Why Are Celiac Disease and Gluten Sensitivity on a Rise?

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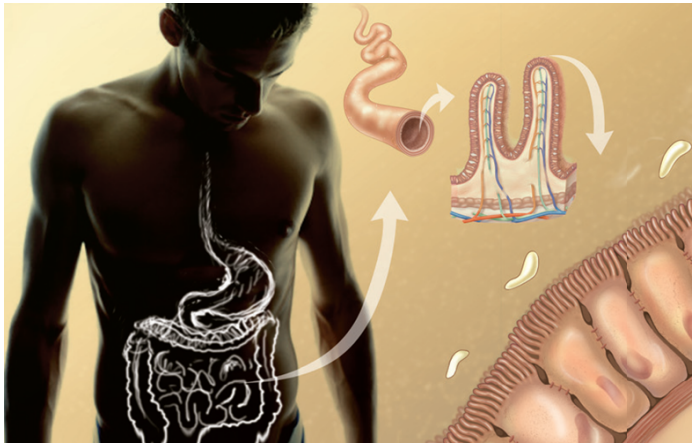
MassGeneral Hospital for Children

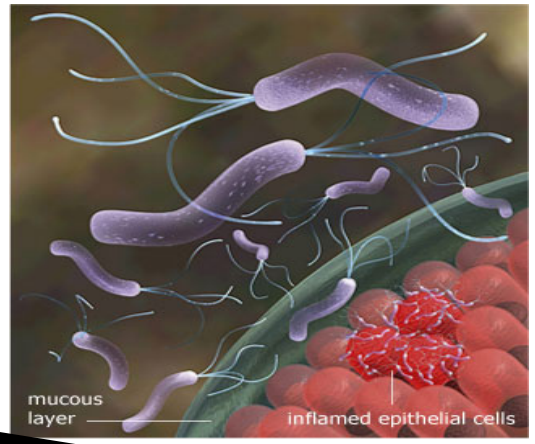
Harvard Medical School

Lecture Objectives

Gluten + Genes = Celiac Disease

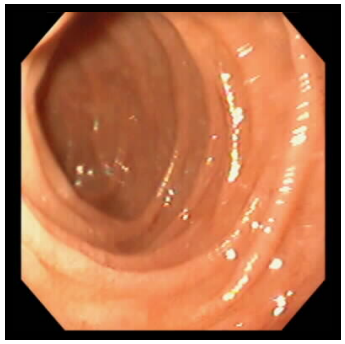
Not So Fast!

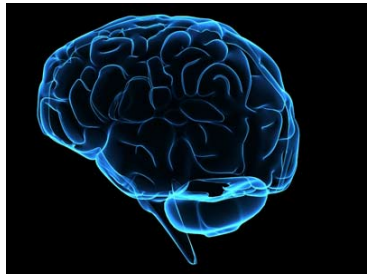


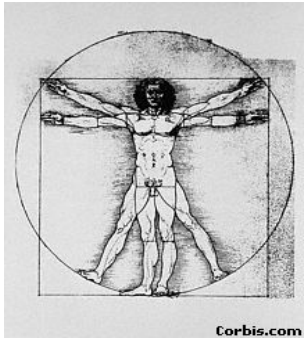


Microbiome

Environmental
Factors







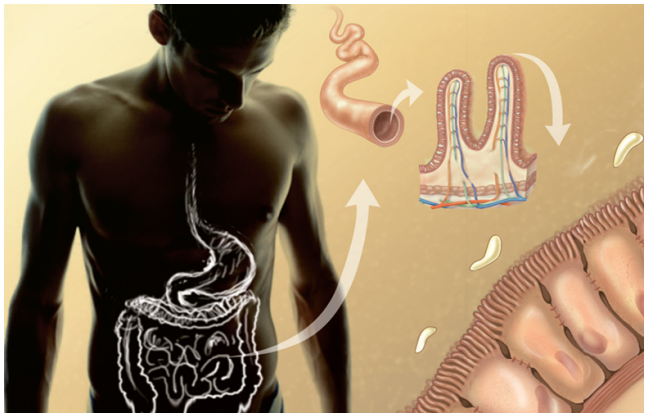
Clinic Outcome

The intestom is a long tube with a clen open om the top and a dirty open at the bottom

All disease begins in the gut - Hippocrates 460 BC

The gut is not like Las Vegas: what happens in the gut does not stay in the gut –
A.F. 2010 AC

The intestinal mucosa is the battlefield on which friends and foes need to be recognized and properly managed to find the ideal balance between tolerance and immune response.



Celiac disease as the ideal paradigm to study how friends can become foes.

The Banana Babies

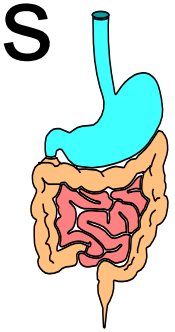
WK Dicke, 1905 - 1962

1st case of CD at UMB: 1938

Celiac Disease as a Unique Model of Autoimmunity

- **The only autoimmune disease in which specific MHC class II HLA (DQ2 and/or DQ8) are present in >95% of patients;**
- **The auto-antigen (tissue Transglutaminase) is known;**
- **The environmental trigger (gluten) is known;**
- **Elimination of the environmental trigger leads to a complete resolution of the autoimmune process that can be re-ignited following re-exposure to gluten**

Gastrointestinal Manifestations ("Classic")



Most common age of presentation: 6-24 months

- Chronic or recurrent diarrhea
- Abdominal distension
- Anorexia
- Failure to thrive or weight loss
- Abdominal pain
- Vomiting
- Constipation
- Irritability

Rarely: Celiac crisis

IG. 2.—Photograph of five cases of coeliac disease showing the general clinical feature

Non Gastrointestinal Manifestations

Most common age of presentation: older child to adult

- **Dermatitis Herpetiformis**
- **Dental enamel hypoplasia of permanent teeth**
- **Osteopenia/Osteoporosis**
- **Short Stature**
- **Delayed Puberty**
- **Iron-deficient anemia resistant to oral Fe**
- **Hepatitis**
- **Arthritis**
- **Epilepsy with occipital calcifications**

Listed in descending order of strength of evidence

The Clinical Manifestations of Celiac Disease are More Heterogeneous Than Previously Appreciated

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

Celiac Disease — How to Handle a Clinical Chameleon

Alessio Fasano, M.D.

Celiac disease is an immune-mediated enteropathy triggered by the ingestion of gluten-containing grains (including wheat, rye, and barley) in genetically susceptible persons. The disease is associated

Epidemiologic studies conducted during the past decade, using specific and sensitive serologic tests, have revealed that celiac disease is one of the most common lifelong disorders in both Europe[4]

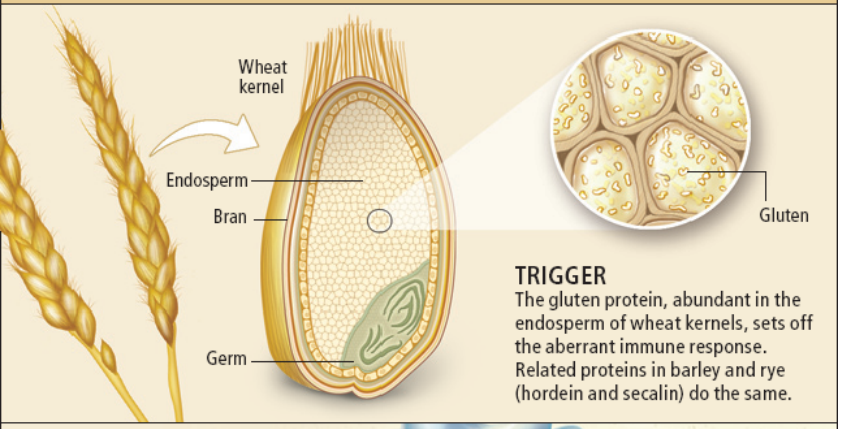
A. Fasano, *N Engl J Med* 2003;348:2568-70.

What is the Recipe to Develop Celiac Disease

The Holy Trinity of the Autoimmune Mechanisms in Celiac Disease

A TRIO OF CAUSES

Three factors underlie celiac disease: an environmental trigger, a genetic susceptibility and, according to the author's research, an unusually permeable gut (*below*). The author suspects that the same basic triad contributes to other autoimmune diseases, although each disorder will have its own triggers and genetic components.

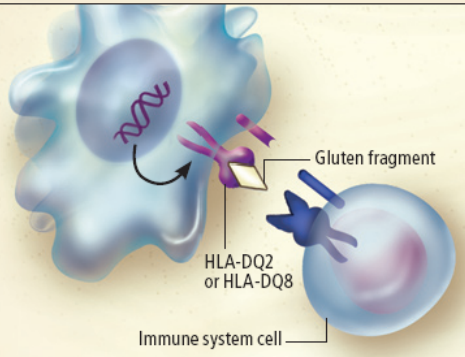


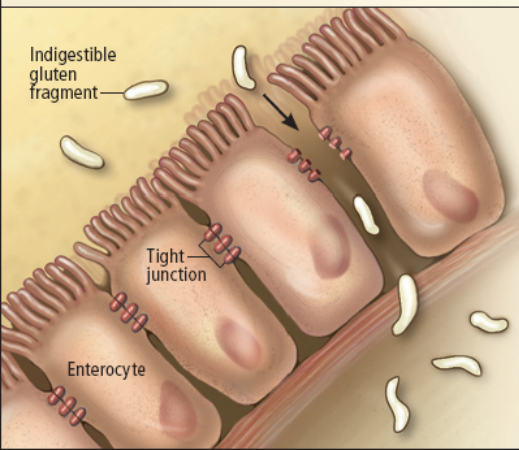
TRIGGER

The gluten protein, abundant in the endosperm of wheat kernels, sets off the aberrant immune response. Related proteins in barley and rye (hordein and secalin) do the same.

GENETIC PREDISPOSITION

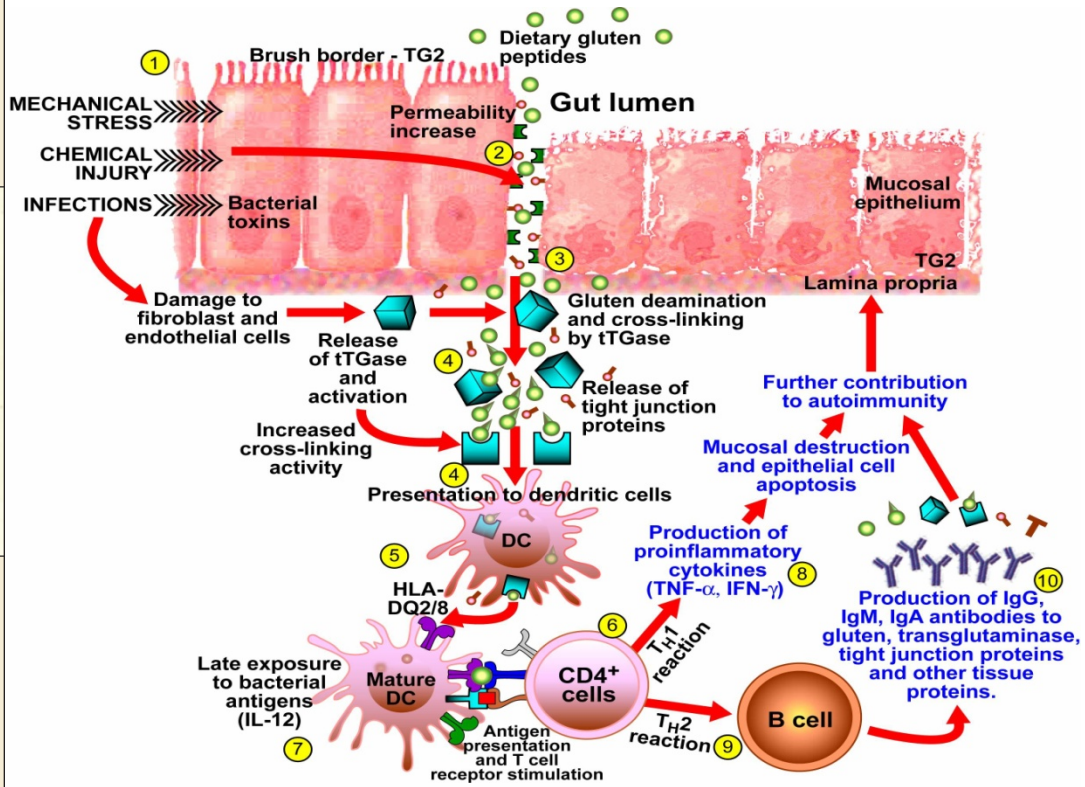
Almost all patients harbor the genes *HLA-DQ2* or *HLA-DQ8*, or both. These genes give rise to proteins of the same name that display gluten fragments to immune system cells, which then direct an attack on the intestinal lining. Other genes are likely to be involved as well, but these additional culprits may differ from person to person.





