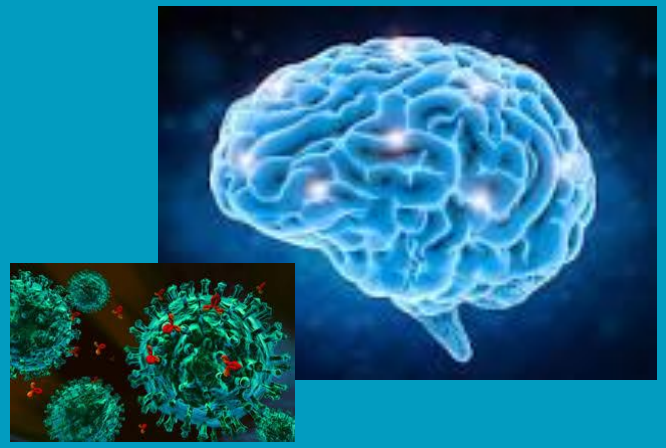

Schizophrenia and Gluten: New Target and Precision Medicine

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What is Gluten?

- Gluten is a protein composite found foods containing wheat*, barley, rye and triticale (a cross between wheat and rye)
- One of gluten's two main proteins, GLIADIN, is a densely packed protein and digested into long amino acid chains with a low surface area to volume ratio, making it difficult to digest.
- Immune reactions to gliadin can occur in 3 forms: Celiac Disease, Non-Celiac Gluten Sensitivity and wheat allergy

*wheatberries, durum, emmer, semolina, spelt, farina, farro, graham, KAMUT® khorasan wheat and einkorn

Rafalski JA. *Gene* 1986;43:122129, Anderson OD, Greene FC. *Theoretical Applied Gen* 1997;95:59-65, Stern et al *Gastroenterol Hepatol* 2001;13:741-7

Celiac Disease vs Gluten Sensitivity?

- Celiac Disease 1% of population
- Primary antibodies:
  - tissue transglutaminase (tTg)
  - endomysial antibodies (EMA)
  - deaminated gliadin peptide (DGP)

  - only in Celiac Disease

- Gluten Sensitivity 10% of population:
- Antibodies:
  - native gliadin antibodies (AGA IgA)- not different in schizophrenia
  - **native gliadin antibodies (AGA IgG)**

Linked to Schizophrenia?

- During World War II, as wheat consumption decreased in Scandinavia, admissions for schizophrenia decreased
- As wheat consumption the United States increased, admissions for schizophrenia increased

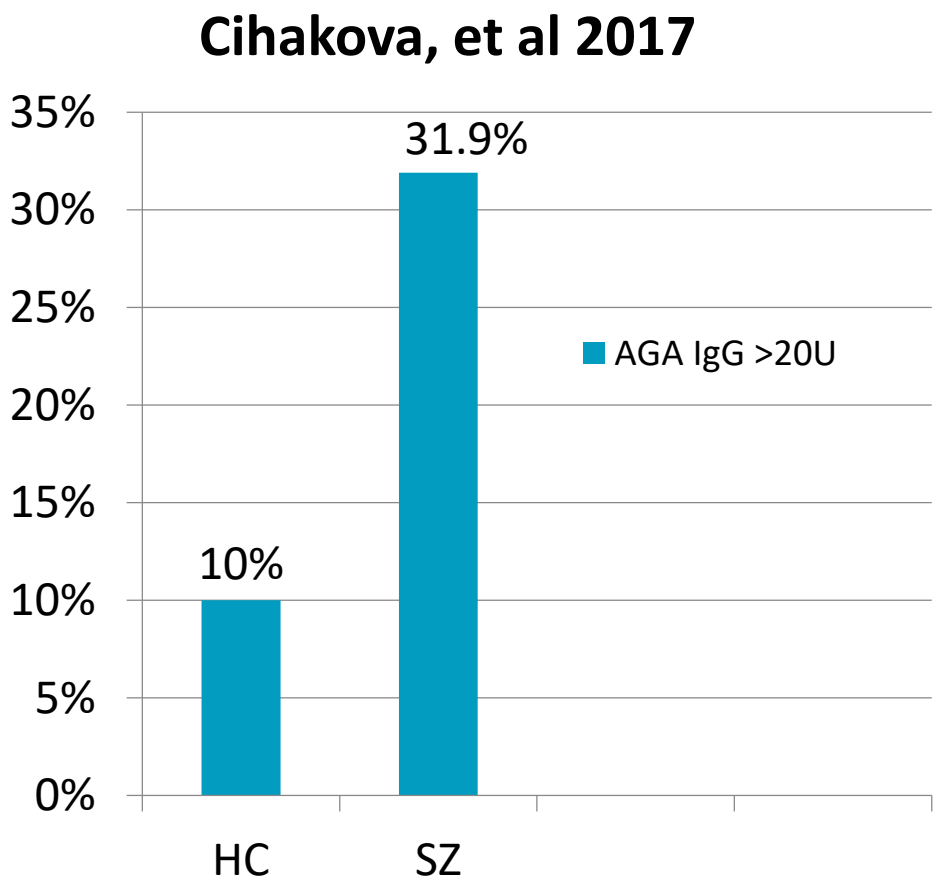
Francis Curtis Dohan
March 24, 1907- Nov 9, 1991
https://en.wikipedia.org/wiki/F._Curtis_Dohan

