TTG6 As Potential Biomarker for GS-Associated Schizophrenia

Second International Expert Meeting On Gluten Sensitivity

November 30th – December 2nd

Munich Germany

Alessio Fasano, M.D.

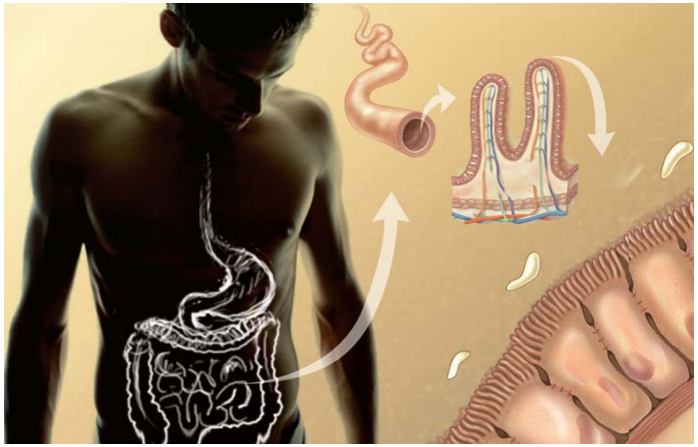
Mucosal Biology Research Center and

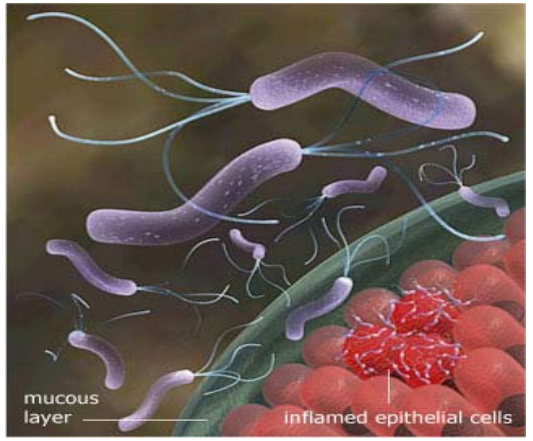
Center for Celiac Research

University of Maryland School of Medicine

Lecture Objectives

Schizophrenia, Gluten, and Antigen Trafficking: Connecting the Dots





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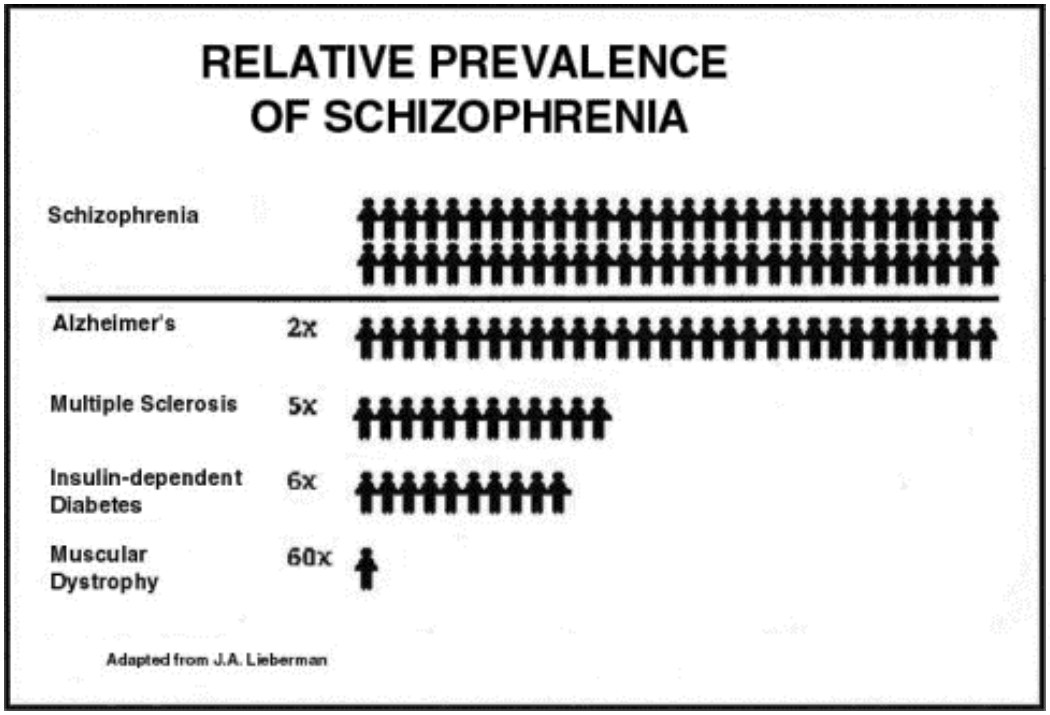
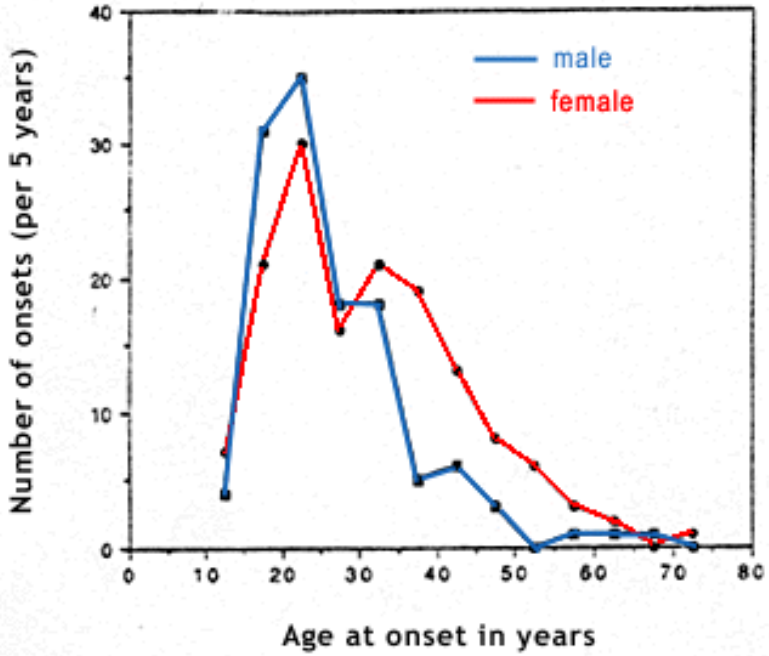
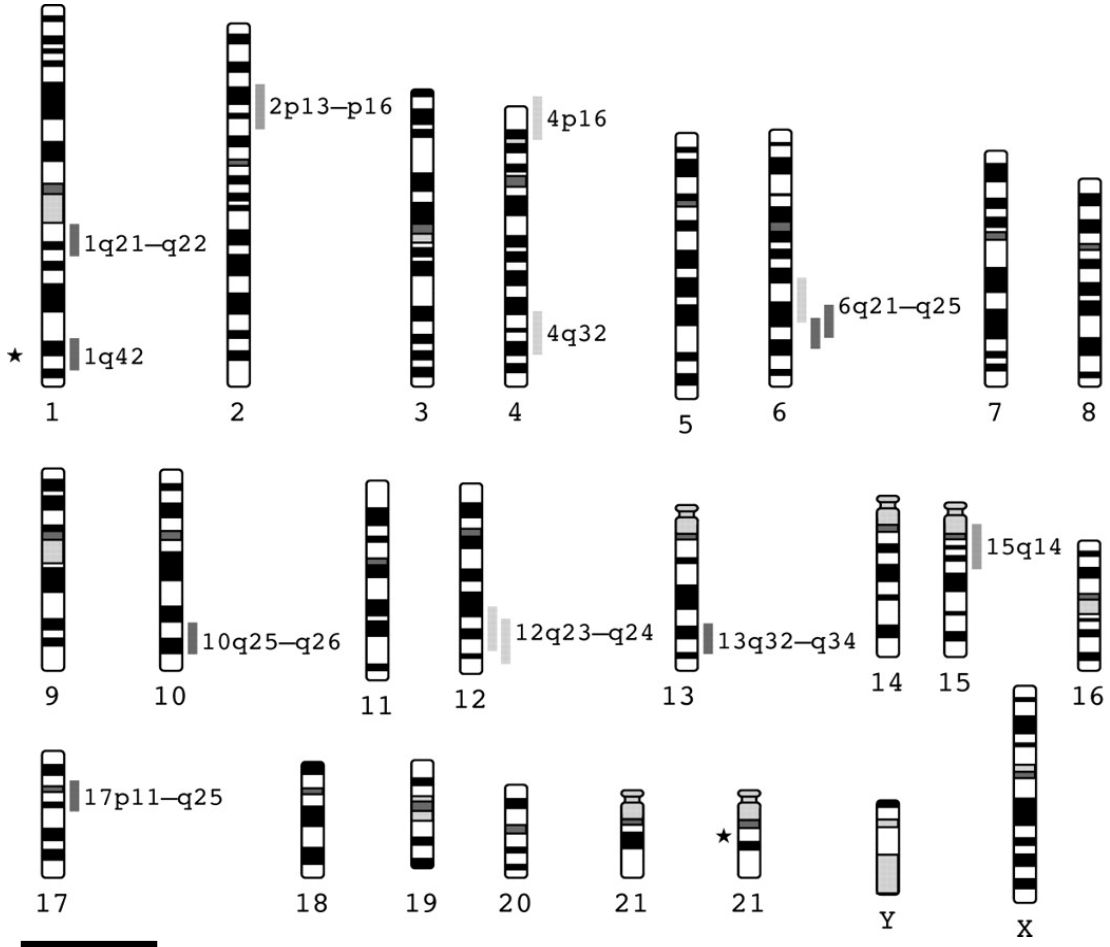
Schizophrenia Prevalence: US

