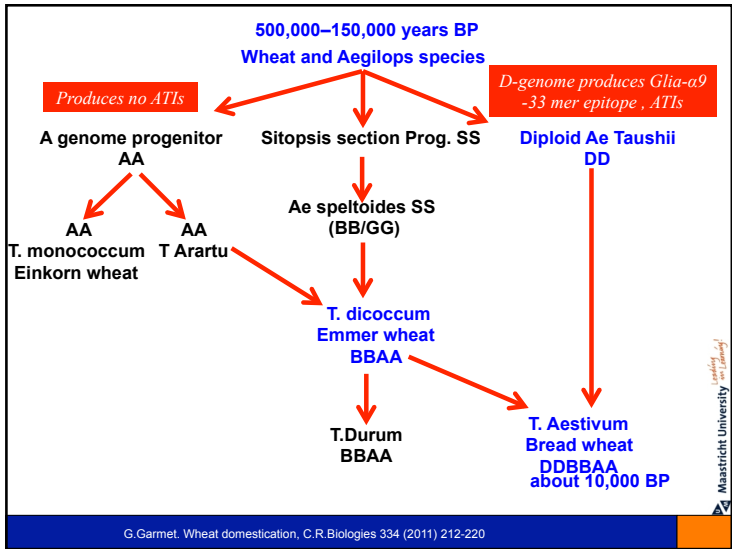
Celiac Disease pathogenesis-https://www.youtube.com/watch?v=IS8lUnYvdD0



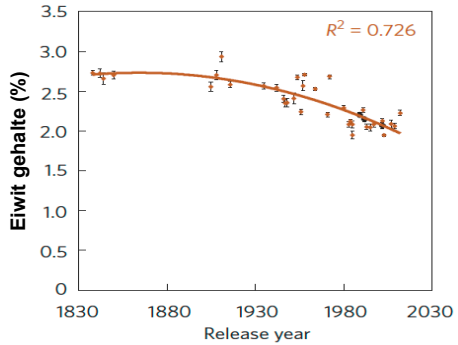


Wheat genomes

- Diploid: AA
  - Einkorn (T-monococcum)
- Tetraploid: AABB
  - Emmer (T. turgidum L. ssp. dicoccum)
  - Durum (T. turgidum L. ssp. Durum)
  - Rivet (T. turgidum L. ssp. Turgidum)
  - Khorasan wheat (Triticum turgidum L. ssp. Turanicum)
- Hexaploid:AABBDD
  - Modern wheat = breadwheat (Triticum aestivum spp. aestivum)
  - Spelt (T. aestivum ssp. Spelta)



Tarwe-eiwit: veranderingen in de tijd



Gegevens van 150 tarwe soorten geteeld onder exact dezelfde omstandigheden (water, stikstof, klimaat, zonlicht, gewasbeschermingsmiddelen)

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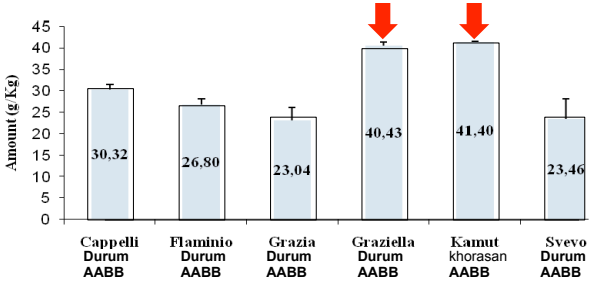
Immunogenicity Characterization of Two Ancient Wheat α-Gliadin Peptides Related to Coeliac Disease

Armando Gregorini [1,*], Mariastella Colomba [2], H. Julia Ellis [3] and Paul J. Ciclitira [3]

Nutrients 2009, 1, 276-290; doi:10.3390/nu1020276

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Ancient tetraploid durum wheats - Graziella Ra® and Kamut® have more gluten than modern varieties and a higher α-gliadin content than modern counterparts