LEAKY SMALL INTESTINE

In most people, links known as tight junctions "glue" intestinal cells together. In those with celiac disease, the junctions come apart, allowing a large amount of indigestible gluten fragments to seep into the underlying tissue and incite immune system cells. Treatments that reduced leakiness could potentially ease not only celiac disease but also other autoimmune disorders involving unusually permeable intestines.



Depiction of the intestinal mucosa with emphasis on the factors involved in the development of celiac disease in individuals with HLA-DQ2/DQ8 positive

Fasano A; Scientific American Aug. 2009

Understanding Why Gluten is Toxic

THE GRAINS IN THE PAST WERE DIFFERENT FROM THE CURRENT GRAINS

T. turgidum AABB
28 chromosomes
100,000 genes

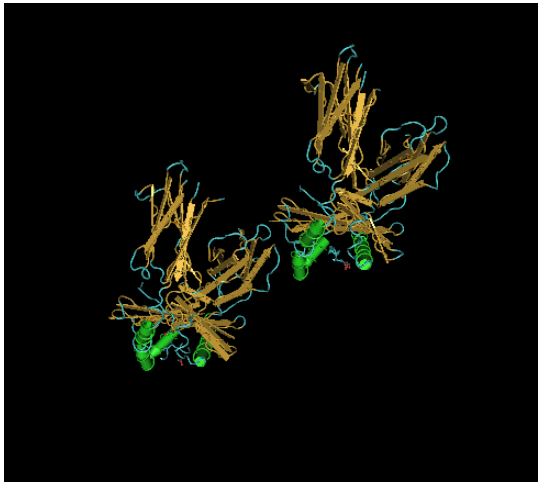
+

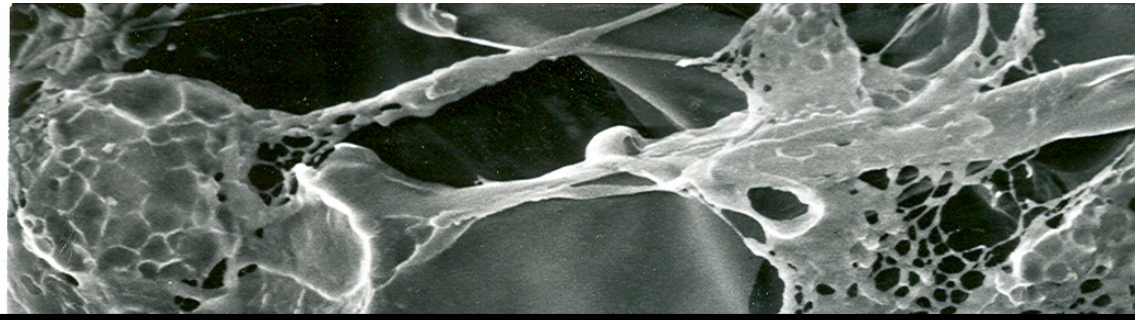
Aegilops tauschii DD
14 chromosomes
50,000 genes

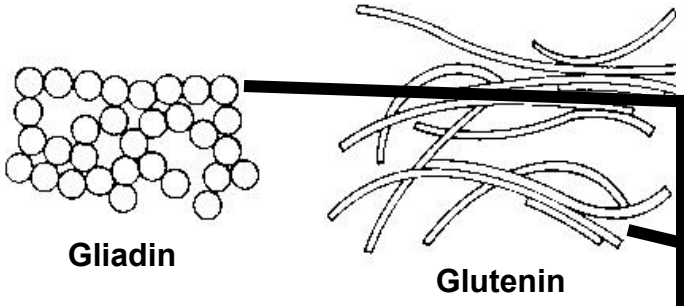
T. aestivum AABBDD
42 chromosomes
150,000 genes

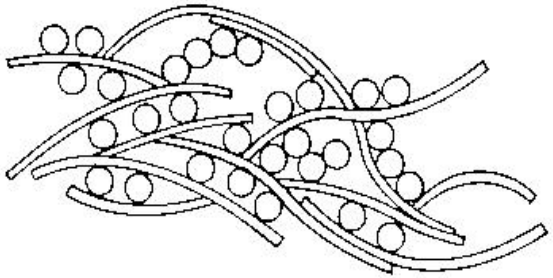
Pieter Bruegel, 1565

What Is So Special About Gluten?

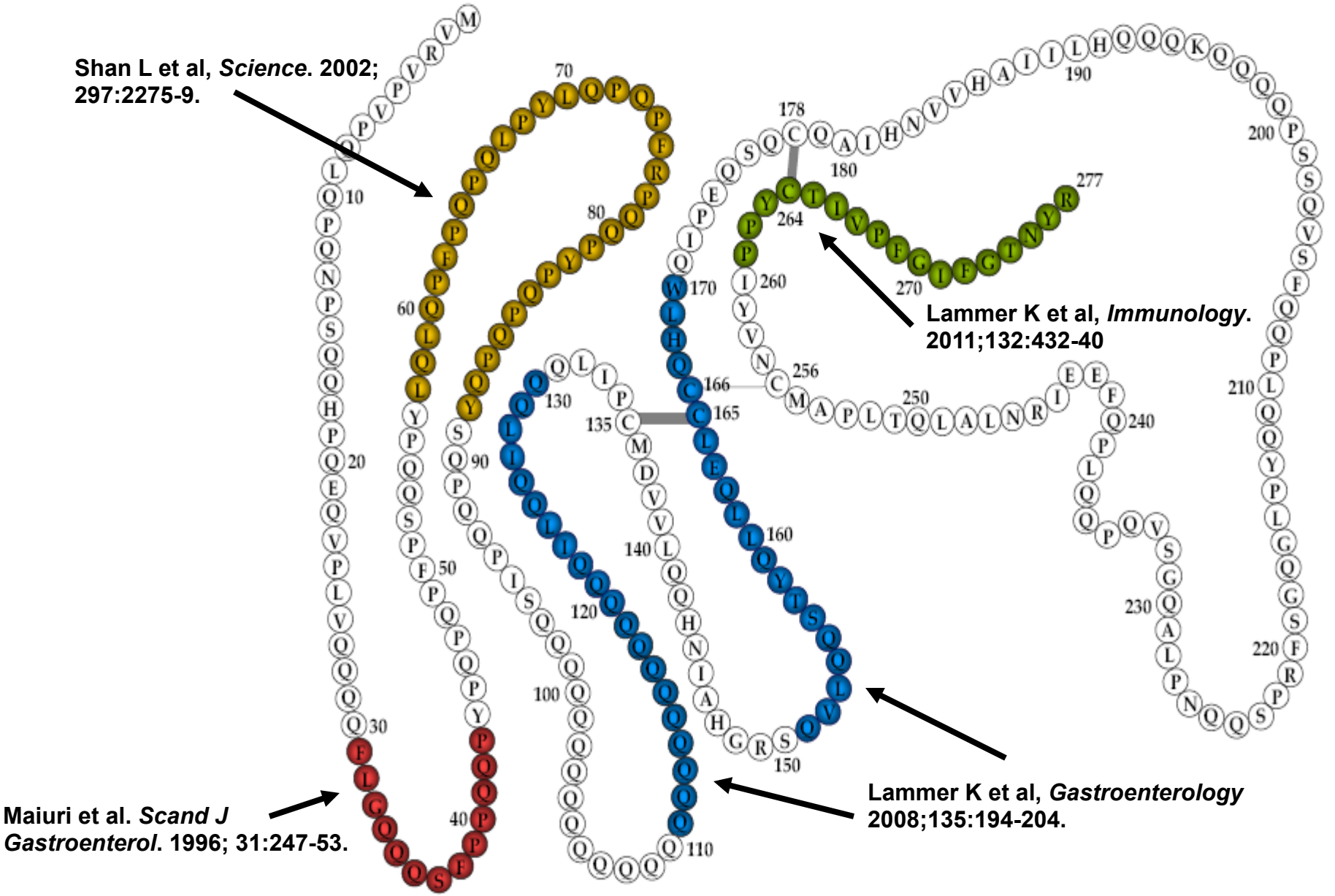




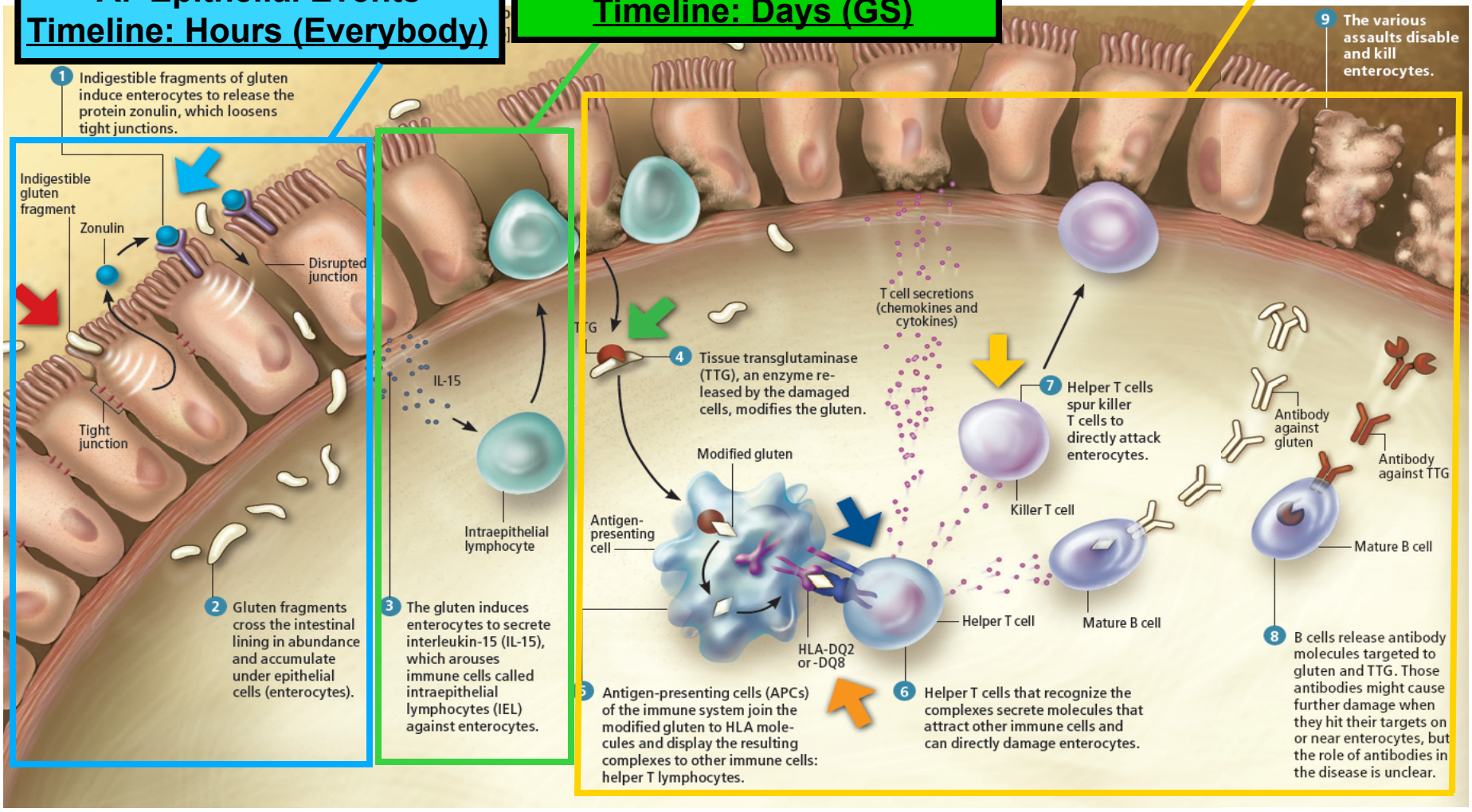




Mapping of α-gliadin motifs exerting cytotoxic activity (red), immunomodulatory activity (light green), zonulin release and gut permeating activity (blue) and CXCR3-dependent IL8 release in CD patients (dark green).