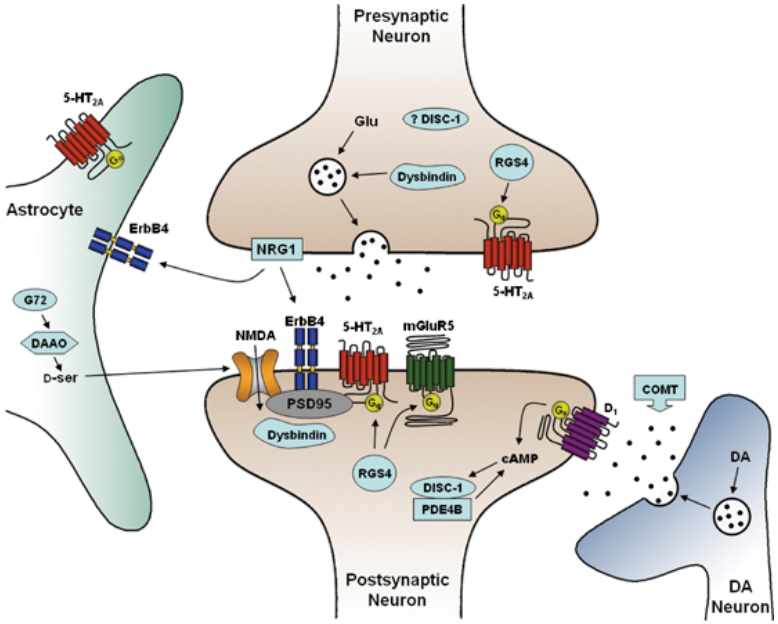




Age at onset in schizophrenia

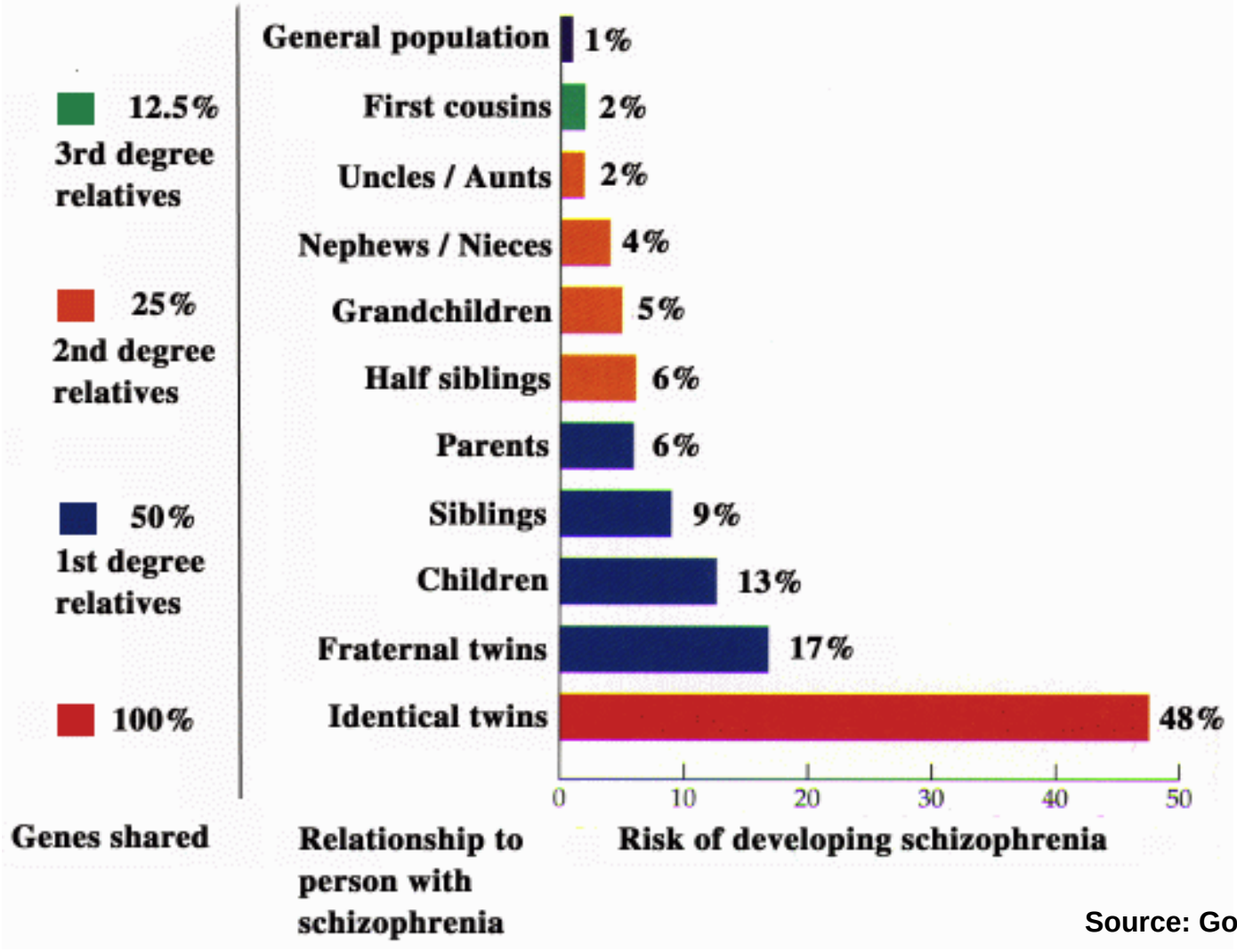
The Genetic Component of Schizophrenia: Summary of Gene Linkage Findings