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Figure 2. A-gliadin peptide p31-49 (LGQQQPFPPQQPYPQPQPF)

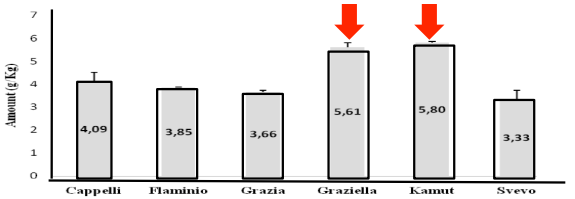
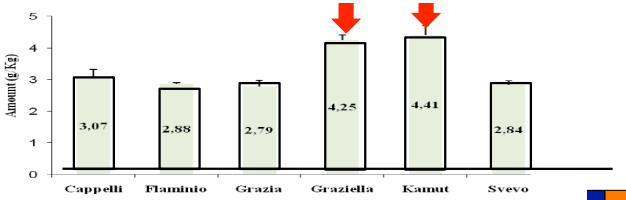


Figure 3. A-gliadin peptide p56-75 (LQLQPFPQPQLPYPQPQLPY)



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Wheat genomes, wheat types

- AA
  - Einkorn
- AABB
  - Emmer
  - Durum
  - Rivet
  - Khorasan wheat
- AABBDD
  - Bread wheat
  - Spelt

Differ in protein content composition depending on genes, environment and climate:

- Gluten composition ➔ toxic epitopes
- ATI content and isoforms
- Fructan content
- etc

Differences in immune reactivity profiles:
- Allergy,
- CD
- NCWS

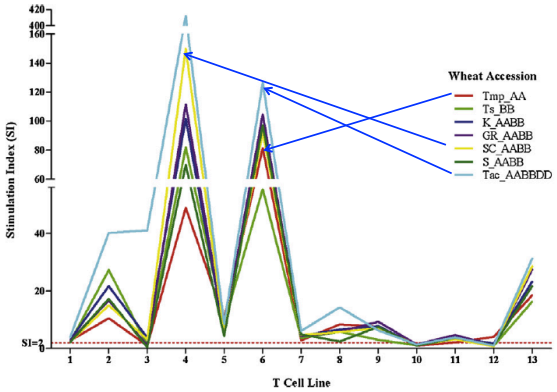
Evaluation of immune reactivity of ancient wheats in coeliac disease

	Wheat species (accession)	Ploidy and genome	Name in the manuscript
Ancient wheat	*T. monococcum precoce*	diploid, AA	Tmp_AA
	T. speltoides	diploid, BB	Ts_BB
	T. turgidum durum (Kamut)	tetraploid, AABB	K_AABB
	T. turgidum durum (Graziella Ra)	tetraploid, AABB	GR_AABB
Modern wheat	*T. turgidum durum* (Senatore Cappelli)	tetraploid, AABB	SC_AABB
	T. turgidum durum (Svevo)	tetraploid, AABB	S_AABB
	T. aestivum compactum	hexaploid, AABBDD	Tac_AABBDD

AB wheat with better tolerance..?

Suligoj et al Clinical Nutrition 32 (2013) 1043e1049

All wheat types appear to be immunoreactive!



Our findings provide further evidence for the need for a strict gluten-free diet in coeliac patients, including avoidance of ancient types of wheat.

Suligoj et al Clinical Nutrition 32 (2013) 1043e1049

Nutritional Wheat Amylase-Trypsin Inhibitors Promote Intestinal Inflammation via Activation of Myeloid Cells

Victor F. Zevallos, Detlef Schuppan et al

Gastroenterology

April 2017

DOI: 10.1053/j.gastro.2016.12.006

Wheat proteins

Albumins & Globulins- 10-20% | **Gluten 80-90%**

14 families of proteins: LTPs, Serpins, Lectins, Purinins, Farinins, ATIs, a.o.