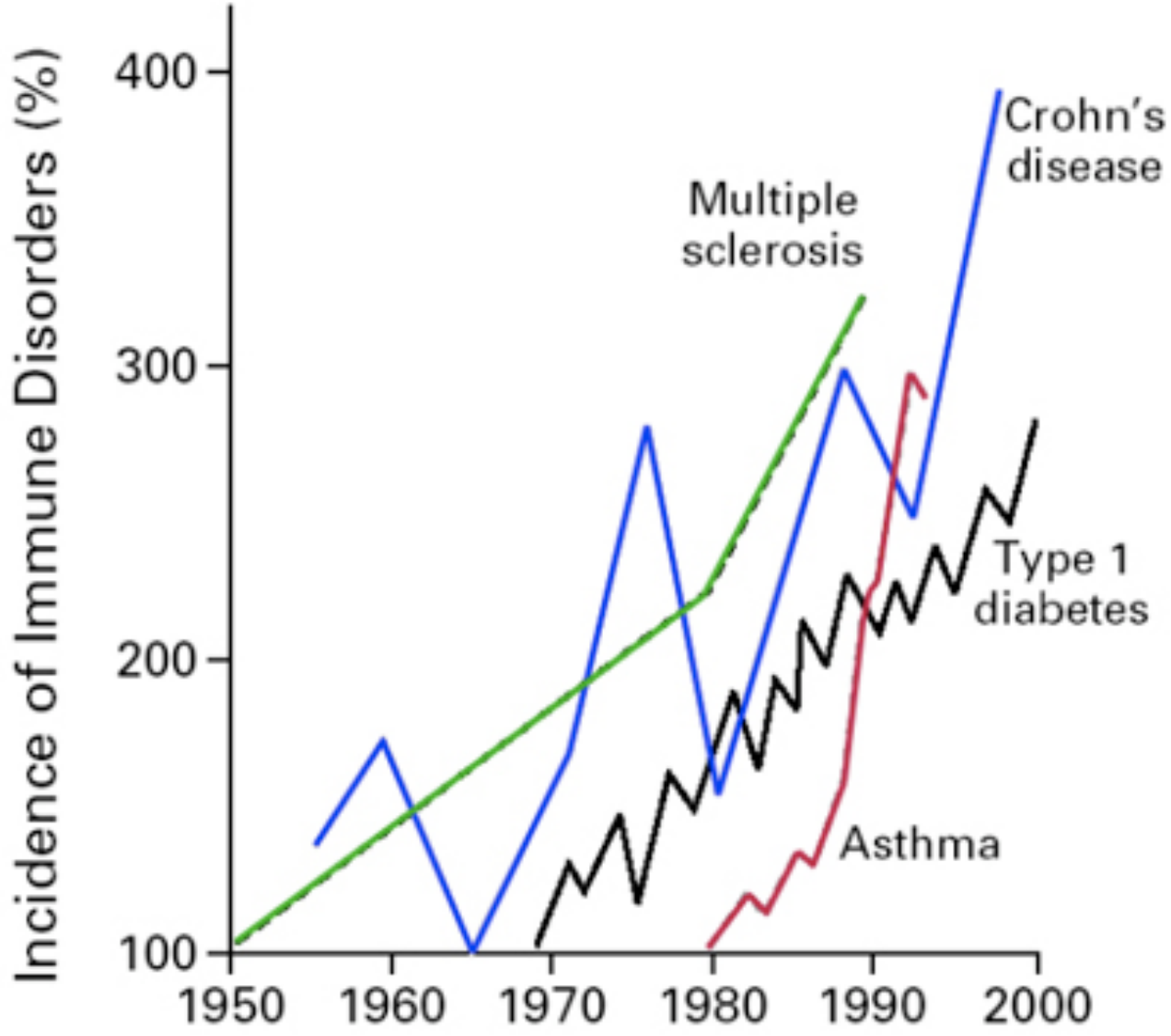
Gluten Triggers Biological Responses In Everybody But Not Everybody Gets Sick Eating Gluten



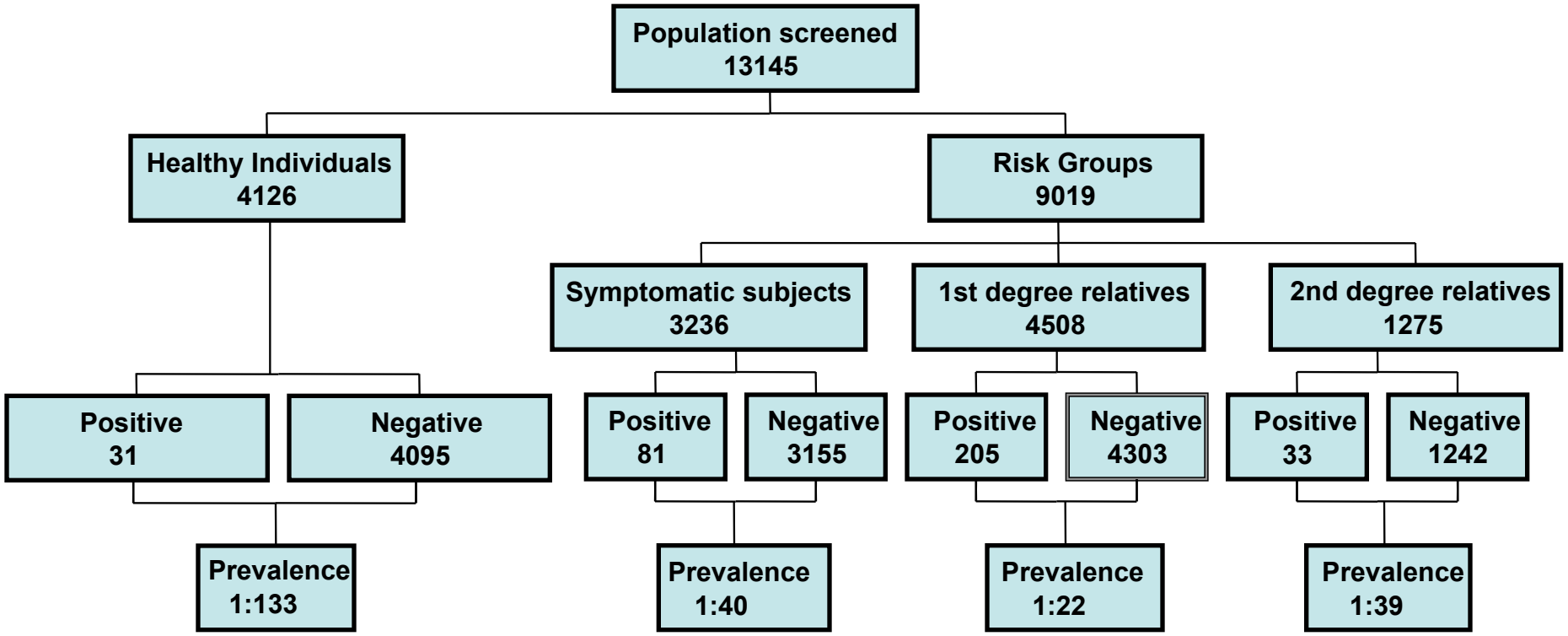
Clemente MG et al *Gut* 2003; Drago et al *Scand J Gastroenterol 2006;* Sapone A. et al. *JADD* 2010

We Are Not Born With The Destiny To Develop Celiac Disease

Autoimmunity Epidemics



Celiac Disease Epidemiological Study in USA

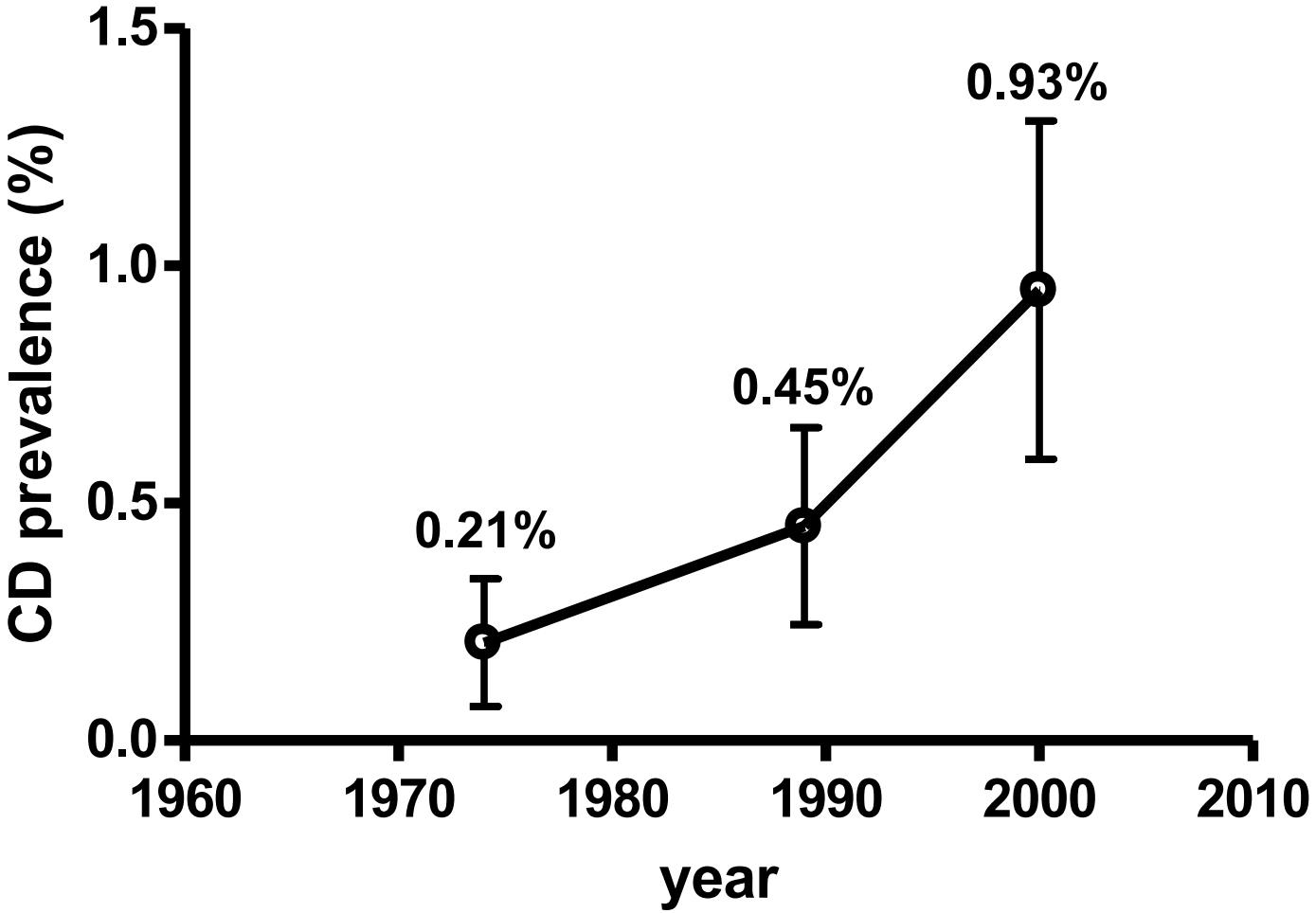


Projected number (conservative) of celiac disease patients in the U.S.A.: 2,115,954
MAJOR PUBLIC HEALTH PROBLEM NATIONAWIDE WITH SOME REGIONAL DIFFERENCES

A. Fasano et al., *Arch Int Med* 2003;163:286-292.

Increased Prevalence Over Time in U.S.A.

(in Line with Other Autoimmune Diseases)



During the past 35 years the true prevalence of CD in USA doubled every 15 years.

C. Catassi et al, Annal Med 2010

Celiac Disease
Autoimmune Pathogenesis

Necessary but <u>NOT</u> Sufficient

Key Questions in CD Pathogenesis

1. What kind of tricks were used by people genetically at risk for CD that were able to tolerate gluten for decades?

2. What happened to them that caused the shift from tolerance to immune response to gluten?

How to Re-Write the Natural History of CD?