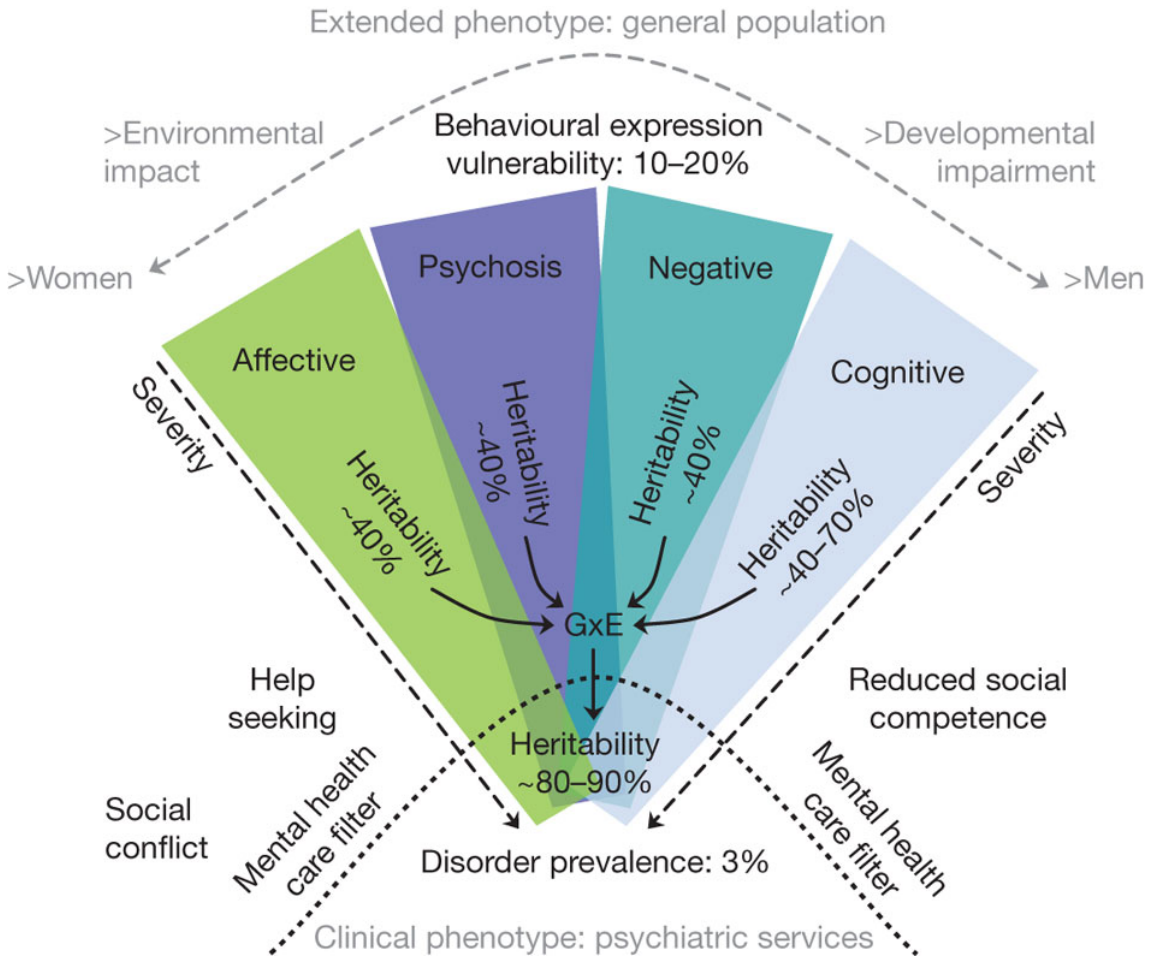
Published data 2004

Schizophrenia is highly heritable but…
The Environmental Component



Source: Gottlesman 1991

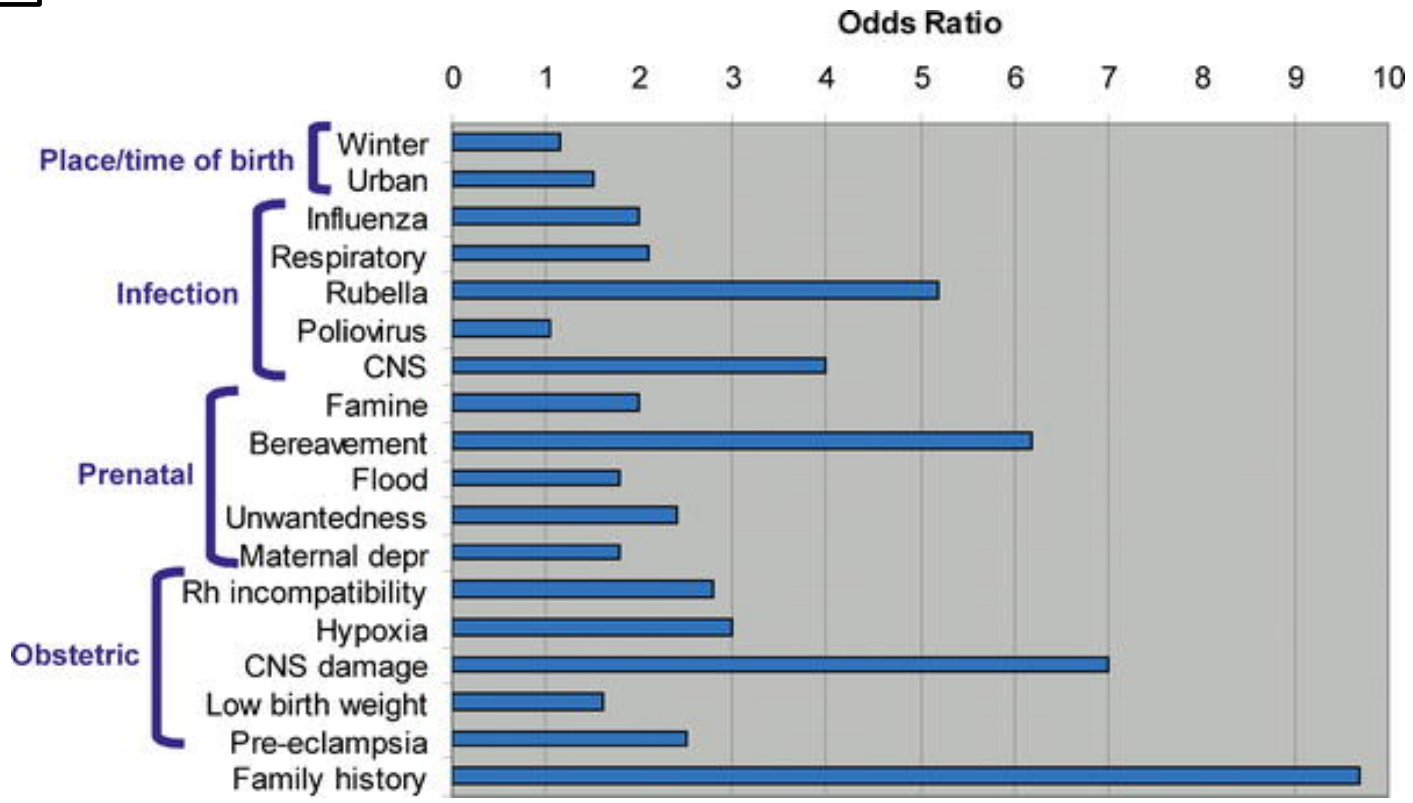
Complexity of the psychotic disorder phenotype in aetiological research.



JV Os *et al. Nature* **468**, 203-212 (2010) doi:10.1038/nature09563

nature

Which Environmental Risk Factors are involved in Schizophrenia ?



Source: Public Library of Science, 2005 - Comparison of a Selected Set of Relatively Well-Established Risk Factors for Schizophrenia, Focusing Mainly on Pre- and Antenatal Factors (abbreviations: CNS, central nervous system; depr, depression).