Gliadins **Glutenins**

- **Highly disulphide linked and protease-resistant proteins**
- **19 encoding genes**
- **19 isoforms**
- **3 subfamilies:**
  - 50–60 kDa subfamily of (CM) protein tetramers,
  - 24-kDa subfamily of dimers
  - 12-kDa subfamily of monomers

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Amylase Trypsin Inhibitors- ATIs

- Present in all cereals to fend off parasites and insects (eg. mealbug, inhibiting digestion)
- Primarily present in endosperm- supporting starch/protein storage.
- Isolated vital wheat gluten used as food technological aid/bread improver contains ATIs (as isolated protein co- passengers)

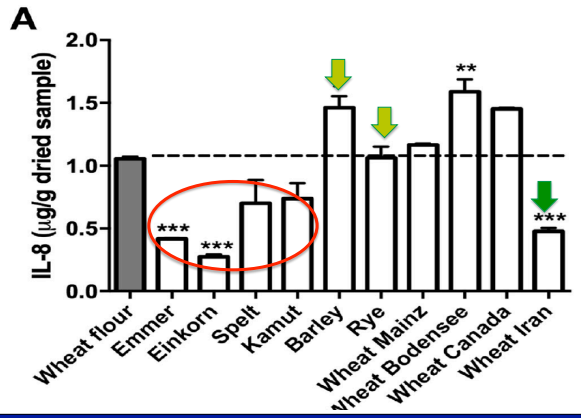
- ATIs largely remain intact during food processing and intestinal digestion;
- Major allergen in baker's asthma (8% of bakers within 2 years after starting profession).

- Bind to and activate the TLR4 (CD14-MD2 toll-like receptor 4) in intestinal myeloid cells, dendritic cells and macrophages in a dose dependent way.

Junker et al. J. Exp. Med. 2012 Vol. 209 No. 13 2395-2408

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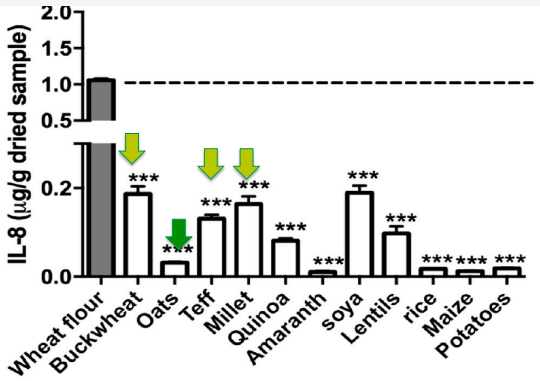
In mice, old wheats (Emmer, Einkorn) have lower ATI bioactivity than modern bread wheat.



Victor F. Zevallos et al. Gastroenterology April 2017

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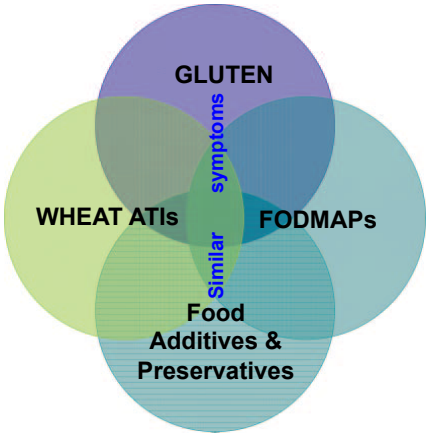
Most wheat-free foods have up to a 100 fold lower ATI activation of TLR4



Victor F. Zevallos et al. Gastroenterology April 2017

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Triggers of NCGS



Volta et al Cellular & Molecular Immunology (2013) 10, 383–392

Wheat & Gluten intolerances: Non celiac gluten sensitivity (NCGS)