The Epidemics Of Celiac Disease:
Which Additional Factors are Driving this Epidemics?

- Quality of gluten;
- Quantity of gluten;
- Breast Feeding;
- Timing of gluten introduction
- Maturity of gut functions influencing Ag trafficking and handling:
    - GALT
    - PRRs
    - Mucous production
    - Barrier function
- Changes in microbiome composition.

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ORIGINAL ARTICLE

Introduction of Gluten, HLA Status, and the Risk of Celiac Disease in Children

Elena Lionetti, M.D., Stefania Castellaneta, M.D., Ruggiero Francavilla, M.D., Ph.D., Alfredo Pulvirenti, Ph.D., Elio Tonutti, M.D., Sergio Amarri, M.D., Maria Barbato, M.D., Cristiana Barbera, M.D., Graziano Barera, M.D., Antonella Bellantoni, M.D., Emanuela Castellano, M.D., Graziella Guariso, M.D., Maria Giovanna Limongelli, M.D., Salvatore Pellegrino, M.D., Carlo Polloni, M.D., Claudio Ughi, M.D., Giovanna Zuin, M.D., Alessio Fasano, M.D., Ph.D., and Carlo Catassi, M.D., Ph.D., for the SIGENP (Italian Society of Pediatric Gastroenterology, Hepatology, and Nutrition) Working Group on Weaning and CD Risk

Published on October 2, 2014

Home Take Messages

- **Window of tolerance concept (4-7 months best period to introduce baby food) not supported anymore;**
- **Breast feeding in general or introduction of gluten while breast feeding showed no protective effect on CD onset in at-risk infants;**
- **Early introduction (16 weeks) of gluten traces to potentially induce tolerance did not protect against CD in at-risk infants;**
- **Delaying the introduction of gluten in at-risk infants does not prevent CD but merely postpones its onset by approximately 8 months (significant difference at 2 years FU that disappeared by 5 years FU);**
- **GI infections during the first year of life seems not influential in increased the risk of CD onset;**
- **High-risk HLA profiles seems to be the most influential factor predictor of increased risk of CD onset;**
- **The high prevalence of CD among the study cohort suggests that the CD epidemics continues.**

The Epidemics Of Celiac Disease:
Which Additional Factors are Driving this Epidemics?

- Quality of gluten;
- Quantity of gluten;
- Breast Feeding;
- Timing of gluten introduction
- Maturity of gut functions influencing Ag trafficking and handling:
    - GALT
    - PRRs
    - Mucous production
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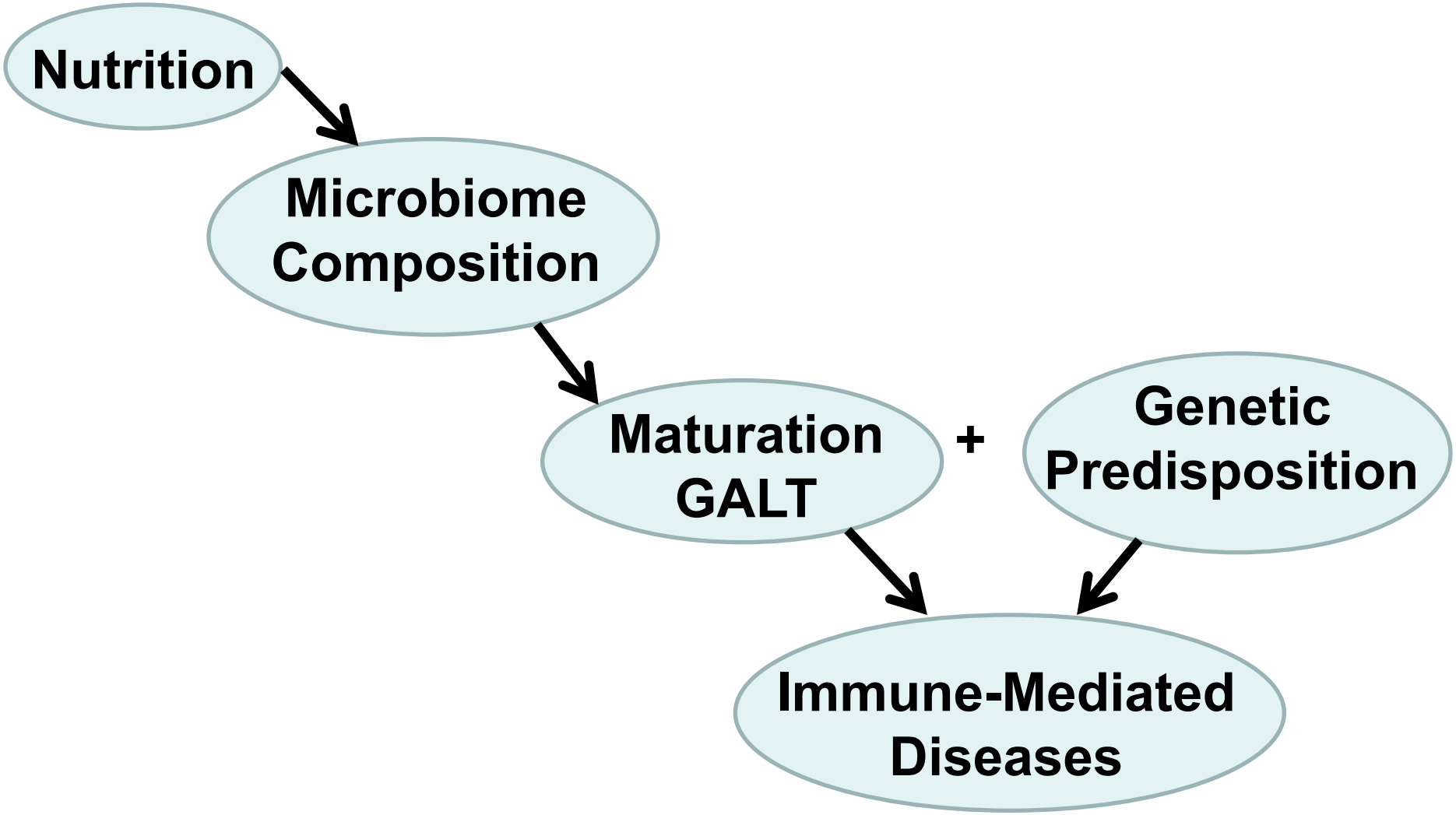
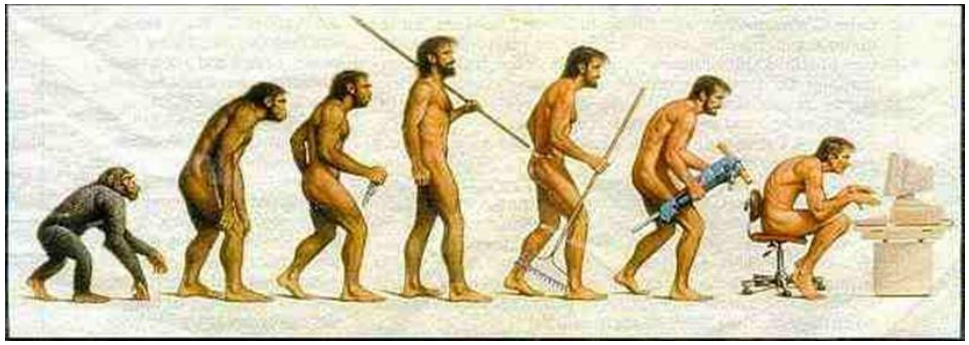
Which Factors are Driving This Autoimmunity Epidemics?



The Complexity of the Human Body

Over the years we came to appreciate the complexity of the human body



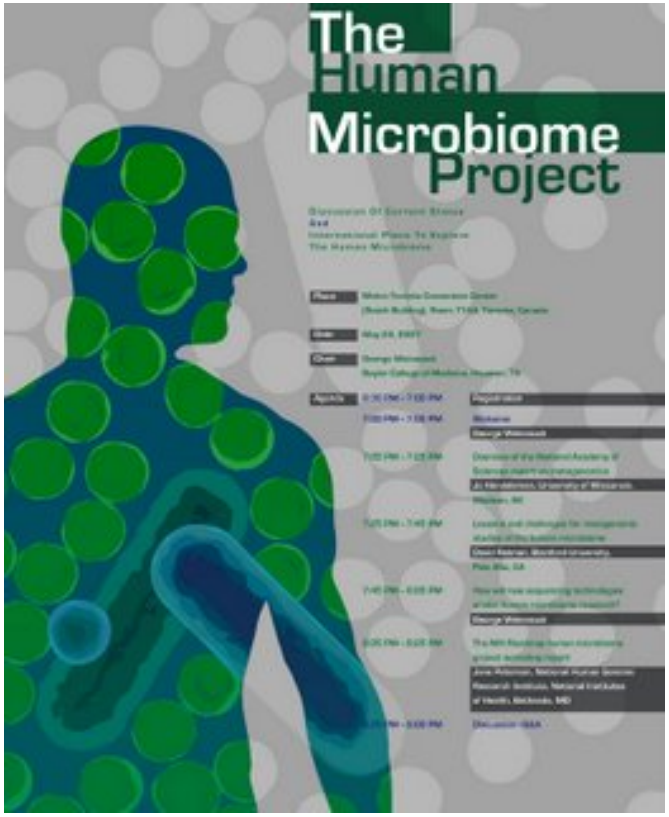
Only 25,000 genes, 99.5% identical to chimpanzee, cannot explain such complexity and difference with other primates.

However, it would be inappropriate to describe the human body without considering the 300,000,000,000 bacteria (collectively defined as microbiome) gladly living inside us and that express ~100 fold more genes that the human genome.

The Real Story of Our Genetic Complexity:
We Inherit two Parallel Genomes

Human Genome:
Inherited from both parents, stable, never change in its composition

Microbiome:
Inherited from the mother, extremely dynamic, changes from individual to individual and in the same individual over time



Higher Risk of Celiac Disease After Elective Cesarean Delivery

Risk of celiac disease after cesarean delivery.

	Matched controls (%)	Celiac disease (%)	Odds ratio; 95% CI OR	P-value	Adjusted odds ratio*, 95% CI AOR	P-value
Cesarean delivery	5,766/53,887 (10.7)	1,299/11,749 (11.1)	1.04; 0.98-1.10	0.232	1.06; 0.99-1.13	0.074
Number of participants			65,636		65,493	
Emergency cesarean delivery †	2,136/41,699 (5.1)	444/8,827 (5.0)	0.99; 0.90-1.10	0.857	1.02; 0.92-1.13	0.749
Number of participants			50,526		50,415	
Elective cesarean delivery †	2,125/41,688 (5.1)	508/8,891 (5.7)	1.11; 1.01-1.22	0.027	1.15; 1.04-1.26	0.005
Number of participants			50,579		50,471	

Mårild et al *Gastroenterology* 2012;*142*(1):39

OPEN ACCESS Freely available online

PLoS one

Proof of Concept of Microbiome-Metabolome Analysis and Delayed Gluten Exposure on Celiac Disease Autoimmunity in Genetically At-Risk Infants

Maria Sellitto[1¤], Guoyun Bai[2], Gloria Serena[1], W. Florian Fricke[2], Craig Sturgeon[1], Pawel Gajer[2], James R. White[2], Sara S. K. Koenig[2], Joyce Sakamoto[2], Dustin Boothe[1], Rachel Gicquelais[1], Deborah Kryszak[1], Elaine Puppa[1], Carlo Catassi[1,3], Jacques Ravel[2]*, Alessio Fasano[1]*

1 Mucosal Biology Research Center, Center for Celiac Research and Departments of Pediatrics, Medicine and Physiology, University of Maryland School of Medicine, Baltimore, Maryland, United States of America, **2** Institute for Genome Sciences and Department of Microbiology and Immunology, University of Maryland School of Medicine, Baltimore, Maryland, United States of America, **3** Department of Pediatrics, Università Politecnica delle Marche, Ancona, Italy

