

# GLUTEN SENSITIVITY AND SCHIZOPHRENIA



UNIVERSITY of MARYLAND  
SCHOOL OF MEDICINE

*Deanna L. Kelly, Pharm.D., BCPP  
Professor of Psychiatry*

*Director, Treatment Research Program  
Maryland Psychiatric Research Center (MPRC)  
University of Maryland School of Medicine*

# What is Schizophrenia?

- A chronic, severe and disabling brain disease that affects about 1% of world's population
- Presents very heterogeneous with many patients having positive, negative and cognitive symptoms
  - Positive symptoms: hallucinations, delusions (lose touch with reality)
  - Negative symptoms: restricted affect, avolition, asociality (disruptions in normal emotions and behaviors)
  - Cognitive symptoms: about one standard deviation below healthy controls



There are several types of schizophrenia, and no one characteristic is common to all. Psychotic symptoms include:

- delusions
- hallucinations
- incoherence
- catatonic or hyperactive behavior
- flat affect

# Schizophrenia and Gluten History

- 1950s and 1960s: first notice of wheat shortage and symptom improvements; epidemiologic studies relate psychiatric admissions to wheat and rye consumption during and after WW II ( $r=0.908, p<0.01$ )
- 1970s: 4 small studies show gluten free diet associated with increase hospital discharge and improvement in symptoms
- 1980s: 3 small negative studies with gluten free diet halt research on the topic
- Mid 1990s: AGA reported to be higher in schizophrenia, case reports full symptom resolution



Bender 1953, Psychiatr Q; Sheldon 1959, Pediatrics; Dohan 1966, Am J of Clin Nutrition Walsh and Walsh 1970, Irish Med Association; Dohan 1973, Am J of Psychiatry; Singh and Kay 1976, Science; Rice et al. 1978, Am J of Psychiatry; Vlissides et al. 1986, Br J of Psychiatry Potkin et al 1981, Am J Psychiatry; Storms et al 1981, Arch Gen Psychiatry, Osbourne et al 1982 Biol Psychiatry Reichelt et al Biological Psychiatry 1995

# AGA Antibodies in Schizophrenia

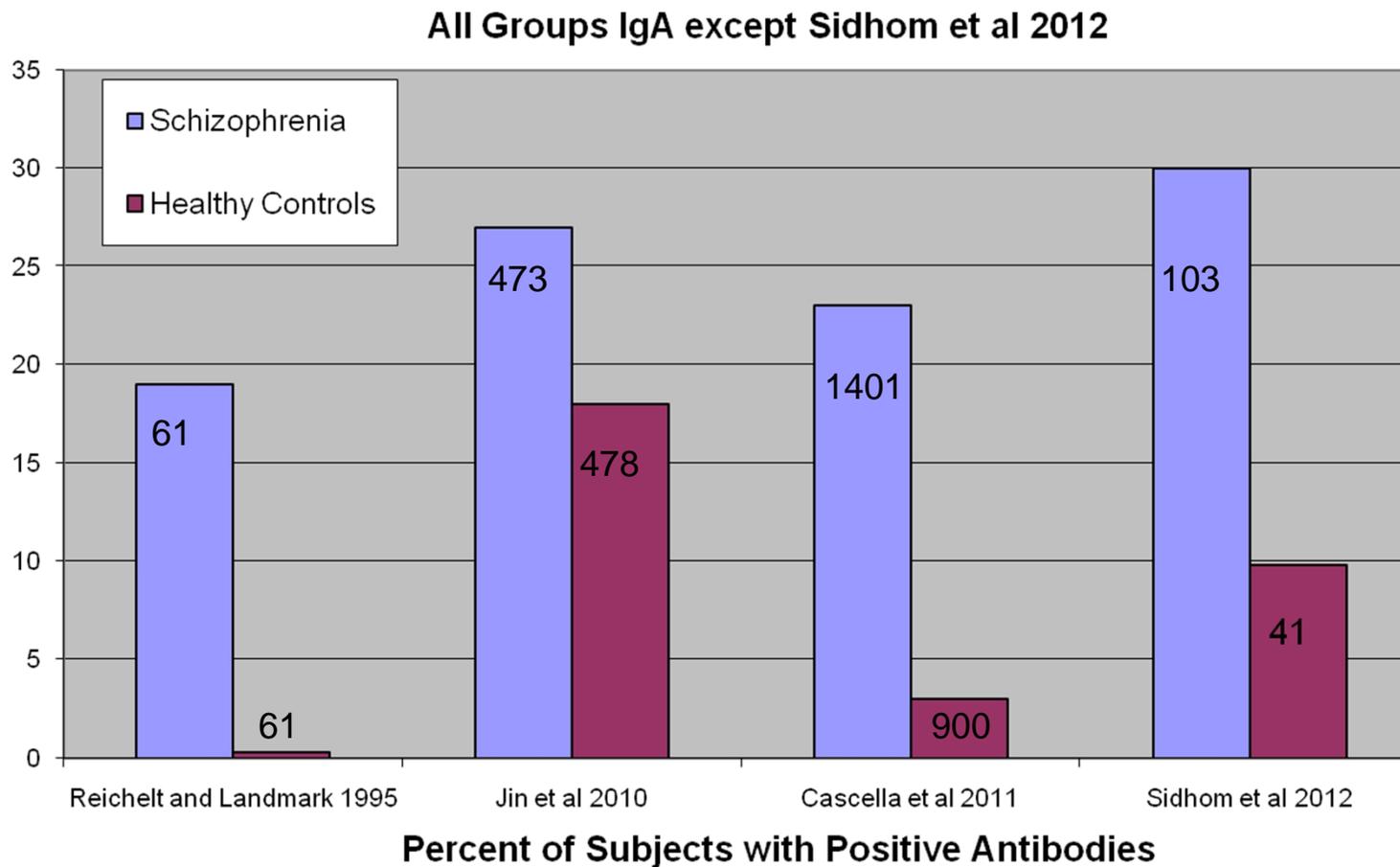
- Goal to evaluate antibodies to gliadin in 1,401 subjects from the CATIE sample
- Assessed tTG, AGA and EMA. Completed in UMB Mucosal Biology Lab
- Compared to age, sex, race matched controls
- Linear regression used to examine PANSS scores (total, positive, negative) and antibodies