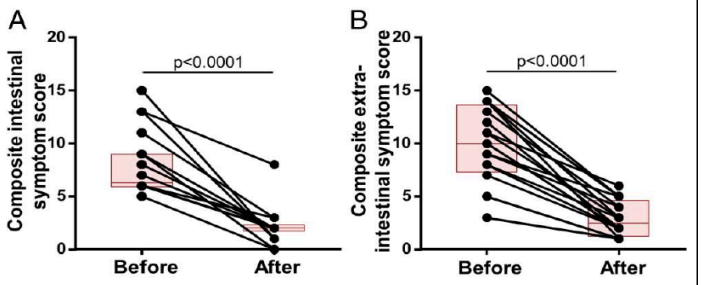
- Estimated prevalence: 3-5% BUT, up to 35% of population may state to feel better when avoiding gluten and/or wheat
- 2/3 of these individuals are higher educated, social media active females.
- Up to 60% of these individuals have a high psychiatric co-morbidity and a high representation of irritable bowel syndrome which has multifactorial food and mental causes.
- Hypnotherapy is as effective as low FODMaP*
- How much is real, how much is based on belief?

* Peters, et al. APT 2016; 44: 447-459

NCWS manifestations

- Gastrointestinal:
  - abdominal pain, nausea, bloating, diarrhea, constipation.
- Extra-intestinal associated conditions:
  - Body: fatigue, headache, dermatitis and joint/muscle pain.
  - Mental: lethargy, depression, anxiety hallucinations, psychosis,.
- Symptoms improve with gluten/wheat avoidance and re-appear with compound re-challenge.
- NCGS/NCWS (IBS) requires a strict multidisciplinary individual guidance: medical, dietary, psychological.

6 months of a diet free of wheat, rye and barley reduces symptoms in NCWS



bloating, abdominal pain, diarrhoea, epigastric pain and nausea

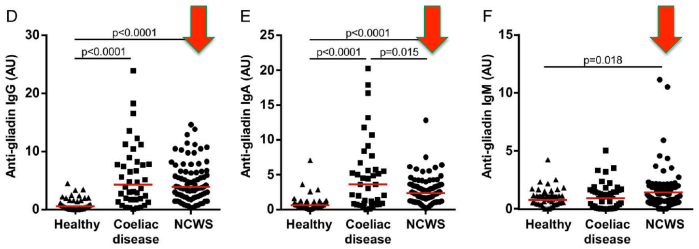
fatigue, headache, anxiety, memory and/or cognitive disturbances, and numbness in arms and/or legs

Uhde M, et al. Gut 2016;0:1–8. doi:10.1136/gutjnl-2016-311964

ORIGINAL ARTICLE

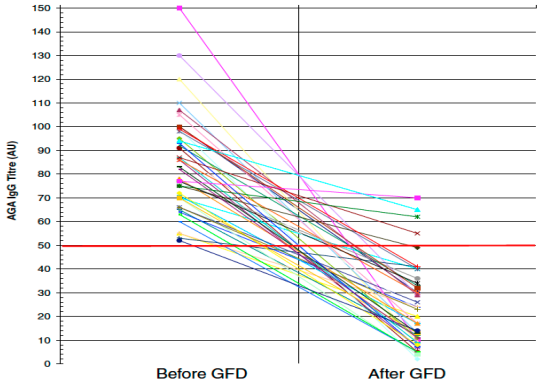
Intestinal cell damage and systemic immune activation in individuals reporting sensitivity to wheat in the absence of coeliac disease

Melanie Uhde,[1] Mary Ajamian,[1] Giacomo Caio,[2] Roberto De Giorgio,[2] Alyssa Indart,[1] Peter H Green,[1,3] Elizabeth C Verna,[1] Umberto Volta,[2] Armin Alaedini[1,3,4]