Wheat "Consumption" Data and Hospital Admissions for Schizophrenia
Summary of Original Data

Country and Period	Mean Annual No. of First Admissions for Schizophrenia*	Mean Annual "Consumption" of Wheat†
Finland*		
1936–1939 (prewar)	1,217	69.5
1940–1942	1,107	60.9
1943–1945	832	48.0
Norway*		
1936–1940	332	(299.6)
1941–1945	201	(123.4)
Sweden		
1937–1939	938	(737.2)
1940–1942	654	(481.3)
1943–1945	608	(458.5)
Canada		
1937–1939	814	84.0
1942–1942	721	75.0
1943–1945	871	84.6
U. S. A.		
1939	9,557	70.5
1940–1942	10,230	70.1
1943–1945	10,943	74.6

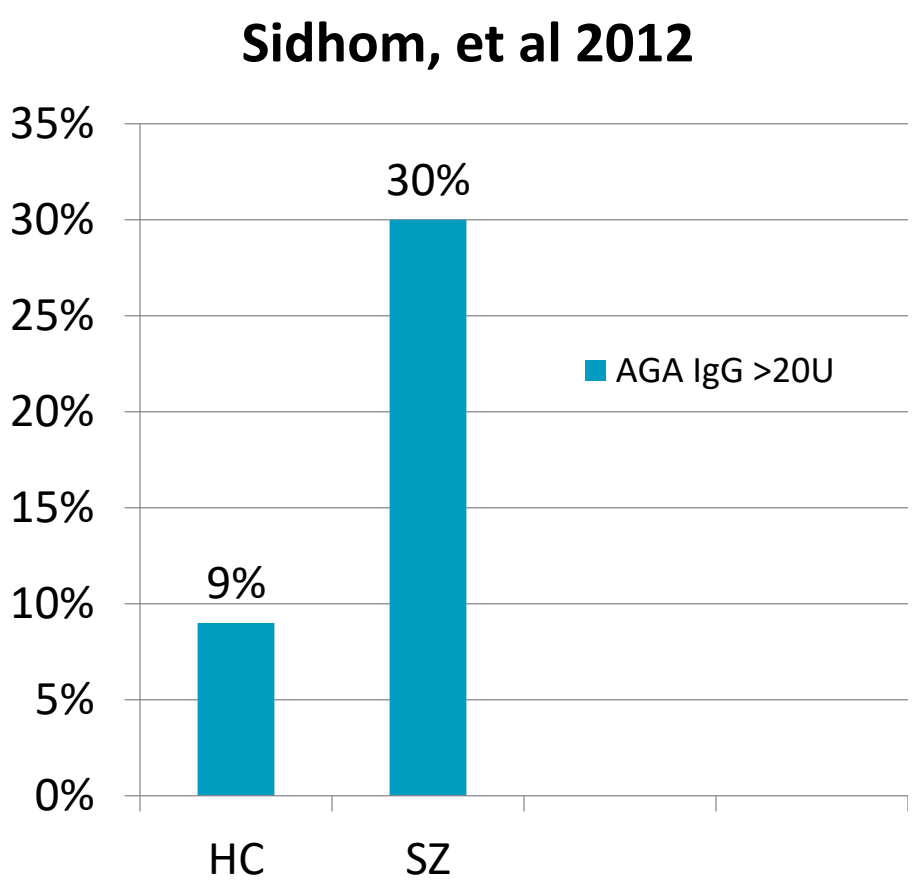
Dohan FC, *Acta Psychiatr Scand.* 1966;42(1):1-2, with permission