# Prevalence of Antibodies in Schizophrenia

	CATIE	Controls
tTG	5.5%	1.1%
AGA- IgA	23.4%	2.9%

Age-adjusted rates significant at  $P < .05$   
AGA-IgA tested using INOVA Diagnostics Kit  
( $>20$  units medium to high)

# Antibodies to Gliadin in Schizophrenia and Control Groups



Not related to antipsychotic treatment, Reichelt study antipsychotic free for 3 months. Catassi et al. (2007) IgA levels in male patients unchanged during three month observation and not related to duration or dose of antipsychotic medications

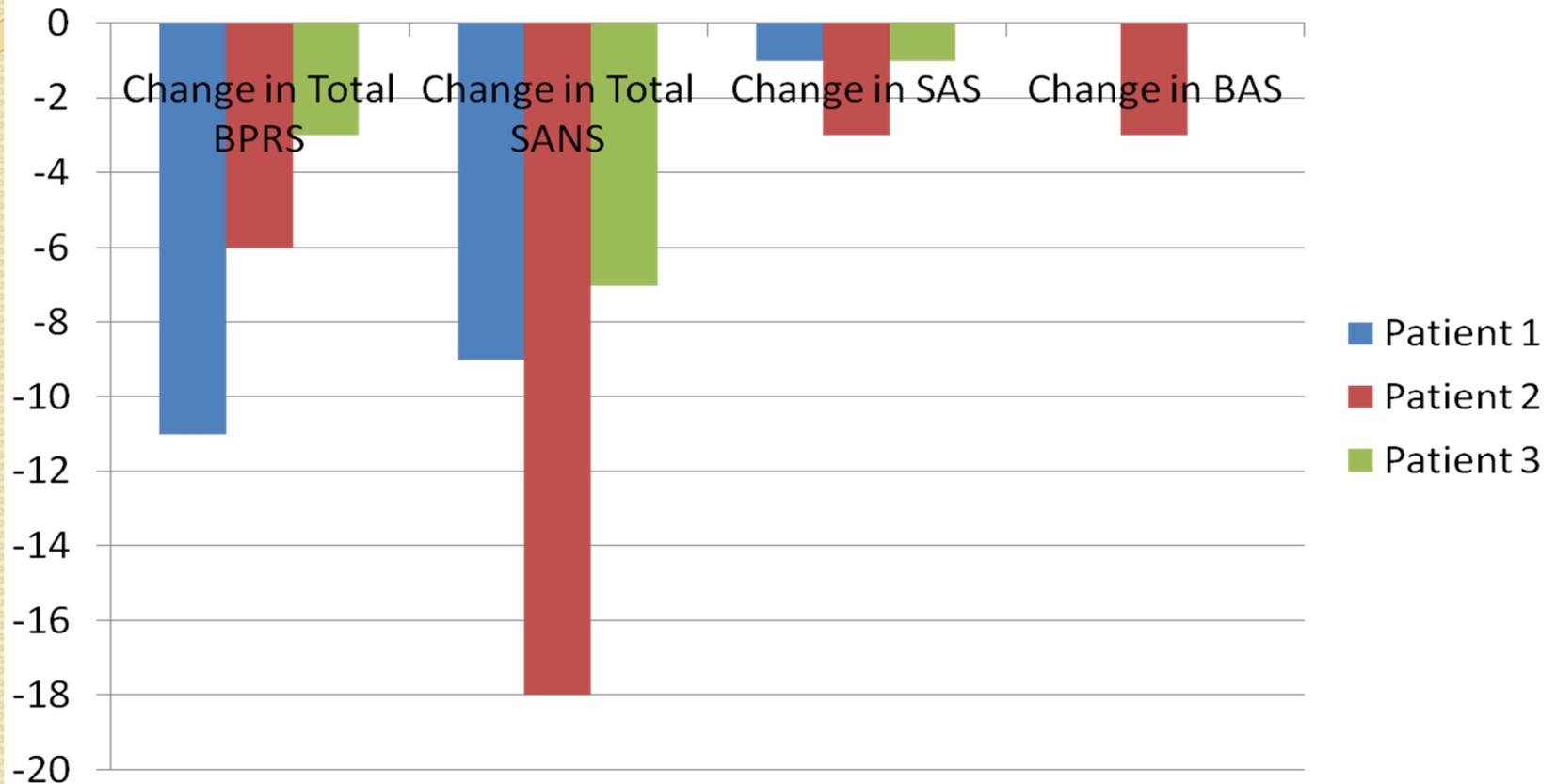
# tTG6 and Schizophrenia

- In CATIE study, many tTG positive cases did not have corresponding EMA positive assays
- tTG6 expressed primarily in the brain and main autoantigen in gluten ataxia
- 74 tTG2 positive schizophrenia patients were compared on tTG6 to 148 age and sex matched HC
- 16/74 (22%) tTG positive were positive for tTG6 while only 2.7% of healthy controls were positive for tTG6 ( $p < 0.001$ ).
- tTG6 may represent biomarker (marker for neuroinflammation) in schizophrenia; explains discrepancy between EMA and tTG, representing extraintestinal source of tTG

# Pilot Study

- Goal: to establish feasibility of initiating and maintaining gluten free diet in tTG and AGA positive patients with schizophrenia
- Voluntarily admitted to inpatient unit
- 2 week gluten-free diet
- Inclusion/Exclusion
  - Age 18-55 years
  - DSM-IV criteria for schizophrenia or schizoaffective disorder
  - Positive for tTG or AGA
  - Clinically stable on same antipsychotic for 2 months with an unchanged dose for prior 4 weeks
  - Able to give informed consent >10 on ESC
  - Pregnant women excluded

# Pilot Study Results



Jackson et al 2012 Schiz Research; Feldman et al 2013, Schiz Bull

# Gluten Free Diet in People with Schizophrenia who are AGA positive

- Newly funded double-blind randomized gluten-free trial (NIMH R34)
- 20 participants with schizophrenia and positive for AGA
- Collaboration with Johns Hopkins (Eaton) and Mass General Celiac for Celiac Research and Treatment (Fasano)
- First study in schizophrenia to select subjects based on antibodies
- ClinicalTrials.gov # NCT01927276

# Summary

- Gluten sensitivity is higher in schizophrenia than the general population
- People with schizophrenia who have positive AGA may respond to a gluten free diet
- tTG6 may be biomarker for neuroinflammation in schizophrenia
- Larger gluten free diet study is underway, mechanisms understudy