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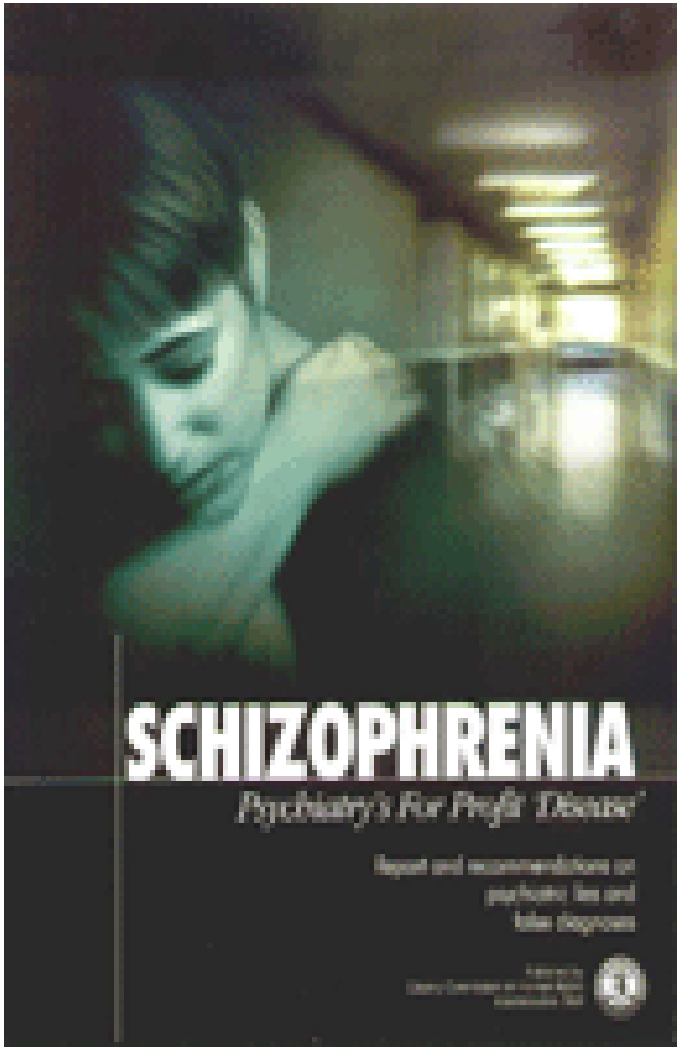
The Controversial Questions About Gluten Sensitivity



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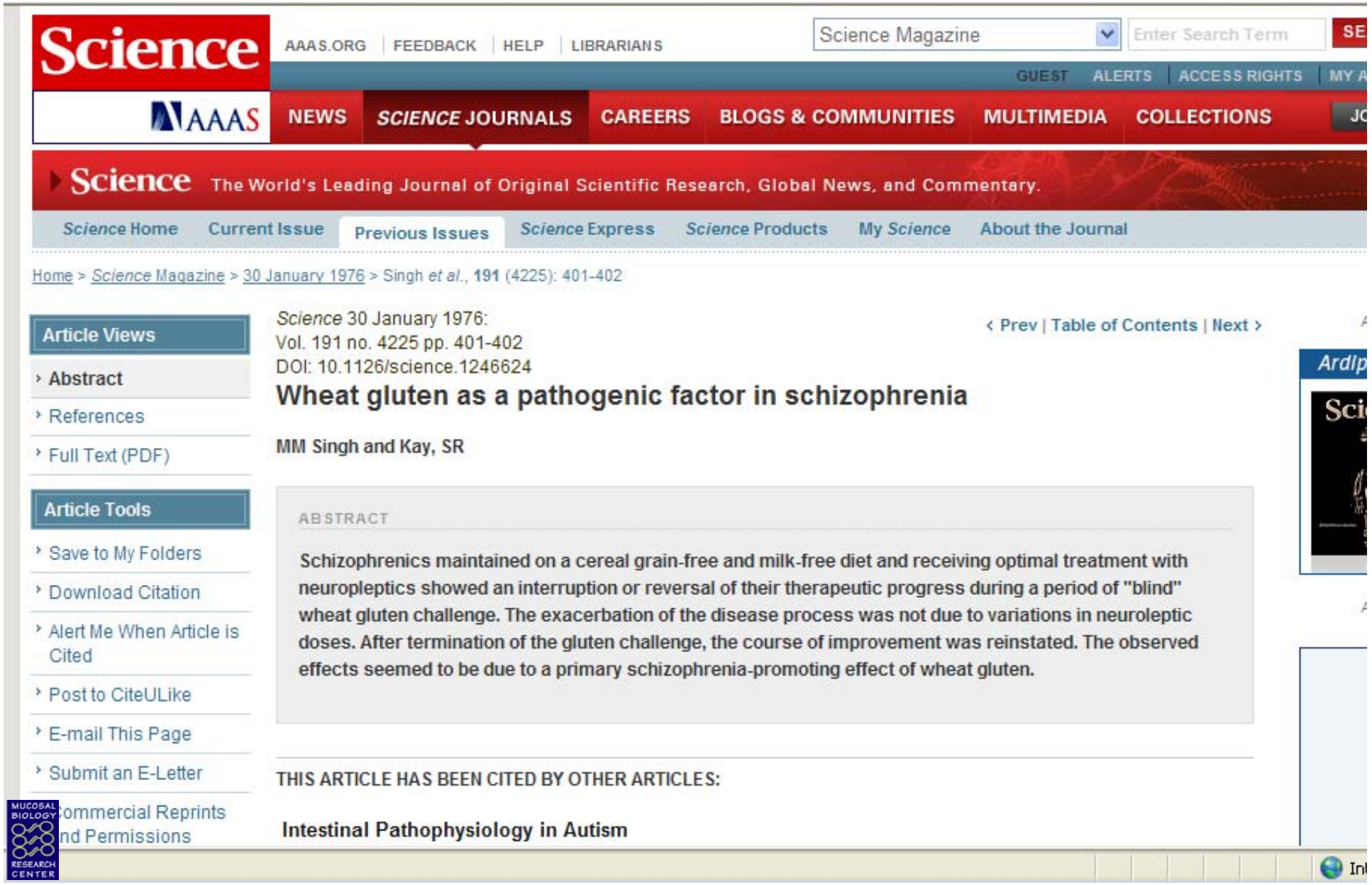
Environmental Triggers:
The Gluten Connection

Fasano A. Sci Am. 2009;301(2):54-61.

Background: Dohan Theory

- The Dohan theory was supported by two series of epidemiologic data:
  - The prevalence of schizophrenia was decreased during periods of low grain consumption
  - The prevalence of schizophrenia was lower in geographic areas with low grain consumption

Gluten And Schizophrenia



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Home > Science Magazine > 30 January 1976 > Singh et al., 191 (4225): 401-402

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Science 30 January 1976:
Vol. 191 no. 4225 pp. 401-402
DOI: 10.1126/science.1246624

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Wheat gluten as a pathogenic factor in schizophrenia

MM Singh and Kay, SR

ABSTRACT

Schizophrenics maintained on a cereal grain-free and milk-free diet and receiving optimal treatment with neuropleptics showed an interruption or reversal of their therapeutic progress during a period of "blind" wheat gluten challenge. The exacerbation of the disease process was not due to variations in neuroleptic doses. After termination of the gluten challenge, the course of improvement was reinstated. The observed effects seemed to be due to a primary schizophrenia-promoting effect of wheat gluten.

THIS ARTICLE HAS BEEN CITED BY OTHER ARTICLES:

Intestinal Pathophysiology in Autism

MUCOSAL BIOLOGY RESEARCH CENTER

Acta Psychiatr Scand. 2006 Feb;113(2):82-90.

The gluten connection: the association between schizophrenia and celiac disease.

Kalaydjian AE, Eaton W, Cascella N, Fasano A.

Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205, USA. akalaydj@jhsph.edu

Abstract

OBJECTIVE: Schizophrenia affects roughly 1% of the population and is considered one of the top 10 causes of disability worldwide. Given the immense cost to society, successful treatment options are imperative. Based on initial findings, gluten withdrawal may serve as a safe and economical alternative for the reduction of symptoms in a subset of patients.

METHOD: A review of the literature relevant to the association between schizophrenia and celiac disease (gluten intolerance) was conducted.

RESULTS: A drastic reduction, if not full remission, of schizophrenic symptoms after initiation of gluten withdrawal has been noted in a variety of studies. However, this occurs only in a subset of schizophrenic patients.

CONCLUSION: Large-scale epidemiological studies and clinical trials are needed to confirm the association between gluten and schizophrenia, and address the underlying mechanisms by which this association occurs.

Schizophrenia Bulletin Advance Access published June 3, 2009

Schizophrenia Bulletin
doi:10.1093/schbul/sbp055

Prevalence of Celiac Disease and Gluten Sensitivity in the United States Clinical Antipsychotic Trials of Intervention Effectiveness Study Population

Nicola G. Cascella[1,2], Debra Kryszak[3], Bushra Bhatti[3], Patricia Gregory[4], Deanna L. Kelly[5], Joseph P. Mc Evoy[6], Alessio Fasano[3], and William W. Eaton[4]

[2]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, 600 North Wolfe Street, Meyer 144, Baltimore, MD 21287; [3]Center for Celiac Research, University of Maryland School of Medicine, Baltimore, MD; [4]Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; [5]Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland School of Medicine, Baltimore, MD; [6]Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine, Durham, NC

Celiac disease (CD) and schizophrenia have approximately the same prevalence, but epidemiologic data show higher prevalence of CD among schizophrenia patients. The reason

bodies. Persons with schizophrenia have higher than expected titers of antibodies related to CD and gluten sensitivity.

Key words: anti-gliadin IgA antibodies/tTG antibodies/EMA antibodies/PANSS

Introduction

Celiac disease (CD) is an immune-mediated enteropathy triggered by the ingestion of gluten-containing grains including wheat, rye, and barley in genetically susceptible individuals.[1] The disease can manifest itself with a range of clinical presentations including the typical malabsorption syndrome and a spectrum of symptoms affecting any organ including the peripheral and central

Schizophr Res. 2010 May;118(1-3):248-55. Epub 2009 Sep 11.

Novel immune response to gluten in individuals with schizophrenia.

Samaroo D, Dickerson F, Kasarda DD, Green PH, Briani C, Yolken RH, Alaedini A.

Department of Neurology and Neuroscience, Weill Medical College of Cornell University, New York, NY, United States.

Abstract

A link between celiac disease and schizophrenia has been postulated for several years, based primarily on reports of elevated levels of antibody to gliadin in patients. We sought to examine the proposed connection between schizophrenia and celiac disease by characterizing the molecular specificity and mechanism of the anti-gliadin immune response in a subset of individuals with schizophrenia. Blood samples from individuals with schizophrenia and elevated anti-gliadin antibody titer were examined for celiac disease-associated biomarkers, including antibodies to transglutaminase 2 (TG2) enzyme and deamidated gliadin peptides, as well as the HLA-DQ2 and -DQ8 MHC genes. The anti-gliadin antibody response was further characterized through examination of reactivity towards chromatographically separated gluten proteins. Target proteins of interest were identified by peptide mass mapping. In contrast to celiac disease patients, an association between the anti-gliadin immune response and anti-TG2 antibody or HLA-DQ2 and -DQ8 markers was not found in individuals with schizophrenia. In addition, the majority of individuals with schizophrenia and anti-gliadin antibody did not exhibit antibody reactivity to deamidated gliadin peptides. Further characterization of the antibody specificity revealed preferential reactivity towards different gluten proteins in the schizophrenia and celiac disease groups. These findings indicate that the anti-gliadin immune response in schizophrenia has a different antigenic specificity from that in celiac disease and is independent of the action of transglutaminase enzyme and HLA-DQ2/DQ8. Meanwhile, the presence of elevated levels of antibodies to specific gluten proteins points to shared immunologic abnormalities in a subset of schizophrenia patients. Further characterization and understanding of the immune response to gluten in schizophrenia may provide novel insights into the etiopathogenesis of specific disease phenotypes.

Biol Psychiatry. 2010 Jul 1;68(1):100-4. Epub 2010 May 14.

Markers of gluten sensitivity and celiac disease in recent-onset psychosis and multi-episode schizophrenia.

Dickerson F, Stallings C, Origoni A, Vaughan C, Khushalani S, Leister F, Yang S, Krivogorsky B, Alaedini A, Yolken R.

Stanley Research Program at Sheppard Pratt, Department of Pediatrics, Johns Hopkins School of Medicine, Baltimore, Maryland 21204, USA. fdickerson@sheppardpratt.org

Abstract

BACKGROUND: Increased immune sensitivity to gluten has been reported in schizophrenia. However, studies are inconsistent about this association.

METHODS: The sample of 471 individuals included 129 with recent-onset psychosis, 191 with multi-episode schizophrenia, and 151 controls. Immunoglobulin (Ig)G and IgA antibodies to gliadin and to tissue transglutaminase, and IgG antibodies to deamidated gliadin were measured. Quantitative levels of antibodies in the psychiatric groups were compared with controls. All participants were categorized as to whether their levels of antibodies met standardized cutoffs for celiac disease. HLA DQ2 and HLA DQ8 alleles were detected by real-time polymerase chain reaction.

RESULTS: Individuals with recent-onset psychosis had increased levels of IgG (odds ratio [OR] 5.50; 95% confidence interval [CI] 2.65-11.42) and IgA (OR 2.75; 95% CI 1.31-5.75) antibodies to gliadin compared with control subjects. Individuals with multi-episode schizophrenia also had significantly increased levels of IgG antibodies to gliadin (OR 6.19; 95% CI 2.70-14.16). IgG antibodies to deamidated gliadin and IgA antibodies to tissue transglutaminase were not elevated in either psychiatric group, and fewer than 1% of individuals in each of the groups had levels of these antibodies predictive of celiac disease. There were no significant differences in the distribution of the HLA DQ2/8 alleles among the groups.

CONCLUSIONS: Individuals with recent-onset psychosis and with multi-episode schizophrenia who have increased antibodies to gliadin may share some immunologic features of celiac disease, but their immune response to gliadin differs from that of celiac disease.

Schizophr Bull. 2012 May;38(3):514-8. Epub 2010 Sep 30.

A study of circulating gliadin antibodies in schizophrenia among a Chinese population.

Jin SZ, Wu N, Xu Q, Zhang X, Ju GZ, Law MH, Wei J.