Abstract

Celiac disease (CD) is a unique autoimmune disorder in which the genetic factors (DQ2/DQ8) and the environmental trigger (gluten) are known and necessary but not sufficient for its development. Other environmental components contributing to CD are poorly understood. Studies suggest that aspects of gluten intake might influence the risk of CD occurrence and timing of its onset, i.e., the amount and quality of ingested gluten, together with the pattern of infant feeding and the age at which gluten is introduced in the diet. In this study, we hypothesize that the intestinal microbiota as a whole rather than specific infections dictates the switch from tolerance to immune response in genetically susceptible individuals. Using a sample of infants genetically at risk of CD, we characterized the longitudinal changes in the microbial communities that colonize infants from birth to 24 months and the impact of two patterns of gluten introduction (early vs. late) on the gut microbiota and metabolome, and the switch from gluten tolerance to immune response, including onset of CD autoimmunity. We show that infants genetically susceptible to CD who are exposed to gluten early mount an immune

Microbiome
(140-fold Human Genome)
Dynamic

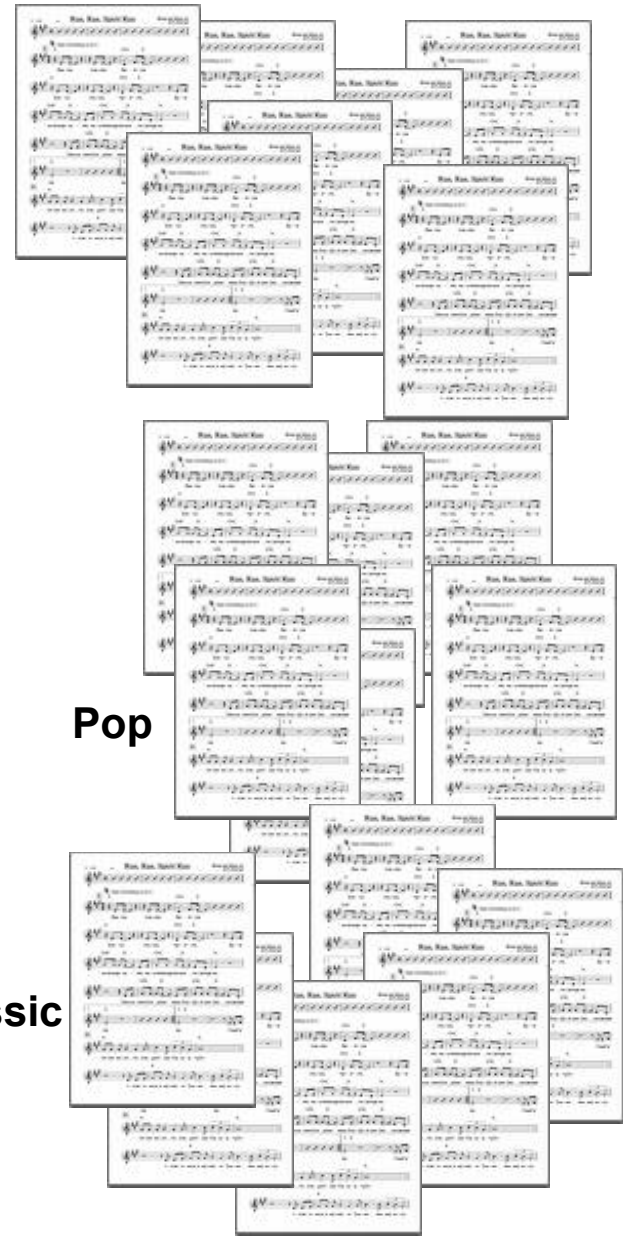
Human Genome
(~30,000 genes)
Stable

Metabonome

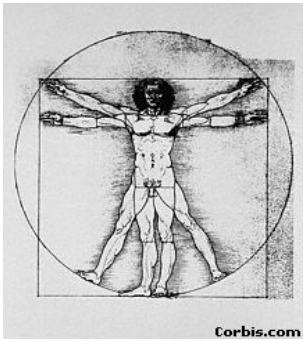
Jazz

Pop

Classic

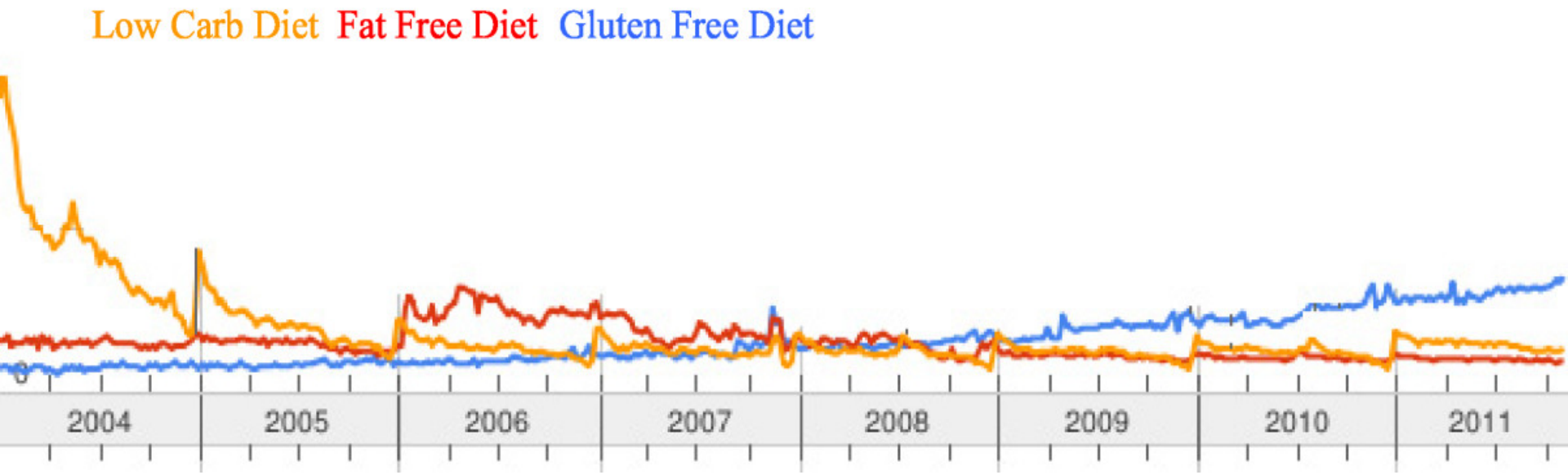


Clinical Outcome



Not Only Celiac Disease

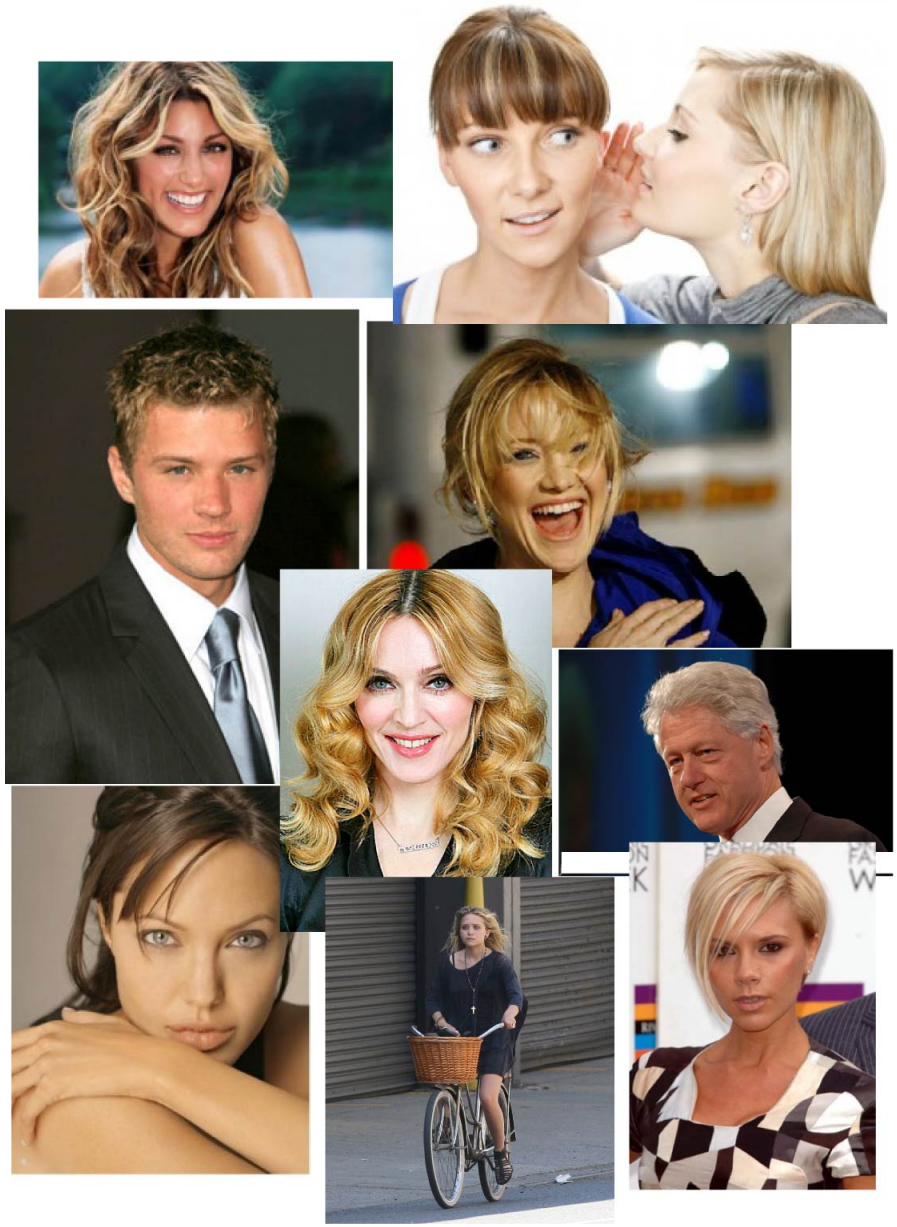
Gluten Free Market



For the American general population adopting a gluten-free diet is becoming an increasingly popular solution. The market for gluten-free food and beverage products grew at a compound annual growth rate of 28 percent/year from 2004 to 2011, to finish with almost $6.7 billion in retail sales last year. By 2014 the market is expected to reach about $10.2 billion in sales.

The fact that approximately 3 million Americans suffer from celiac disease and only a fraction of these patients have been diagnosed implies that patients suffering of other forms of proven gluten reaction, including gluten sensitivity and wheat allergy, contribute to this market growth. The rest of the market is filled by people affected by maladies claimed to be affected by gluten exposure, including autism, ADHD, multiple sclerosis, IBS, and ADHD.