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Thank You  
😊



# WHAT COULD BE THE MECHANISM?

- Gliadin mediated cytokine production?
  - Gliadin can activate cytokine production in monocytes and macrophages
    - In murine peritoneal macrophages treated with different concentrations of gliadin there was potent induction of proinflammatory genes including  $\text{TNF}\alpha$ , IL6, IL12, IL15 and others (Thomas et al 2006)
  - Increased permeability of immune related cytokines or antibodies into CNS

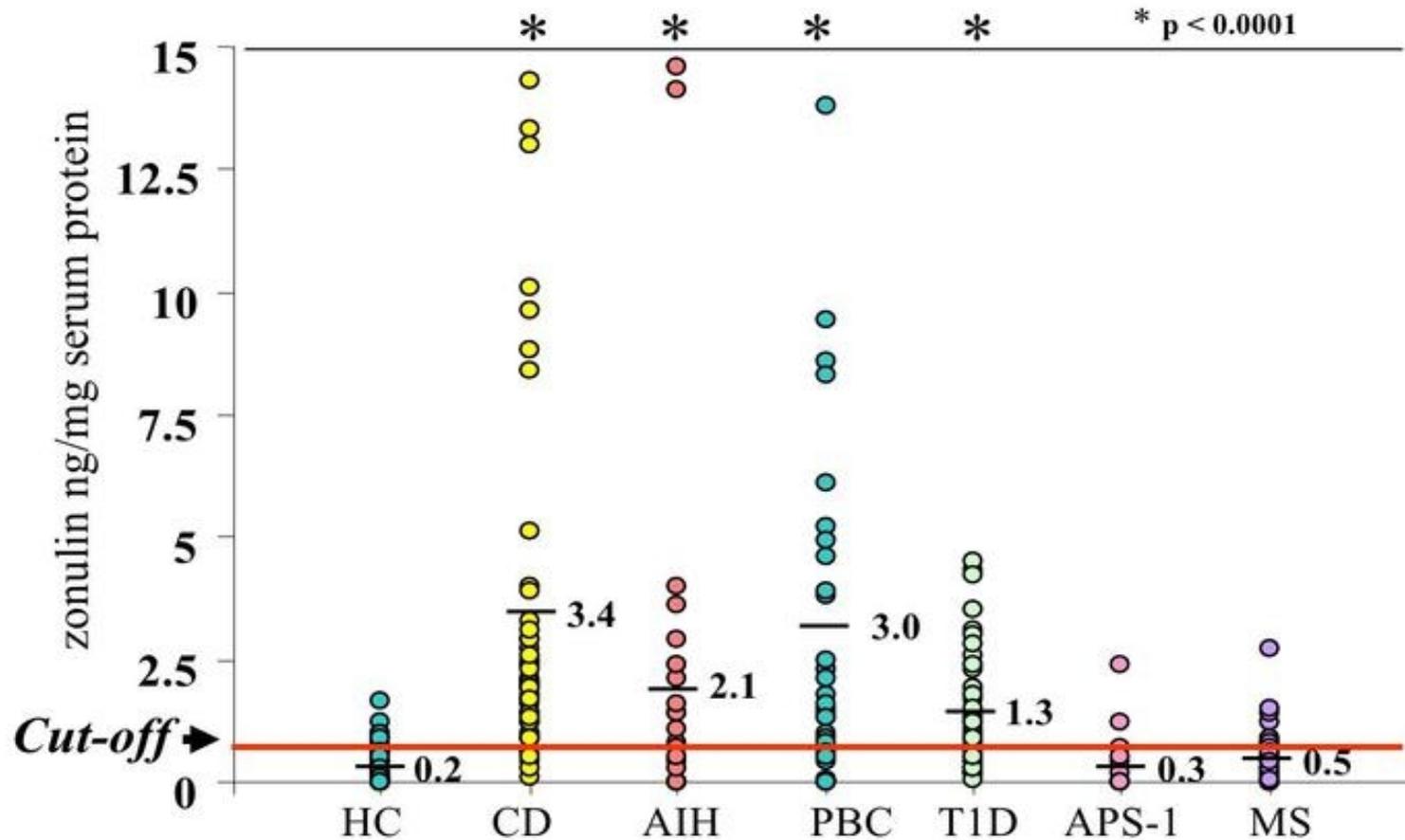
# BBB QUICK REVIEW IN SCHIZOPHRENIA

- Several studies in people with schizophrenia have found that some patients have ↑ permeability of the BBB (Axelsson et al. 1982; Torrey et al. 1985; Bauer and Kornhuber 1987; Kirch et al. 1992).
- Hanson and Gottesman (2005) hypothesize that abnormalities in blood flowing to the brain or passage of substances into the brain may lead to altered neuronal-glial function, that in turn may lead to schizophrenia psychopathology.
- A post mortem study found that ultrastructural abnormalities of capillaries and of pericapillary cellular environment suggest that BBB dysfunction might contribute to the pathogenesis of cortical lesions in schizophrenia (Uronova et al. 2010)