AGA (IgG) in Schizophrenia vs. Healthy Controls



HC=healthy controls
SZ=schizophrenia

Using INOVA First Generation Kits for Native Gliadin



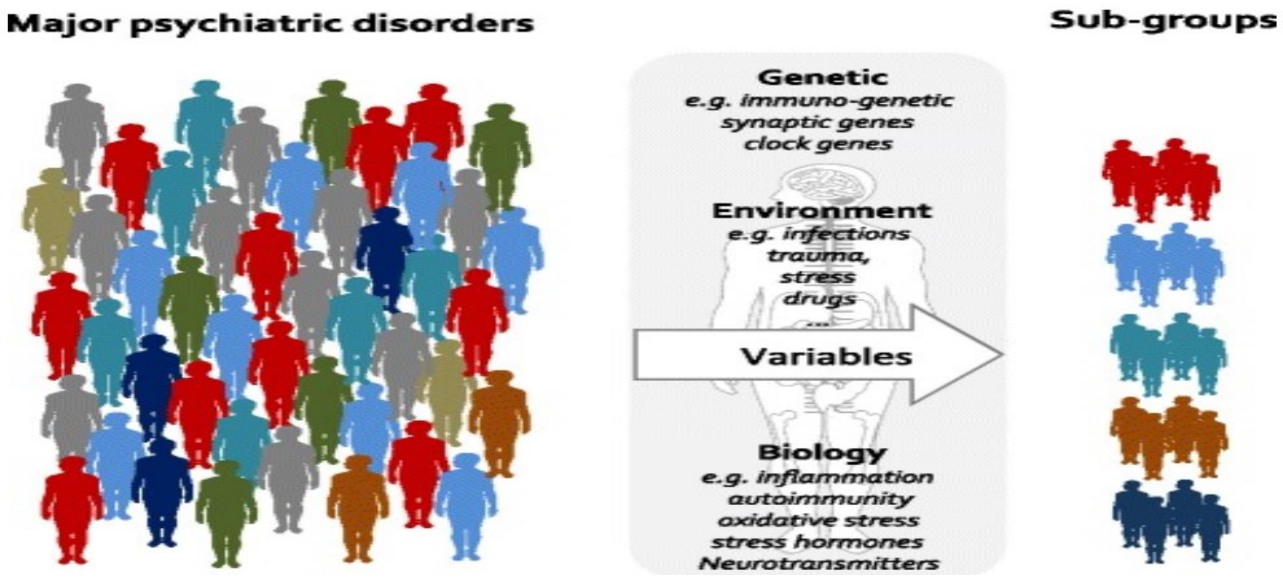
AGA IgG Mean Values 17.9 ± 21.4 SZ
AGA IgG Mean Values 9.2 ± 13.2 HC $p<0.001$

Two other published papers have shown increased OR of 2-5 for AGA IgG in schizophrenia