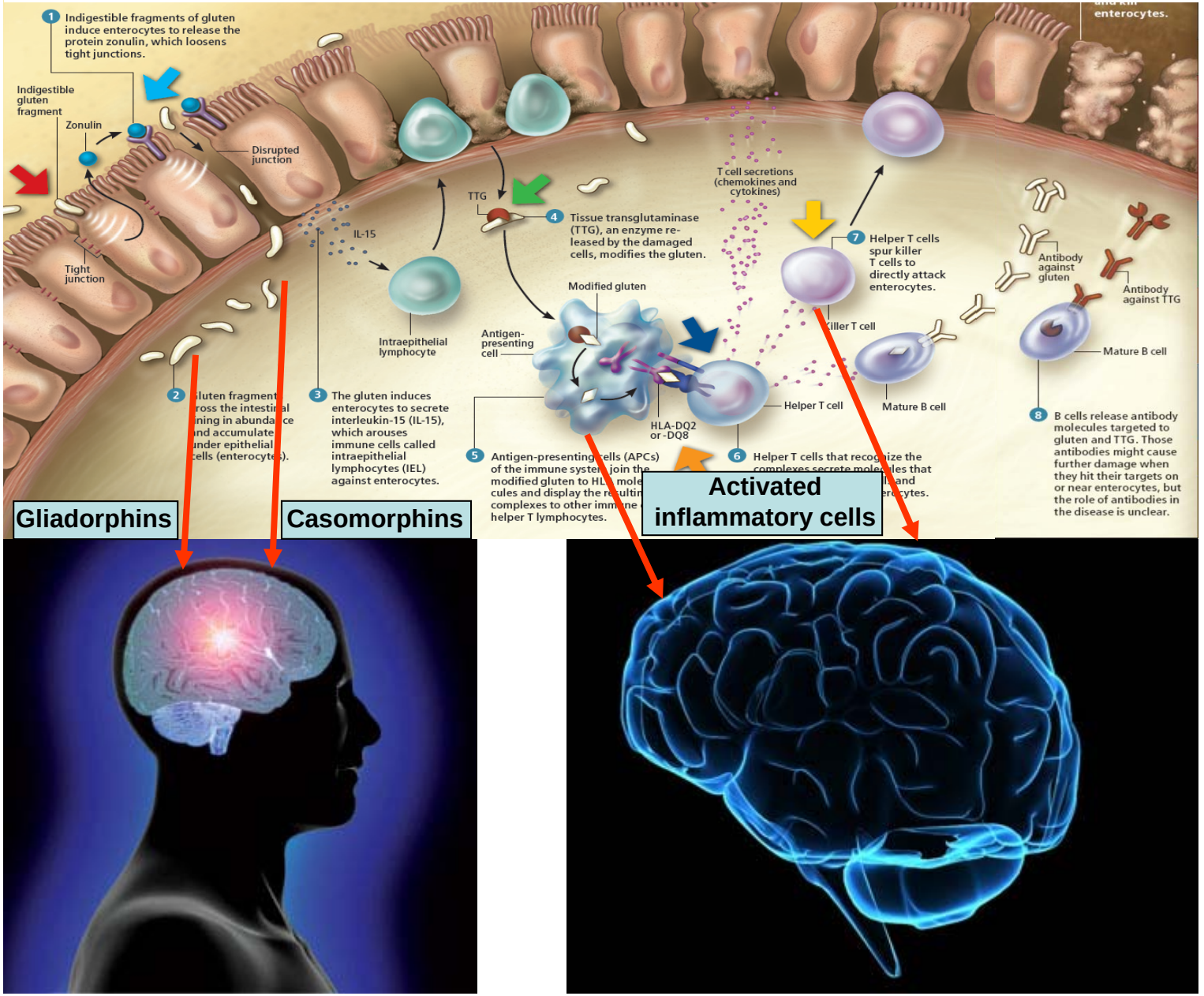
School of Public Health and MH Radiobiology Research Unit, Jilin University, Changchun, China.

Abstract

The present work measured circulating antibodies against native gliadins, deamidated gliadin-derived epitopes, and transglutaminase 2 (TGM2) in 473 patients with schizophrenia and 478 control subjects among a Chinese population. The results showed that 27.1% of patients with schizophrenia were positive for the IgA antibody against native gliadins compared with 17.8% of control subjects ($\chi(2) = 11.52$, $P = .0007$, OR = 1.72, 95% CI 1.25-2.35), although this significant difference appeared to be due mainly to low IgA gliadin antibody levels in female controls. A total of 27.6% of female patients were positive for IgA gliadin antibodies compared with 13.9% of female controls ($\chi(2) = 10.46$, $P = .0012$, OR = 2.36, 95% CI 1.39-4.01), and 26.4% of male patients were positive for IgA antibodies compared with 19.8% of male controls ($\chi(2) = 3.26$, $P = .071$, OR = 1.46, 95% CI 0.97-2.19). Of 128 patients who were positive for the IgA antibody against native gliadins, 8 were positive for the IgA antibody against deamidated gliadin epitopes and 1 was positive for IgA anti-TGM2 antibody. However, quantitative analysis demonstrated that the mean levels of IgA antibodies against deamidated gliadin epitopes and TGM2 were significantly lower in patients with schizophrenia than the control subjects ($P < .001$ and $P = .008$, respectively). The prevalence of IgG antibodies against native gliadins was not significantly different between the patient group and the control group ($\chi(2) = 2.25$, $P = .134$, OR = 1.32, 95% CI 0.92-1.88). This study suggests that specific gliadin-derived epitopes may be involved in schizophrenia.

PMID: 20884755 [PubMed - indexed for MEDLINE] PMCID: PMC3330001 [Available on 2013/5/1]

How Gluten and Inflammation Relate to Schizophrenia?



Discrepancy Between EMA and TTG2 Positivity in CATIE Is Related to Neuronal-Derived TTG6 Auto-Antibodies

	Controls (N=148)			TTG2 Positive CATIE (N=74)		
	High	Moderate	Negative	High	Moderate	Negative
EMA	0	0	148	5	0	69
TTG2 IgA	0	0	148	15	59	0
AGA-IgG	0	0	148	3	0	71
AGA IgA	2	0	146	19	12	43

Cascella N et al. Schiz Bul 2009

tTG Isoforms as Biomarkers of Tissue-Specific Inflammation Caused by Gluten

Isoforms		Associated Condition
Tissue Transglutaminase 2	tTG 2	Celiac Disease
Epidermal Transglutaminase 3	tTG 3	Dermatitis Hepetiformis
Neuronal Transglutaminase 6	tTG 6	Gluten Ataxia