# ZONULIN

- In the late 1990s zonula occludens toxin (ZOT), a protein from *Vibrio cholerae*, was found to reversibly regulate the permeability of tight junctions in the GI tract (Fasano et al. 1997).
- Soon after it was discovered that ZOT mimicked an endogenous modulator of tight junctions, zonulin.
- Zonulin is a protein that participates in the physiological regulation of tight junctions and their opening
- Zonulin-mediated dysregulation of the intestinal barrier may lead to the passage of environmental antigens that may cause immune reactions or autoimmune disorders (Fasano et al. 2000) in both GI and BBB (Skardelly et al. 2009).
- Zonulin is the only physiological modulator of intercellular tight junctions described so far that is involved in trafficking of macromolecules and, therefore, in tolerance/immune response balance.
- When the zonulin pathway is deregulated, autoimmune, inflammatory, and neoplastic disorders can occur. “Gatekeeper”
- This may also help understand diseases of inflammatory nature such as schizophrenia.

# Serum Zonulin in Autoimmune Disorders



Clemente et al. *Gastroenterology* 2002;122 :A15

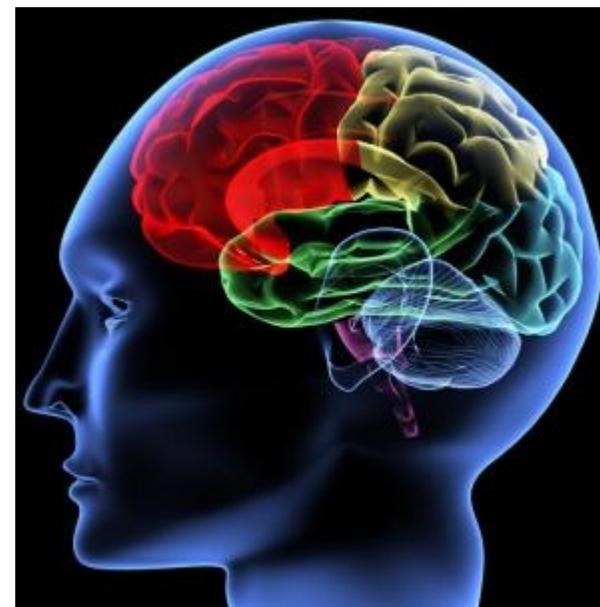
Celiac Disease, Autoimmune Hepatitis, Primary Biliary Cirrhosis, Type I Diabetes, Autoimmune Polyendocrine Syndrome, Multiple Sclerosis

# EVIDENCE OF ZONULIN AND SCHIZOPHRENIA

- Zonulin, same as protein formerly referred to as prehaptoglobin-2 (Tripathi et al. 2009)
  - Haptoglobin binds to hemoglobin inhibiting oxidative activity
  - Prehaptoglobin elevated in schizophrenia (Wan 2007)
- Haptoglobin has been known to be elevated in schizophrenia relative to controls for decades (Seal and Eist 1966) and the haptoglobin gene has been implicated as a significant genetic risk factor in a meta-analysis of more than 1,000 genetic association studies (Allen et al. 2008).
- Pursuing zonulin serum levels and BBB permeability markers in schizophrenia

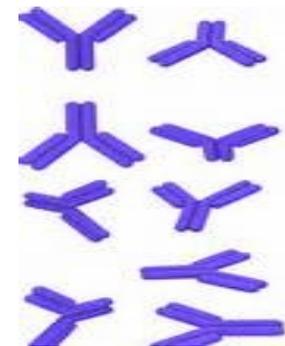
# What Causes Schizophrenia?