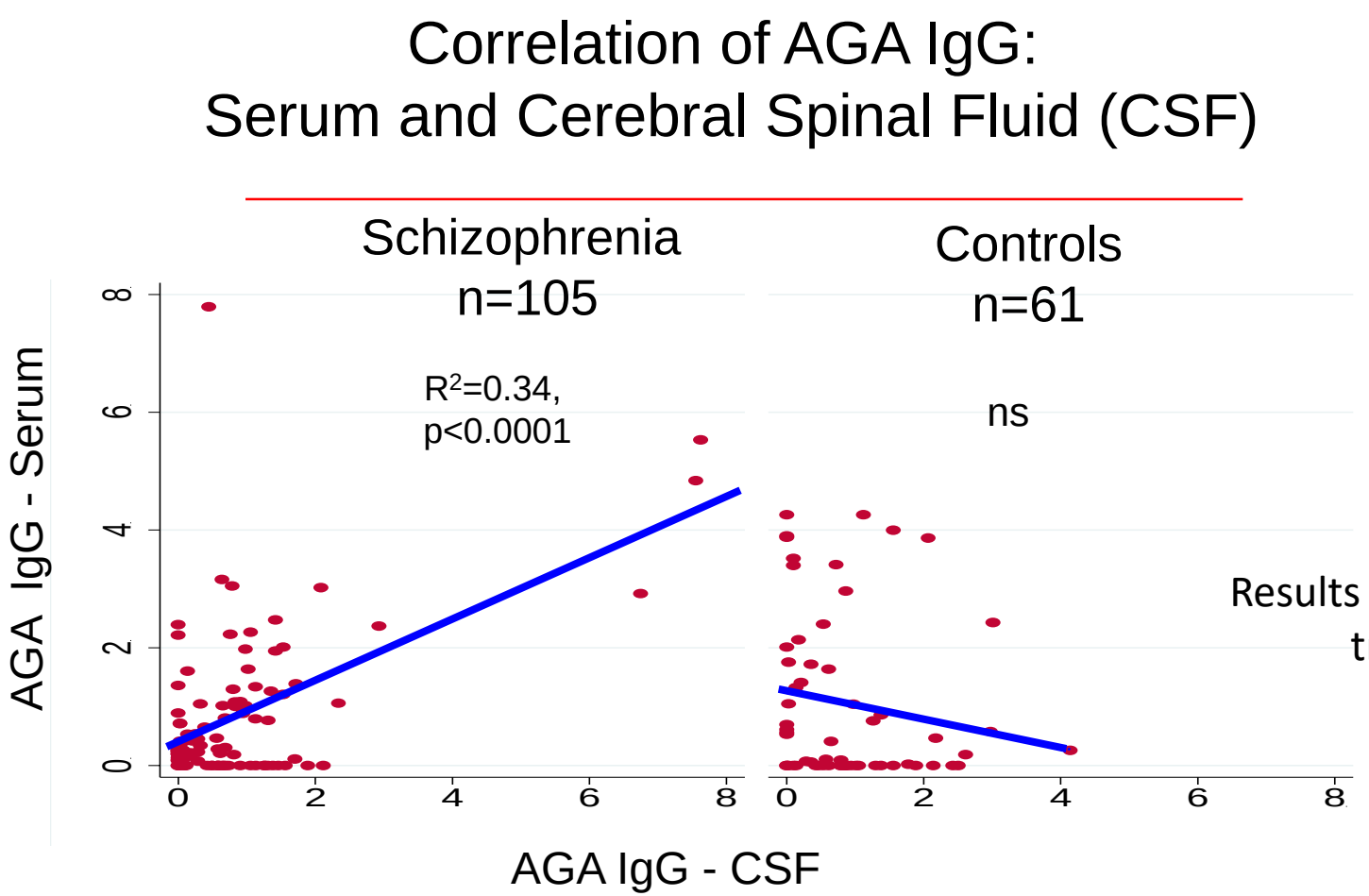
Cihakova D, et al, *Schiz Res* 2018; Sidhom OL, et al. *Immunol Invest* 2012;41(5):538-549, Dickerson et al. *Biol Psychiatry.* 2010:68(1):100-4; Okusga O, et al. *World J Biol Psychiatry*. 2013 Sep;14(7):509-15.

Could this be a schizophrenia subgroup??

- A subgroup with inflammation?
- A subgroup with different underlying disease etiology?
- A subgroup with a different treatment strategies?
- Moving towards precision medicine in schizophrenia?



AGA IgG and the Brain?