Uhde M, et al. Gut 2016;0:1–8. doi:10.1136/gutjnl-2016-311964

Effect of wheat free diet on immune response to gluten in NCGS patients



Caio et al. BMC Gastroenterology 2014, 14:26

The Dietary Fibers–FODMAPs Controversy

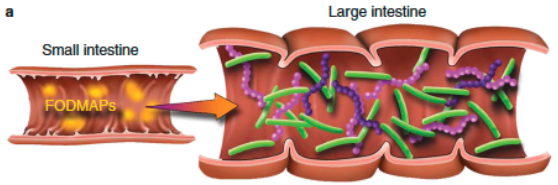
F. Brouns,[1] N. Delzenne,[2] and G. Gibson[3]



Holland Belgium England

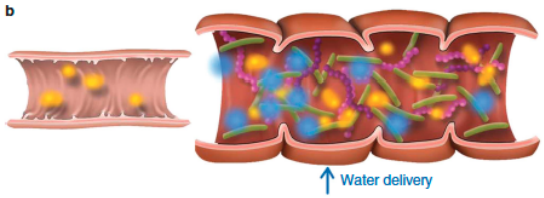
Cereal Foods World issue May/June 2017, Vol 62, nr 3, p 98-103

FODMaPs rapid fermentation effects



Shepherd , et al. Am J Gastroenterol 2013; 108:707–717; doi: 10.1038/ajg.2013.96

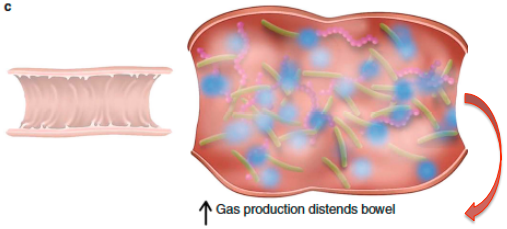
FODMaPs rapid fermentation effects



Shepherd , et al. Am J Gastroenterol 2013; 108:707–717; doi: 10.1038/ajg.2013.96

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FODMaPs rapid fermentation effects



Shepherd , et al. Am J Gastroenterol 2013; 108:707–717; doi: 10.1038/ajg.2013.96

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Fiber and FODMaP content in grains

Grain	TDF	IDF	SDF	inulin	β-glucan	AX
Whole Wheat	11.6-17.0	10.2-14.7	1.4-2.3	0.6-1.8	0.2-0.7	5.2-7.8
Wheat Bran	36.5-52.4	35.0-48.4	1.5-4.0	-	-	-
Whole rye	15.2-20.9	11.5-16.0	3.7-4.5	0.6-1	0.13-.17	8.2-10.0
Rye bran	35.8	30.3	5.3	-	-	-
Whole oat	11.5-37.7	8.6-33.9	2.9-3.8	0.6-1	1.7-5.7	3.5-12.6
Oat bran	18.1-25.2	14.4-20.2	3.6-5.0	-	-	-

TDF-total dietary fiber (DF); IDF insoluble DF, SDF-soluble DF, AX-arabinoxylan.
(Sources: Vitaglione et al. 2008,, ElKhoury,et al 2006 , MESSIA 2012, et al, Andersso nd Aman P.. 2001, Biesiekierskie 2011)

Based on the low fructan content (0.1-1.0g/portion) it is unlikely that wheat FODMAPS play a sign role in intolerance.

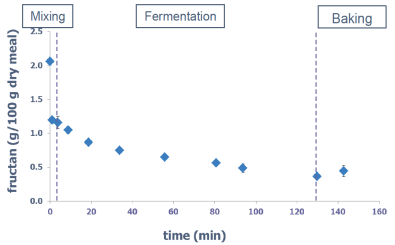
Brouns, Delzenne and gibson. Cereal Foods World- May-June 2017 vol 62, nr 3

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Degradation during food processing