- We don't know for sure
- We don't have objective measures for diagnosis
- Many medications that block dopamine have efficacy, also glutamate may be involved
- May be neurodevelopmental disease, most people have age of onset 18-22 years
- Current treatment is lifelong antipsychotic medications and psychosocial interventions
- Genes and environment may be causal



# Schizophrenia Subtypes or Possible Endophenotypes

- Current lack of objective diagnostic measures or biomarkers may group many similar diseases into schizophrenia
- Lack of biomarkers prevents individualized treatment
- Gluten sensitivity may represent a biomarker that may define a subgroup or endophenotype of the illness we call schizophrenia





# Assessments

- Baseline labs and physical, vitals, BMI
- Symptom ratings
  - Brief Psychiatric Rating Scale
  - Scale for the Assessment of Negative Symptoms
  - Calgary Depression Scale

## Side effect (neurological/extrapyramidal) ratings

- Simpson Angus Scales
- Barnes Akathisia Scale
- SF-36 Health Survey and Patient Global Improvement

# Pilot Study Results

	CGI	PGI	SF-36	BMI (kg/m <sup>2</sup> )
Subject 1 Baseline	5	4	118	23.2
Subject 1 Endpoint	4	1	122	23.6
Subject 2 Baseline	4	4	126	23.1
Subject 2 Endpoint	4	4	130	22.5
Subject 3 Baseline	4	4	122	25.7
Subject 3 Endpoint	4	3	120	26.1

# Gluten Free Diet in People with Schizophrenia who are AGA positive

- Newly funded double-blind randomized gluten-free trial
- 20 participants with schizophrenia and positive for AGA
- Collaboration with Johns Hopkins (Eaton) and Mass General Celiac for Celiac Research and Treatment (Fasano)
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# Other Studies (IgG)

- Mean AGA in schizophrenia  $0.81 \pm 0.79$  vs.  $0.52 \pm 0.56$  in healthy controls ( $p < 0.0001$ ); OR in schizophrenia = 2.13 (95% CI 1.57-2.91)
- OR of IgG = 5.50 (95% CI 2.65-11.42) and OR of IgA = 2.75 (95% CI 1.31-5.75)
- In schizophrenia AGA antibodies do not correlate to tTG, HLA DQ2 or DQ8, demonstrating separate entity from celiac disease process

# Symptoms and Antibodies

- Okusaga 2012 finds negative correlation between AGA levels and total PANSS score ( $r=-0.073$ ,  $p=0.026$ )
- Our recent data shows significantly lower levels of positive symptoms in people who are AGA positive compared to AGA negative
- CATIE data in total symptoms lower in AGA negative but not significantly so. Total PANSS 73.5 (SE=1.91) vs. 75.8 (SE=0.48)
- Thus, no symptom profile is associated with antibodies. Data suggests that due to lower symptom levels could represent separate phenotype

## CELIAC DISEASE

- 1% of population
- Autoimmune disorder
- Damage to intestinal villi
- Gastrointestinal symptoms- bloating, constipation, diarrhea, vomiting



## GLUTEN SENSITIVITY

- 3-5% of population
  - Damage to nervous system
  - Neurologic and psychiatric symptoms- schizophrenia, ataxia, epilepsy, anxiety, depression, ADHD
- Triggered by ingestion of gluten (wheat, rye, barley)
  - Underdiagnosed
  - Treated with gluten-free diet

Zarkadas, M., Cranney, A., Case, S., Molloy, M., Switzer, C., Graham, I. D., Butzner, J. D., Rashid, M., Warren, R. E., & Burrows, V. The impact of a gluten-free diet on adults with coeliac disease: results of a national survey. *Journal of Human Nutrition and Dietetics*, 19(1), 41-49.