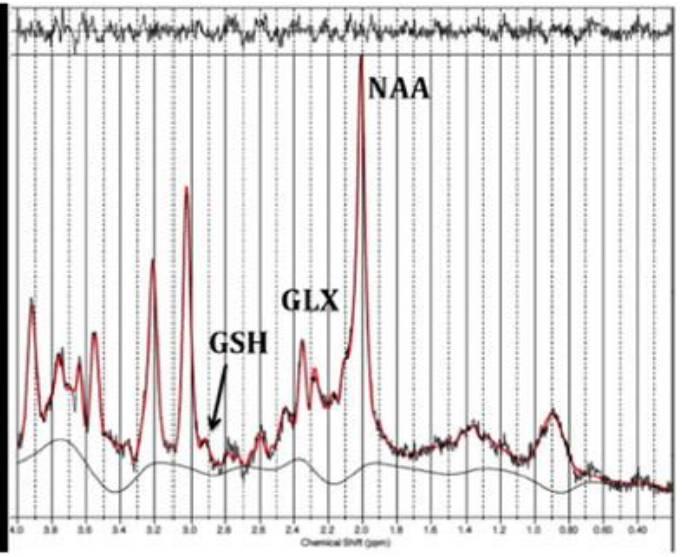


Results independent of Antipsychotic treatment (N=75 naïve)

Leaky Gut and Blood Brain Barrier?

Severance EG, et al. *Brain Behav Immun,* 2015;44*:* 148-158; figure provided and used with permission
Axelsson et al. 1982; Torrey et al. 1985; Bauer and Kornhuber 1987; Kirch et al. 1992). Uronova et al. 2010; Hanson and Gottesman 2005

AGA IgG Linked to Peripheral and Brain Inflammation?



Can brain function be altered by removing gluten?

33 year old man with schizophrenia having severe diarrhea and weight loss.

Use of single photon emission computed tomography (SPECT) showed hypoperfusion in the left prefrontal cortex without evidence of structural cerebral abnormalities.

Jejunal biopsy showed villous atrophy and EMA antibodies present. Gluten free diet started.

Six months after a gluten-free diet, cerebral blood flow normalized, duodenal findings resolved and all psychiatric symptoms disappeared.