The Fad Factor of the GFD

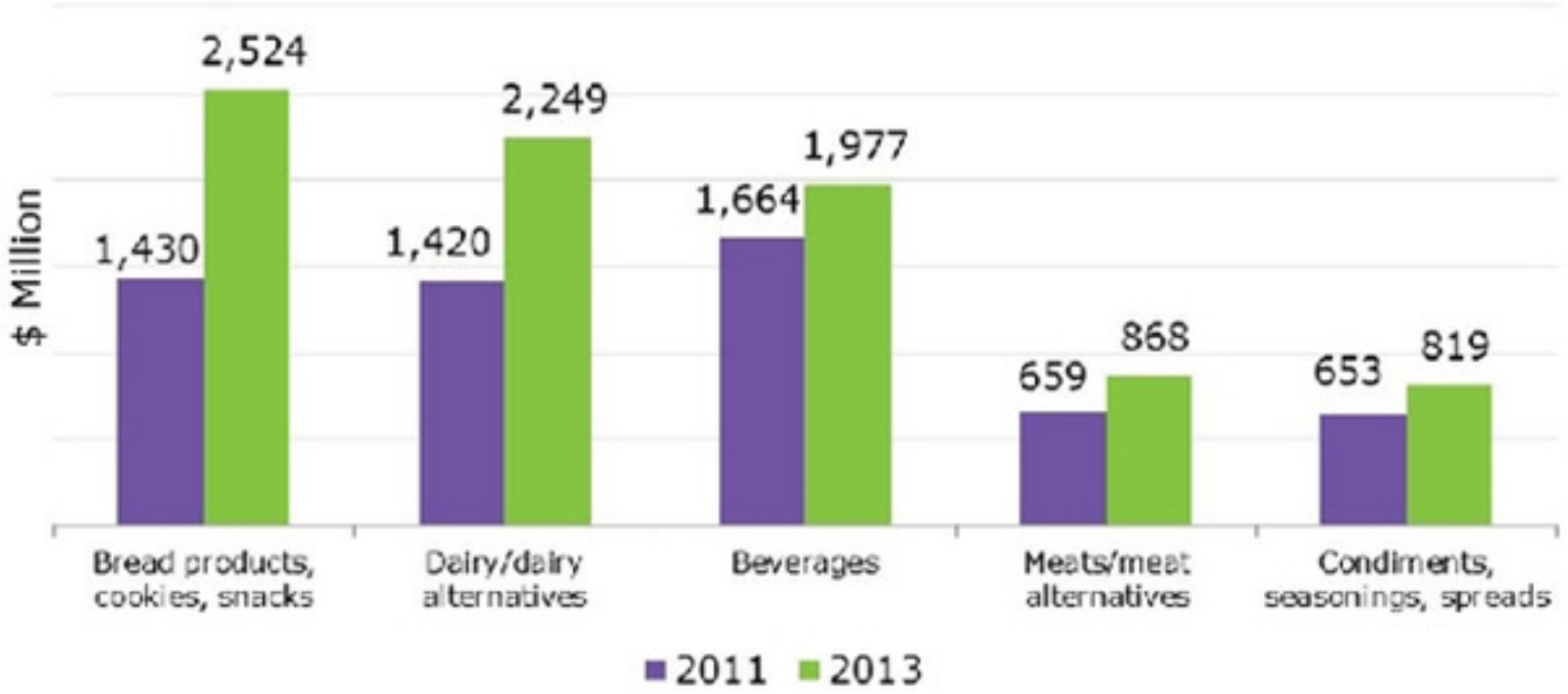


Estimated US GF Retail Market:

- **Mintel: $10.5 B in 2013, predicted to raise 48% to $15.6 B in 2016;**
- **Packages Facts: $4.2 B in 2012, predicted to raise 55% to 6.6 B;**
- **Food Standard Agency: $2.6B in 2011;**
- **Euromonitor: $486.5 M in 2013 (limited to products specifically formulated GF)**

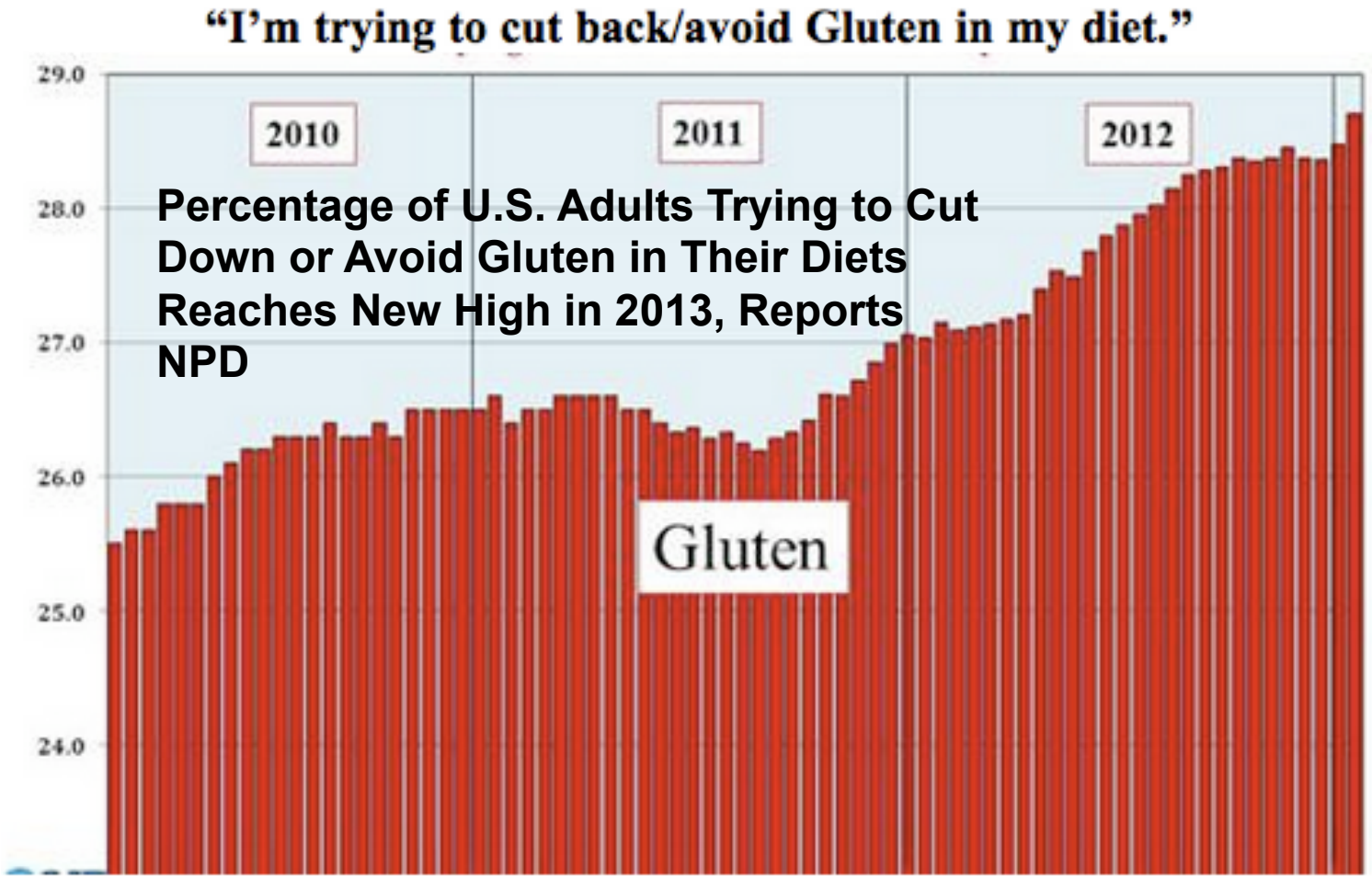
Change of US GF Market 2011-13:

FIGURE 2: Retailer sales of gluten-free foods, by segment, at current prices, 2011-13 (Top 5)



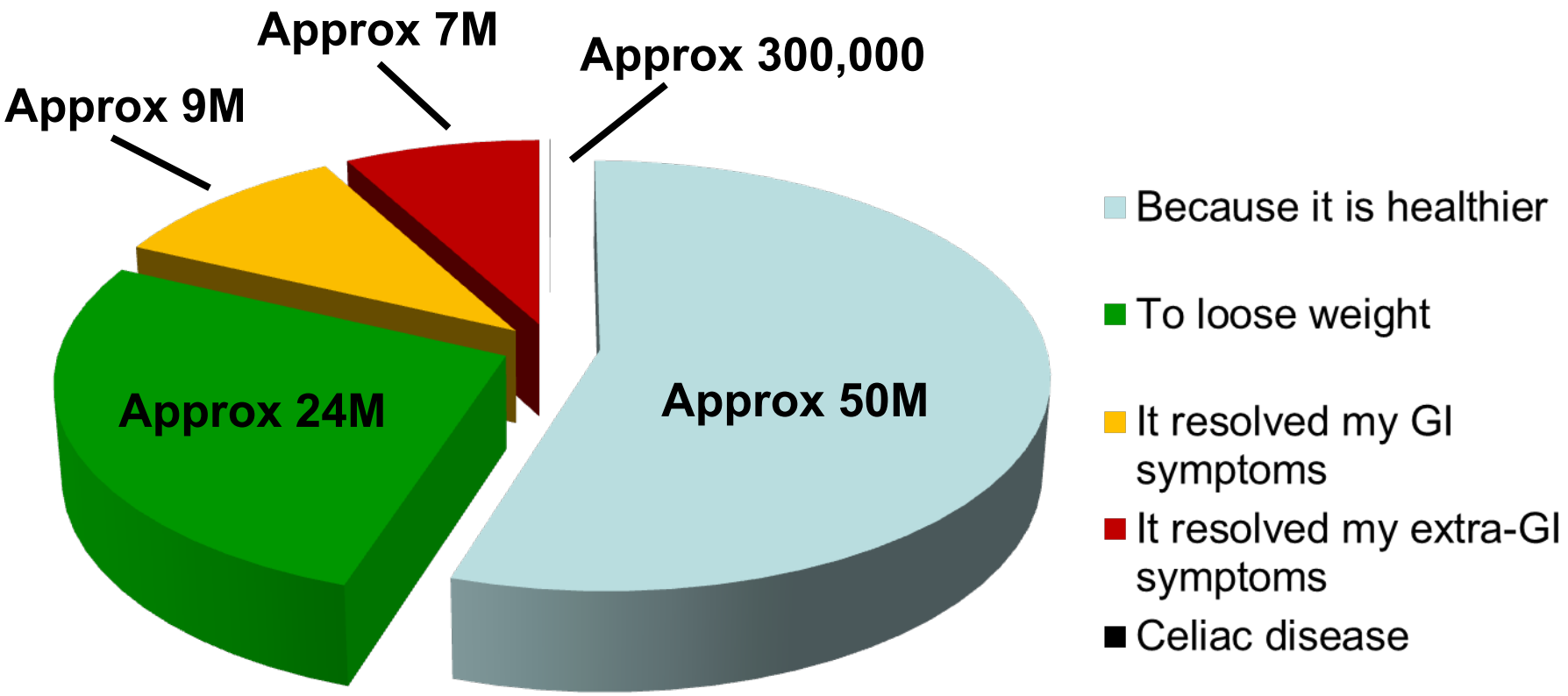
* 52 weeks ending June 11, 2011; June 9, 2012; June 8, 2013
Note: Numbers may not equal total due to rounding
Source: SPINS/Nielsen/Mintel

How Many People in the US Are Embracing a GFD?:



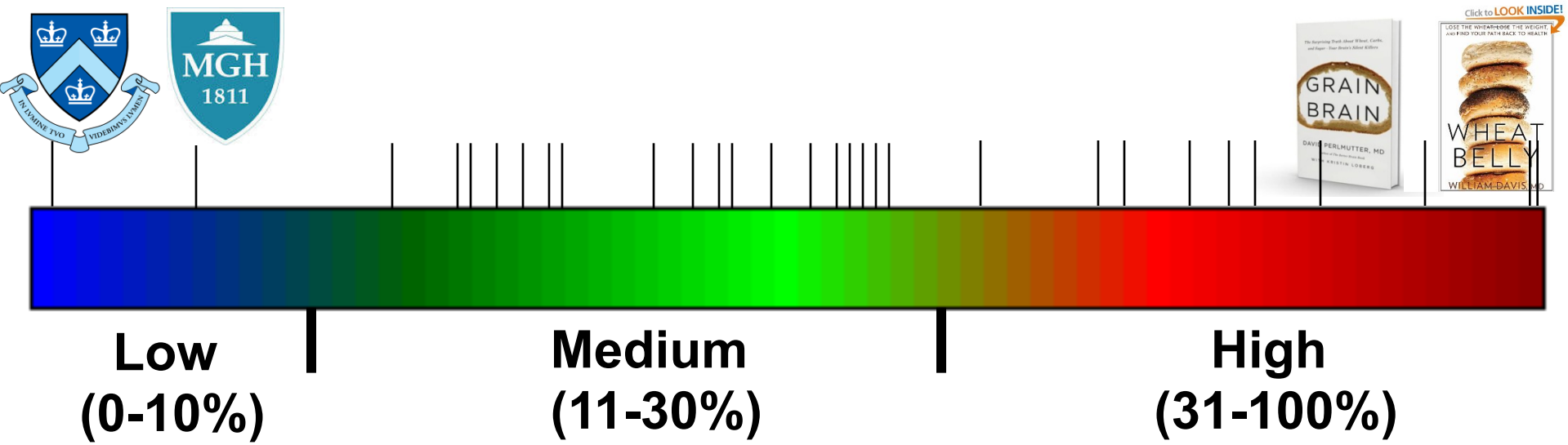
Source: The NPD Group/Dieting Monitor, 52 week data year ending January 30, 2013

Why People in the US Embrace a GFD?:

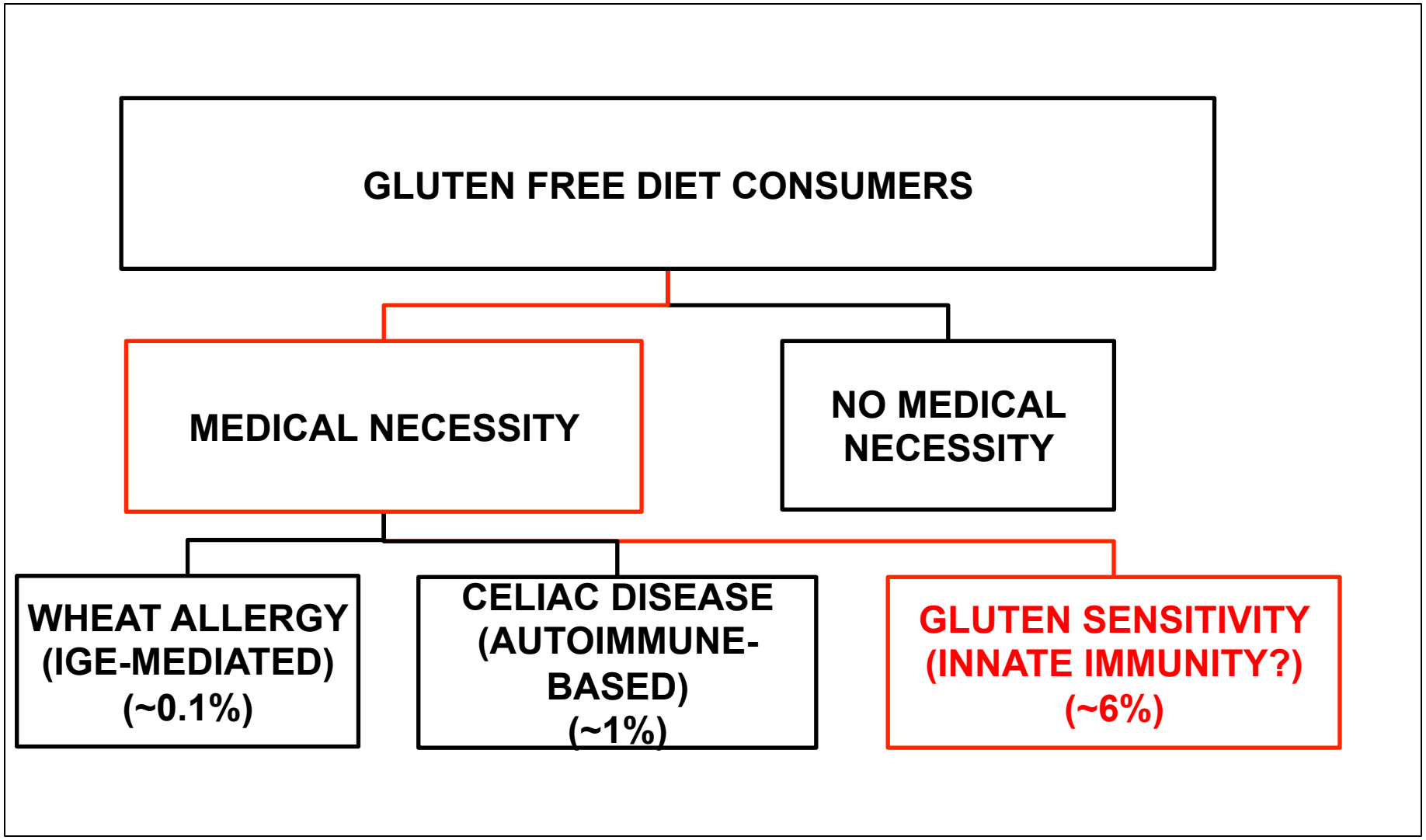


Based on internet interview users age 18y+ who eats GF food

Estimated Prevalence of NCGS:



The Gluten Free Diet:
Not Only Celiac Disease



Gluten Sensitivity (NCGS): Facts
Definition

Cases of reaction to ingestion of gluten-containing grains in which both allergic and autoimmune mechanisms have been ruled out (diagnosis by exclusion criteria)

- Triggered by the ingestion of gluten-containing grains;
- Negative immuno-allergy tests to wheat;
- Negative CD serology (EMA and/or tTG) and in which IgA deficiency has been ruled out;
- Negative duodenal histopathology;
- Possible presence of biomarkers of gluten immune-reaction (AGA+);
- Presence of clinical symptoms that can overlap with CD or wheat allergy symptomatology;
- Resolution of the symptoms following implementation of a GFD and relapse after re-exposure to gluten-containing grains (double blind)

Sapone A. et al BMC Med 2012, Ludvigsson JF et al Gut 2013, Catassi C. Et al, Nutrients 2013

Non Celiac Gluten Sensitivity: What is the Magnitude of the Problem?

The CFCR Experience (2004-2010)

- Nr. of the patients seen at the CFCR clinic: **5,896**
- Nr. of patients fulfilling criteria for GS: **347**
- Prevalence in our cohort: **1:17 (6%)**
- Symptoms:
  - Abdominal pain: 68%
  - Eczema and/or rash: 40%
  - Headache: 35%
  - "Foggy mind": 34%
  - Fatigue: 33%
  - Diarrhea: 33%
  - Depression: 22%
  - Anemia: 20%
  - Numbness legs/arms/fingers: 20%
  - Joint pain: 11%

Gluten Sensitivity and IBS

Am J Gastroenterol. 2011 Mar;106(3):508-14; quiz 515. doi: 10.1038/ajg.2010.487. Epub 2011 Jan 11.

Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial.

Biesiekierski JR, Newnham ED, Irving PM, Barrett JS, Haines M, Doecke JD, Sh erd SJ, Muir JG, Gibson PR.

Source

Monash University Department of Medicine and Gastroenterology, Box Hill Hospita

Abstract

OBJECTIVES:

Despite increased prescription of a gluten-free diet f celiac disease, there is minimal evidence that suggests that whether gluten ingestion can induce symptoms in non

METHODS:

A double-blind, randomi patients with irritable bowel syndrome in whom celiac dis on a gluten-free diet. Participants received either gluten or day with a gluten-free diet for up to 6 weeks. Symptoms w estinal inflammation, injury, and immune activation were mo

RES

A tota men) completed the study as per protocol. Overall, 56% had human leukocyte antige Q8. Adherence to diet and supplements was very high. Of 19 patients (68%) in the gluten group, mptoms were not adequately controlled compared with 6 of 15 (40%) on placebo (P=0.0001; generali ing equation). On a visual analog scale, patients were significantly worse with gluten within 1 week for overall symptom =0.047), pain (P=0.016), bloating (P=0.031), satisfaction with stool consistency (P=0.024), and tiredness (P=0.001). Anti-gliadin antibodies were not induced. There were no significant changes in fecal lactoferrin, levels of celiac antibodies, highly sensitive C-reactive protein, or intestinal permeability. There were no differences in any end point in individuals with or without DQ2/DQ8.

CONCLUSIONS:

"Non-celiac gluten intolerance" may exist, but no clues to the mechanism were elucidated.

No effects of gluten in patients with self-reported non-celiac gluten sensitivity after dietary reduction of fermentable, poorly absorbed, short-chain carbohydrates.

Biesiekierski JR, Peters SL, Newnham ED, Rosella O, Muir JG, Gibson PR.

Source

Department of Gastroenterology, Eastern Health Clinical School, Monash University, Box Hill, Victoria, Australia; Department of Gastroenterology, Central Clinical School, Monash University, The Alfred Hospital, Melbourne, Victoria, Australia.

Abstract

BACKGROUND & AIMS:

Patients with non-celiac gluten sensitivity (NCGS) do not have celiac disease but their symptoms improve when they are placed on gluten-free diets. We investigated the specific effects of gluten after dietary reduction of fermentable, poorly absorbed, short-chain carbohydrates (fermentable, oligo-, di-, monosaccharides, and polyols [FODMAPs]) in subjects believed to have NCGS.

METHODS:

We performed a double-blind cross-over trial of 37 subjects (aged 24-61 y, 6 men) with NCGS and irritable bowel syndrome (based on Rome III criteria), but not celiac disease. Participants were randomly assigned to groups given a 2-week diet of reduced FODMAPs, and were then placed on high-gluten (16 g gluten/d), low-gluten (2 g gluten/d and 14 g whey protein/d), or control (16 g whey protein/d) diets for 1 week, followed by a washout period of at least 2 weeks. We assessed serum and fecal markers of intestinal inflammation/injury and immune activation, and indices of fatigue. Twenty-two participants then crossed over to groups given gluten (16 g/d), whey (16 g/d), or control (no additional protein) diets for 3 days. Symptoms were evaluated by visual analogue scales.

RESULTS:

In all participants, gastrointestinal symptoms consistently and significantly improved during reduced FODMAP intake, but significantly worsened to a similar degree when their diets included gluten or whey protein. Gluten-specific effects were observed in only 8% of participants. There were no diet-specific changes in any biomarker. During the 3-day rechallenge, participants' symptoms increased by similar levels among groups. Gluten-specific gastrointestinal effects were not reproduced. An order effect was observed.

CONCLUSIONS:

In a placebo-controlled, cross-over rechallenge study, we found no evidence of specific or dose-dependent effects of gluten in patients with NCGS placed diets low in FODMAPs. www.anzctr.org.au. ACTRN12610000524099.

Non Celiac Gluten Sensitivity: Facts

Definition of Food Reactions

(Consensus NIAID 2011)

Food intolerance occurs when the body lacks a particular enzyme to digest nutrients, nutrients are too abundant to be completely digested, or a particular nutrient cannot be properly digested, Common examples are lactose intolerance, FODPAM intolerance, or lactulose intolerance (side effect of laxatives).

Food sensitivity, an understudied area, are immune-mediated reaction to some nutrients and these reactions do not always occur in the same way when eating that particular nutrient.

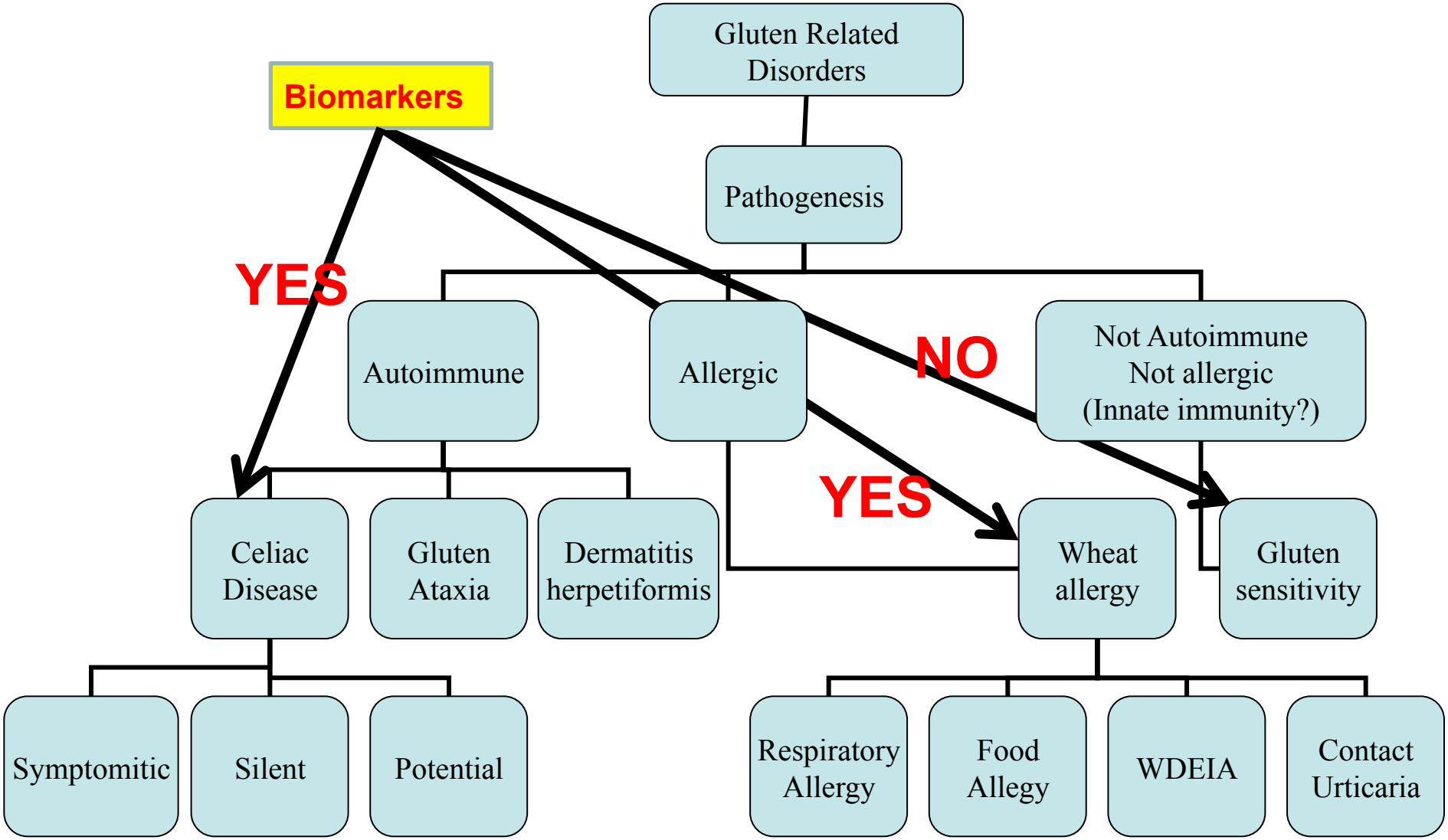
Food allergy is a very specific immune system response involving either the immunoglobulin E (IgE) antibody or T-cells. Both are immune system cells that react to a particular food protein, such as milk protein.