<http://digestive.niddk.nih.gov/ddiseases/pubs/ceciac/>

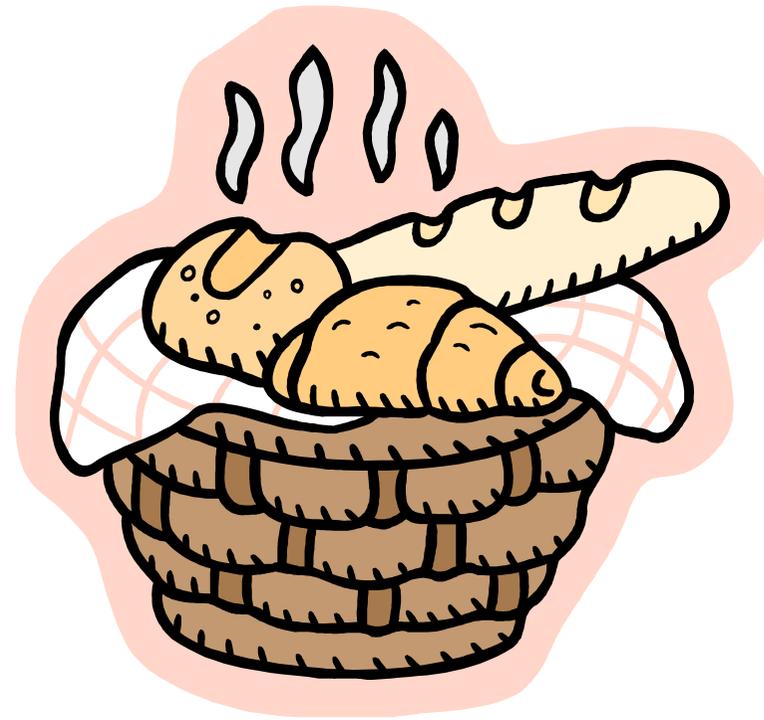
Catassi C, Kryszak D, Louis-Jacques O et al. Detection of Celiac disease in primary care: a multicenter case-finding study in North America. *Am J Gastroenterol* 2007 July;102(7):1454-60.

Fasano A, Berti I, Gerarduzzi T et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. *Arch Intern Med* 2003 February 10;163(3):286-92.

Jackson J, Eaton W, Cascella N, Fasano A, Kelly D: Neurologic and psychiatric manifestations of celiac disease and gluten sensitivity. *Psychiatric Quarterly*, Epub ahead of print.

# WHAT IS GLUTEN?

- Gluten is a protein composite found in foods containing wheat, barley and rye
- Gives elasticity to dough, helping it to rise and keep its shape
- The composite is gliadin and glutenin (gliadin is alcohol soluble and glutenin is soluble in dilute acids).
- Gluten is fairly indigestible in most people





## What other evidence in schizophrenia?

- Schizophrenia related to 50% greater likelihood of autoimmune disorder
- History of autoimmune disease related to 45% greater likelihood of developing schizophrenia

# DIAGNOSIS

## Celiac Disease

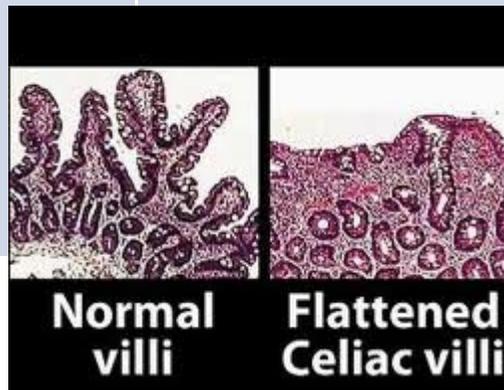
### 4/5 of the following:

- Positive Antibody Tests:
  - Antitissue transglutaminase (tTG)
  - Antiendomysial antibodies (EMA)
  - Antigliadin antibodies (AGA)

- Presence of symptoms
- HLA DQ2 or HLA DQ8
- Small bowel biopsy
- Symptoms improve on GFD (Catassi and Fasano 2010)

## Gluten Sensitivity

- Positive antigliadin antibodies
- Neurological or psychiatric symptoms (Jackson et al. 2011)



# GLUTEN SENSITIVITY

- Associated with neurologic and psychiatric disturbances
- One study neurologic dysfunction of unknown origin had 57% test positive for AGA
- Gluten ataxia is well described, hypothesized to occur due to lymphocytic infiltration in areas of CNS, specifically the Purkinje cell layer of the cerebellum and dorsal columns of spinal cord.

# PILOT STUDY RESULTS

	<b>BPRS total</b>	<b>SANS Total</b>	<b>BAS</b>	<b>SAS</b>
Subject 1 Baseline	55	48	0	3
Subject 1 Endpoint	44	39	0	2
Subject 2 Baseline	40	60	5	3
Subject 2 Endpoint	34	42	2	0

# INTRACELLULAR TIGHT JUNCTION PERMEABILITY IN SCHIZOPHRENIA: FOCUS ON ZONULIN

- 100 participants with schizophrenia
- Blood test for zonulin level, AGA, and tTG
- Psychiatric assessments; BPRS and SANS
- Inclusion/Exclusion
- 100 matched samples by age, race and sex