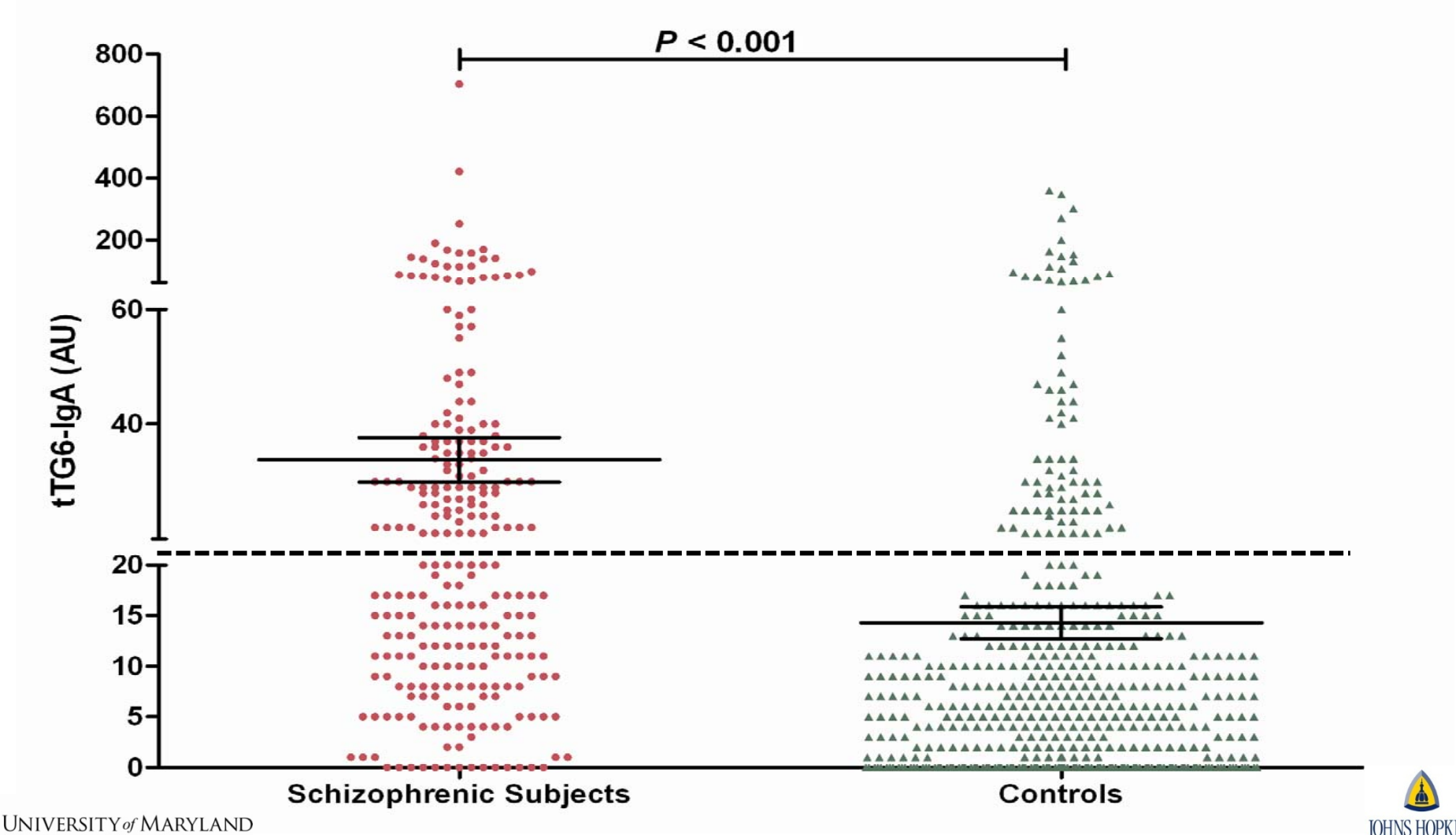
Aim

- **To evaluate whether antibodies against neuronal tTG6 IgA antiobodies can be used as a biomarker of gluten-dependent neuro-inflammation in a randomized group of schizophrenic subjects.**

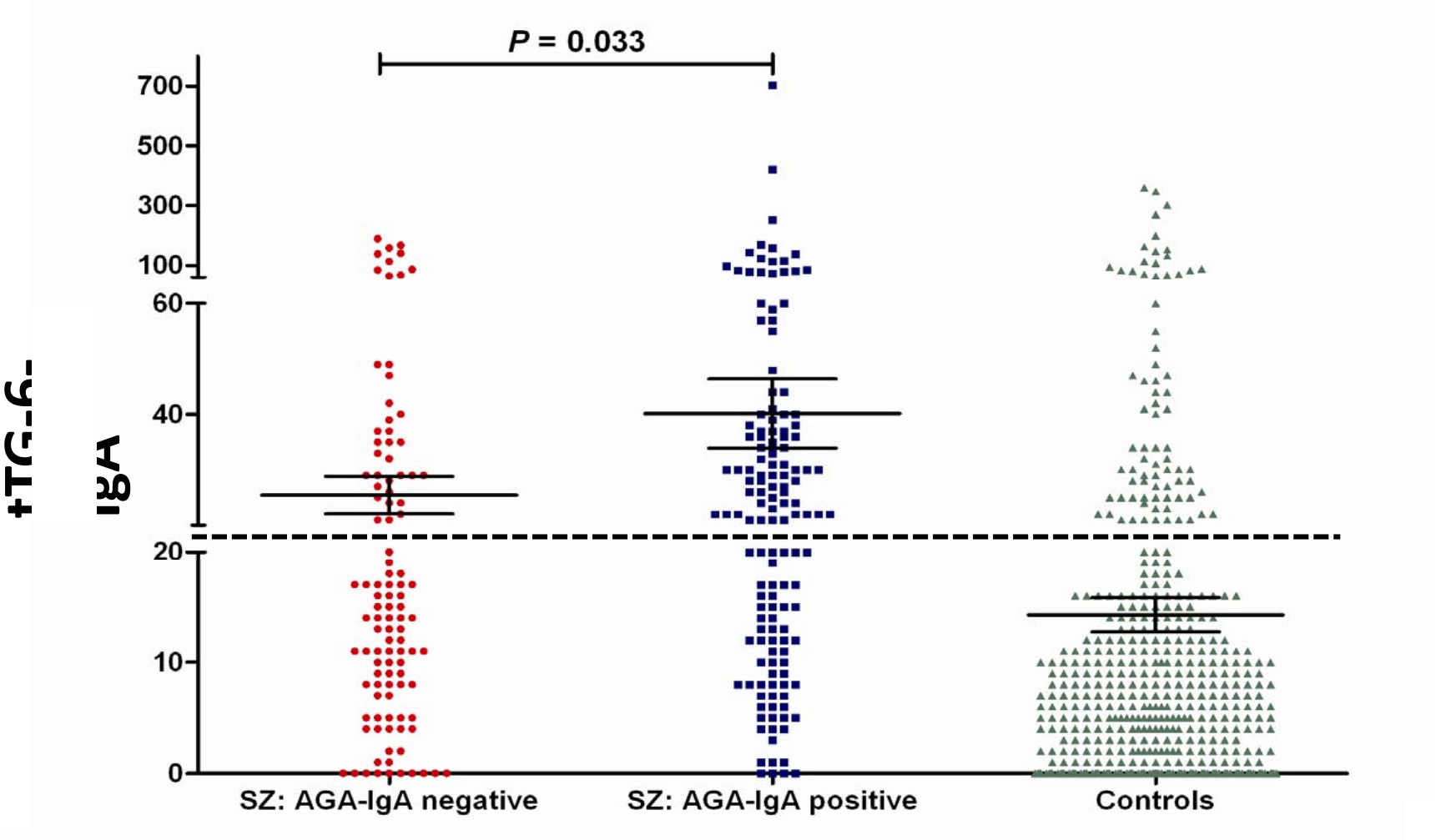
Methods

- **Serum samples obtained from schizophrenic subjects enrolled in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) N=1419**
- **249 randomly selected samples were divided into two groups**
  - **Negative for AGA-IgA antibodies (N = 107)**
  - **Positive for the AGA-IgA antibodies (N = 142)**
- **Neuronal anti-tTG-IgA-6 antibodies were assayed in both schizophrenic patients and age- and gender-matched controls (1:2)**

Results:
Schizophrenic vs Controls



Results:
AGA-IgA: Negative vs Positive



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Conclusions

- **These results point to a possible role of tTG-6 IgA antibodies as a biomarker of gluten sensitivity among schizophrenic patients.**

Schizophr Bull. 2012 Apr 19. [Epub ahead of print]

Increased Prevalence of Transglutaminase 6 Antibodies in Sera From Schizophrenia Patients.

Cascella NG, Santora D, Gregory P, Kelly DL, Fasano A, Eaton WW.

1Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, 600 North Wolfe Street, Meyer 144, Baltimore, MD 21287.

Abstract

Gluten can cause extraintestinal manifestations with or without gastrointestinal symptoms and elevated antitissue transglutaminase 2 (tTG2) autoantibodies. Organ-specific gluten reaction involves immune response toward other transglutaminase (TG) isoforms including tTG3 (expressed in the skin, leading to dermatitis herpetiformis) and tTG6 (expressed in the brain, causing gluten ataxia). This analysis focuses on tTG6 antibodies, which have never been studied before in schizophrenia (SZ) and its relationships to tTG2 and to antigliadin antibodies. We previously showed an increased prevalence of tTG2 antibodies in gluten sensitive SZ patients compared with healthy controls (HC) that was not paralleled by an increased prevalence of antiendomysial antibody. To elucidate this discrepancy, we examined those tTG2 positive SZ patients for the presence of tTG6 antibody. We also searched for tTG6 antibodies in our sample of antigliadin (AGA) positive and AGA and tTG2 negative SZ patients. Seventy-four tTG2 positive SZ patients were compared with 148 age and gender-matched HC. Of the 74 tTG2 positive SZ patients, 16 were positive for tTG6 IgA for a prevalence of 22%. Only 4 HC were positive for tTG6 IgA for a prevalence of 2.7%. Among the AGA positive SZ patients, the prevalence of tTG6 IgA was 21.3% while 13.1% of the AGA and tTG2 negative SZ patients were positive for tTG6 IgA. The HC had a prevalence of 6%. Our results indicate a higher prevalence of tTG6 antibodies in SZ that may represent a biomarker useful to identify SZ patients who would benefit from a gluten-free diet.