Fructan degradation during bread making

Fructan is degraded during bread making by yeast

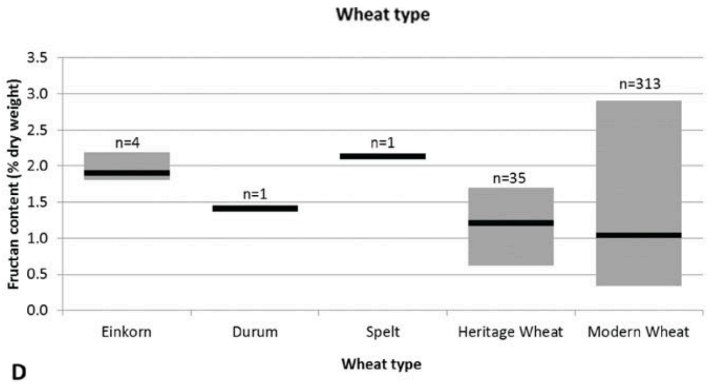


- Degradation mainly during mixing and first 30 min of fermentation
- ± 80% fructan degradation with 5.3% yeast

jJ.Verspreet, C.Courtin, Health Grain Forum, Leuven, May 2, 2017

KU LEUVEN

(D) fructan content



Kissing Kucek- Sorrells et al Vol.14,2015 ComprehensiveReviewsinFoodScienceandFoodSafety

Take home messages

Tarwe en Gluten Intoleranties

Coeliakie	Tarwe allergie	Sensitief, geen coeliakie
Gluten	Gluten en andere eiwitten	Tarwe eiwitten, nog niet duidelijk welk(e)
Specifieke antistoffen: oa. TTG, anti-D-gliadine	IgE antistoffen	TTG, IgE negatief, vaak anti-D-gliadine positief

Catassi et al. Nutrients 2015, Fasano et al Gastroenterol 2015, Catassi et al. Nutrients 2017,.

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CD/Allergy or NC-sensitivity?

- CD: diagnosis after clinical evaluation of specific serology, and histopathology of duodenal biopsy.
- CD treatment is a lifelong avoidance of gluten.
- Allergy: skin prick testing and specific IgE as first-line test (not 100% sure). Check relevance of + test by elimination diet

- NCGS/NCWS: is an emerging cluster of clinical features.
- Mucosal gene expression and intestinal barrier function data point to adaptive immune involvement in CD and innate immune activation in NCGS/NCWS.
- Avoid self diagnosis, FIRST rule out CD, in case of negative follow-up with GFD- rechallenge testing

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Carlo Catassi et al
An intl. expert panel paper

Article

Diagnosis of Non-Celiac Gluten Sensitivity (NCGS): The Salerno Experts' Criteria

A full diagnostic procedure should:

1. assess the clinical response to the wheat/gluten-free diet (GFD)
2. measure the effect of a gluten re-challenge after a period of GFD

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Take home messages

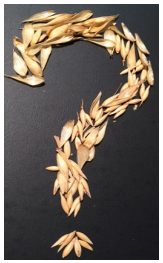
- ≥ 90% whole wheat/whole grain is GREAT food with disease preventive properties.
- All wheats are immuno-reactive in ALA= DQ2 / DQ8 persons
- None of the ancient or modern wheats are safe for CD
- 3-5% (?) of individuals develop symptoms without CD or Allergy ➔ NCWS- No diagnostic test available!
- ATI's are being suggested to play a significant role in NCWS/NCGS. Yet, tested only in animals and cell lines by one research group.
- NCWS/NCGS; **how much is real, how much is based on belief?**

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Suggested ways to reduce grains reactivity:

- Use old wheat varieties einkorn, emmer ➔ CD unsafe!
- Select for varieties low in gluten epitopes ➔ CD unsafe!
- Select for types low in ATI reactivity ➔ better tolerance??
- Reduce gluten content by using proteases during dough making ➔ loss of gluten structure ➔ poor baking quality ➔, CD unsafe (>20ppm)!
- Breakdown gluten in the small intestine by ingesting capsule with glutanase/proteases➔ 100% degradation ??➔CD unsafe!
- Gluten free➔ CD safe only when processed in a gluten free agri-food chain!

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WELL ON WHEAT?

http://www.wellonwheat.org

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