Food sources of FODMAPs (where FODMAPs are problematic based on standard serving size) and suitable alternatives

FODMAP	Excess fructose	Lactose	Oligosaccharides (fructans and/or galactans)	Polyols
Problem high FODMAP food source	*Fruits:* apples, pears, nashi pears, clingstone peaches, mango, sugar snap peas, watermelon, tinned fruit in natural juice *Honey* *Sweeteners:* fructose, high fructose corn syrup *Large total fructose dose:* concentrated fruit sources; large serves of fruit, dried fruit, fruit juice	*Milk:* cow, goat and sheep (regular & low-fat), Ice cream *Yoghurt* (regular & low-fat) *Cheeses:* soft & fresh (e.g. ricotta, cottage)	*Vegetables:* artichokes, asparagus, beetroot, Brussels sprout, broccoli, cabbage, fennel, garlic, leeks, okra, onions, peas, shallots. *Cereals:* wheat & rye when eaten in large amounts (e.g. bread, pasta, couscous, crackers, biscuits) *Legumes*: chickpeas, lentils, red kidney beans, baked beans *Fruits:* watermelon, custard apple, white peaches, rambutan, persimmon	*Fruits:* apples, apricots, cherries, longon, lychee, nashi pears, nectarine, pears, peaches, plums, prunes, watermelon *Vegetables:* avocado, cauliflower, mushrooms, snow peas *Sweeteners:* sorbitol(420), mannitol(421), xylitol(967), maltitol (965), isomalt (953) & others ending in '-ol'
Suitable alternative low-FODMAP food source	*Fruit:* banana, blueberry, carambola, durian, grapefruit, grape, honeydew melon, kiwifruit, lemon, lime, mandarin, orange, passionfruit, paw paw, raspberry, rockmelon, strawberry, tangelo. *Honey substitutes:* maple syrup, golden syrup *Sweeteners:* any except polyols	*Milk:* lactose-free, rice milk *Cheese:*'hard' cheeses including brie, camembert *Yoghurt:* lactose-free *Ice cream substitutes:* gelati, sorbet *Butter*	*Vegetables:* bamboo shoots, bok choy, carrot, celery, capsicum, choko, choy sum, corn, eggplant, green beans, lettuce, chives, parsnip, pumpkin, silverbeet, spring onion (green only), tomato *Onion/garlic substitutes:* garlic-infused oil *Cereals:* gluten-free & spelt bread/cereal products	*Fruits:* banana, blueberry, carambola, durian, grapefruit, grape, honeydew melon, kiwifruit, lemon, lime, mandarin, orange, passionfruit, paw paw, raspberry, rockmelon *Sweeteners:* sugar (sucrose), glucose, other artificial sweeteners not ending in 'ol'

Gibson PR, Sheperd SJ. J Gastroenterol Hepatol. 2010;25:252-258

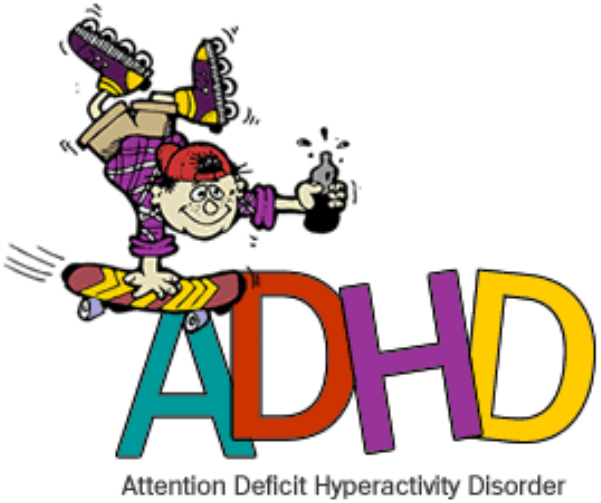
Proposed New Classification of Gluten Related Disorders

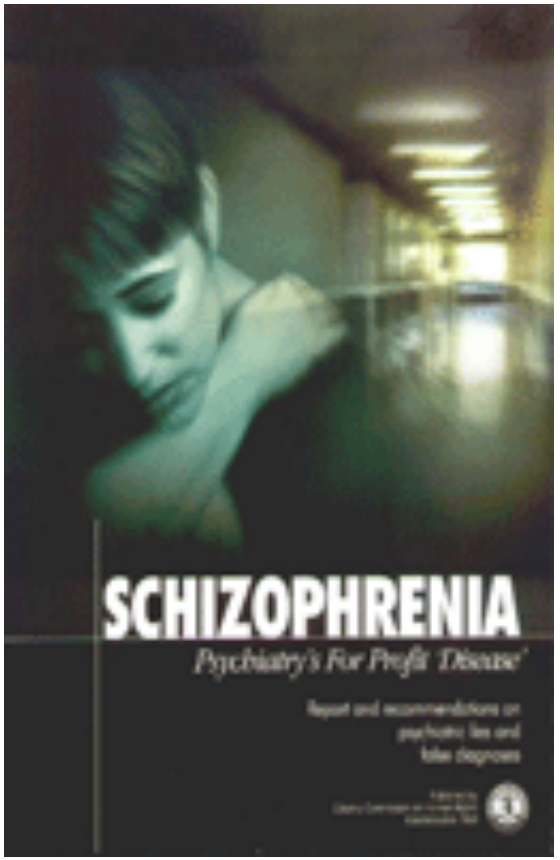


Differential Diagnosis Between CD, GS, and WA

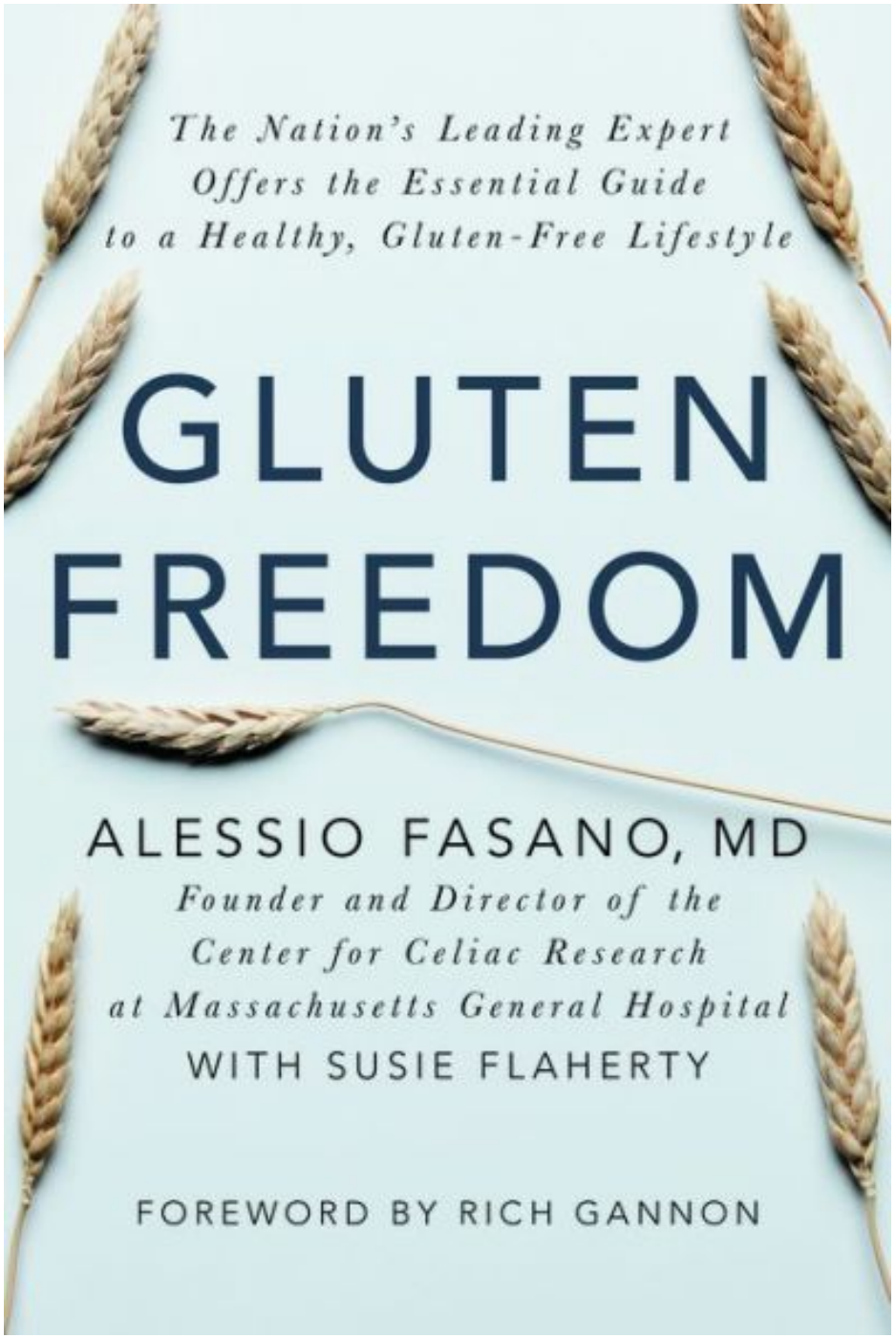
	Celiac Disease	Gluten Sensitivity	Wheat Allergy
Time interval between gluten exposure and onset of symptoms	Weeks-Years	Hours-Days	Minutes-Hours
Pathogenesis	Autoimmunity (Innate+ Adaptive Immunity)	Immunity? (Iinnate Immunity?)	Allergic Immune Response
HLA	HLA DQ2/8 restricted (~97% positive cases)	Not-HLA DQ2/8 restricted (50% DQ2/8 positive cases)	Not-HLA DQ2/8 restricted (35-40% positive cases as in the general population)
Auto-antibodies	Almost always present	Always absent	Always absent
Enteropathy	Almost always present	Always absent (slight increase in IEL)	Always absent (eosinophils in the lamina propria)
Symptoms	Both intestinal and extra-intestinal (not distinguishable from GS and WA with GI symptoms)	Both intestinal and extra-intestinal (not distinguishable from CD and WA with GI symptoms)	Both intestinal and extra-intestinal (not distinguishable from CD and GS when presenting with GI symptoms)
Complications	Co-morbidities Long term complications	Absence of co-morbidities and long term complications (long follow up studies needed to confirm it)	Absence of co-morbidities. Short-term complications (incliuding anaphylaxis)

The Controversial Questions About Gluten Sensitivity





Are The Epidemics Of Autism, ADHD and Schizophrenia Also Related to The Rise of Non-Celiac Gluten Sensitivity?


The Nation's Leading Expert
Offers the Essential Guide
to a Healthy, Gluten-Free Lifestyle
GLUTEN
FREEDOM
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FOREWORD BY RICH GANNON