PMID: 22516148 [PubMed - as supplied by publisher]

Schizophrenia Research xxx (2012) xxx–xxx

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Letter to the Editor

A gluten-free diet in people with schizophrenia and anti-tissue transglutaminase or anti-gliadin antibodies

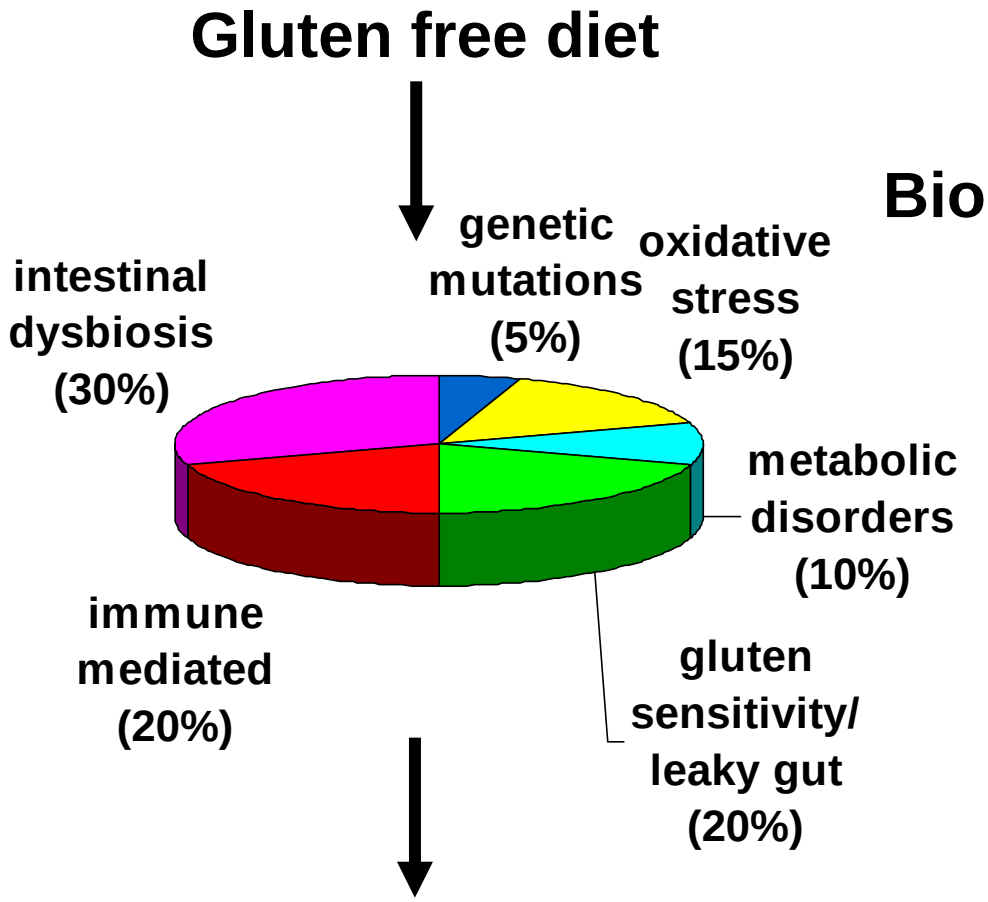
Dear Editors,

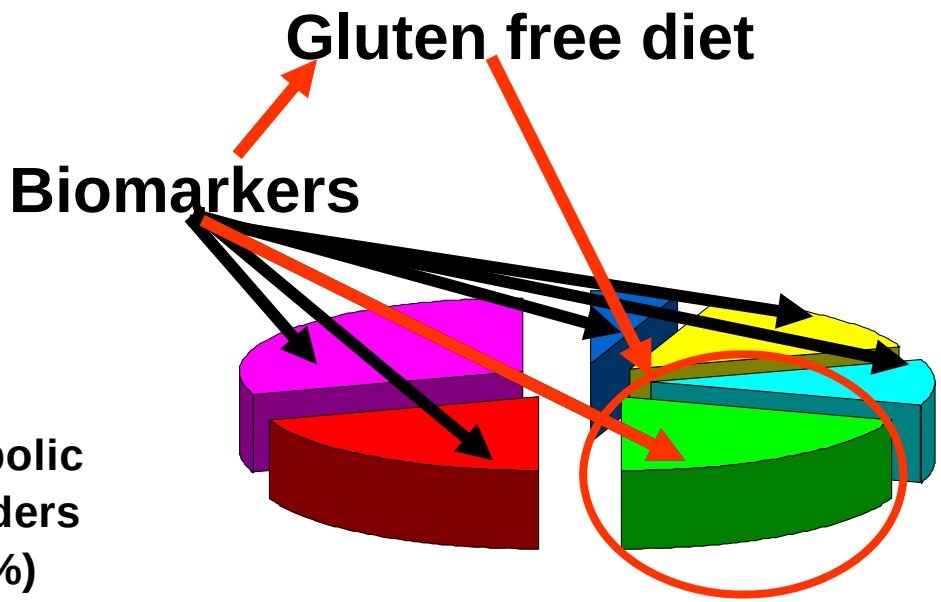
Celiac disease is an immune-mediated disease involving a reaction to gluten, presenting with diarrhea, weight loss, abdominal complaints and a range of less common associated neurologic and psychiatric symptoms. Several epidemiologic studies have linked celiac disease to schizophrenia, however only recently have direct antibody assessment for the detection of celiac disease (anti-tissue transglutaminase (anti-tTG) and anti-endomysial antibodies (EMA)) become available (reviewed in Kalaydjian et al., 2006). Antibodies to gliadin (AGA) and not anti-tTG suggest an immune-mediated reaction distinct from celiac disease, gluten sensitivity. Gluten sensitivity is thought to be associated with neurologic and psychiatric manifestations, but free from the gastrointestinal symptoms seen in celiac disease (Jackson et al., 2012), however this separation has only recently been recognized. In a previ-

robust improvements in extrapyramidal side effects (EPS). Both participants saw notable improvements on the BPRS and SANS. Both participants also had improvements in akathisia and EPS with participant B having notable changes in both at the end of the trial. The data shows that a GFD can be maintained in individuals with schizophrenia with no negative effects on behavior or attitude and no need for medication changes. Overall the diet was easily maintained, however it is recognized that much education would be needed to help patients understand the importance of a GFD and the gluten content of food and snacks.

The pilot study is obviously limited by the small sample and no control group or placebo; however no studies to date have been performed in antibody-positive patients and with the robust findings, this information is critical to share with the field to encourage future research in this area. Other potential limitations are the short period of withdrawal from gluten and that the improvements could be in part due to participants entering an experimental treatment protocol in general. A longer-term study may produce more robust changes over time. Bowel symptoms in celiac disease are often rapidly improved when a patient begins

Schizophrenia Is A Complex and Heterogeneous Diseases That Require Customized Treatments:





20% efficacy (failure)

100% efficacy (success)

Gluten Free Diet in People With Schizophrenia: A Pilot Study

This study is currently recruiting participants.

Verified October 2012 by University of Maryland

Sponsor:
University of Maryland

Information provided by (Responsible Party):
MPRC, University of Maryland

ClinicalTrials.gov Identifier:
NCT01558557

First received: March 15, 2012
Last updated: October 11, 2012
Last verified: October 2012
History of Changes

Working Hypothesis