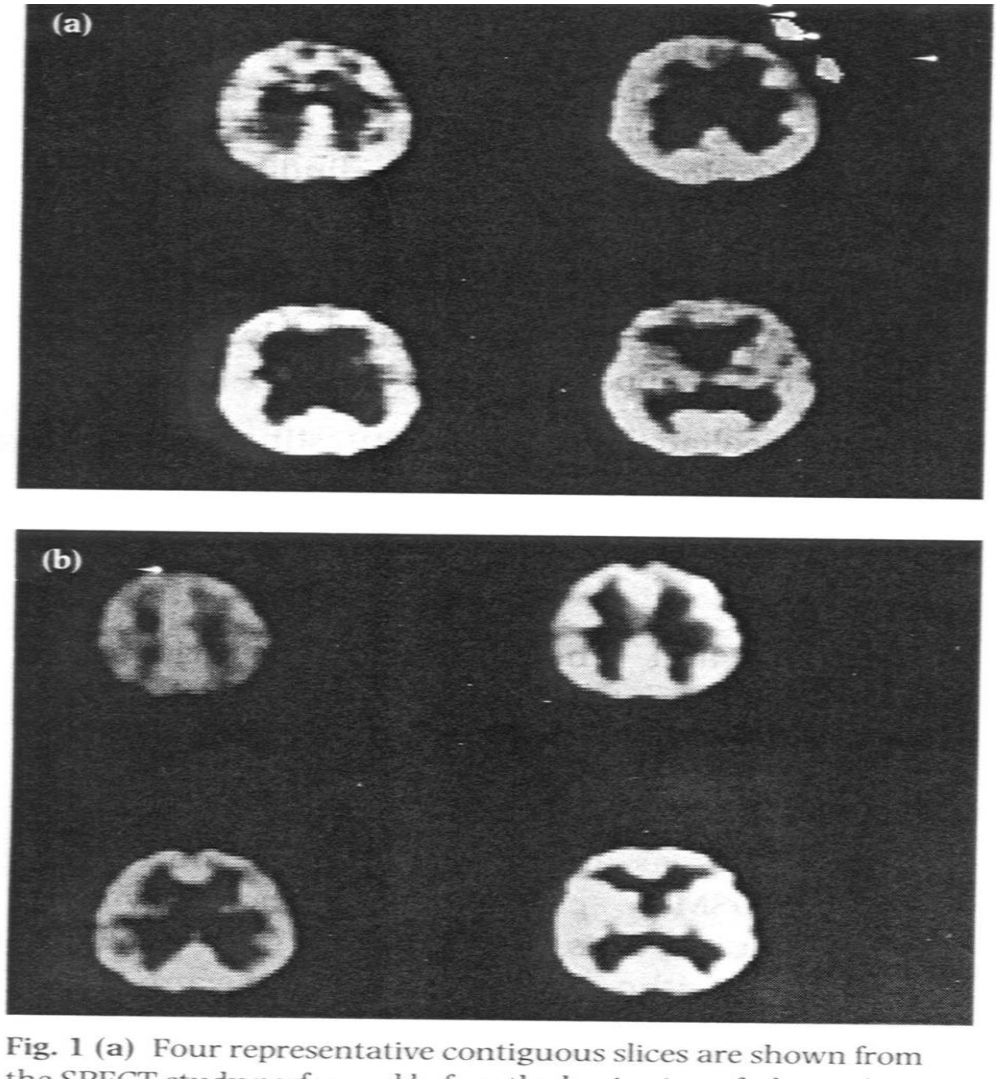


Fig. 1 (a) Four representative contiguous slices are shown from

De Santis et al. *Journal of Internal Medicine* 1997; 242:421-423.

Pilot Study Results – 2 patients for 2 weeks

Jackson et al. *Schiz Research* 2012:140(1-3):262-3

Randomized Double-Blind Gluten-Free Diet Study

- Double-blind randomized gluten-free inpatient feasibility study for 5 weeks
- All participants received a gluten free diet
  - Protein shake daily with 10 gm of Gluten flour or 10 gm of Rice flour
- First gluten free diet study in schizophrenia to recruit a subgroup
- Clinical Trials.gov NCT#01927276 (NIMH funded R34)

Kelly D, Eaton WW, et al. *Journal of Psychiatry and Neuroscience*, 2019

Results?

- Exciting results to share at Grand Rounds in October
- Replication randomized double blind inpatient study underway with larger sample
- Screening approximately 500-800 people with schizophrenia or schizoaffective disorder at University of Maryland and Johns Hopkins for AGA IgG positive

NCT03183609 NIMH
R01MH112617-01 Kelly and Eaton PIs

Call Megan Powell: 410-402-6413 for free screening information

With Many Thanks!

MPRC

- Megan Powell
- Haley Demyanovich
- Laura M. Rowland
- Anne Werkheiser
- Heidi J. Wehring
- Ann Marie Kearns
- Fang Liu
- S. Andrea Wijtenburg
- Stephanie Feldman
- William T. Carpenter Jr.
- Frank Blatt
- Frank Gaston
- Ana Pocivavsek
- Robert P. McMahon
- Robert W. Buchanan
- Spring Grove Clinical Team

Johns Hopkins University

- William W. Eaton– Co-PI
- Katrina Rodriguez
- Daniela Cihakova
- Monica V. Talor
- Nicola Cascella
- Bruce Patterson
- Emily Severance
- Robert Yolken

Harvard Medical School

- Alessio Fasano
- Craig Sturgeon

University of Maryland

- Debbie Santora
- Greg Barber

Other Trainees and Staff

- Kelli Sullivan
- Jessica Jackson

The work was supported by NIMH R34 MH100776-01 and NIMH R01MH112617-01 (Kelly and Eaton MPIs)

And Brain & Behavior Research Foundation (BBRF) for the Maltz Prize for Innovative and Promising Schizophrenia Research

https://www.youtube.com/watch?v=y-9lOpPUdg0

Disclosures: Dr. Deanna L. Kelly has served as a consultant for Lundbeck and Alkermes and has been an advisor for HLS Therapeutics. She has Dr. Kelly is currently funded by NIMH.