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Gut permeability and mimicry of the *Glutamate Ionotropic Receptor NMDA type Subunit Associated with protein 1* (GRINA) as potential mechanisms related to a subgroup of people with schizophrenia with elevated antigliadin antibodies (AGA IgG)

Daniela Čiháková [a,b], William W. Eaton [c], Monica V. Talor [a], Uasim H. Harkus [a], Haley Demyanovich [d], Katrina Rodriguez [c], Stephanie Feldman [d], Deanna L. Kelly [d,*]

[a] Department of Pathology, The Johns Hopkins University School of Medicine, Baltimore, MD 21205, United States of America
[b] W. Harry Feinstone Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205, United States of America
[c] Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205, United States of America
[d] Maryland Psychiatric Research Center, University of Maryland School of Medicine, Baltimore, MD 21228, United States of America

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ABSTRACT

About one third of people with schizophrenia have elevated IgG antibodies to gliadin (AGA IgG) and increased inflammation. Understanding the mechanism by which this immune response occurs is critical to the development of personalized treatments. We examined gut permeability and mimicry to the glutamate receptor as possible mechanisms related to high gliadin antibodies (AGA IgG) seen in some people with schizophrenia. The *Glutamate Ionotropic Receptor NMDA type Subunit Associated with protein 1* (GRINA) has a similar protein structure to gliadin representing a potential target for cross reactivity or mimicry. In a population of schizophrenia subjects (N = 160) and healthy controls (N = 80) we analyzed serum samples for both GRINA and *Anti-Saccharomyces Cerevisiae* antibodies (ASCA), related to gut permeability. Schizophrenia patients compared to controls had a higher prevalence of positivity to ASCA IgA ($p = 0.004$) and IgG ($p < 0.001$). Multinomial logistic regression showed an association between AGA IgG and ASCA IgG in schizophrenia ($p = 0.05$ for the estimated regression coefficient) but not in healthy controls ($p = 0.13$). GRINA IgG was higher in schizophrenia patients than in healthy controls (0.43 ± 0.30 vs. 0.22 ± 0.24, $p < 0.001$). Logistic regressions showed an association between AGA IgG and GRINA IgG in schizophrenia ($p = 0.016$ for the estimated regression coefficient) but not for the controls ($p = 0.471$). Thus, we propose that mimicry through the presence of cross-reactivity between gliadin and GRINA might disrupt the functions of the glutamate system and relate to illness pathophysiology in those with schizophrenia and elevated AGA IgG.

1. Introduction

Deconstructing the illness of schizophrenia is of particular research and clinical interest as this heterogeneous disorder may be composed of etiologically distinct disorders with different mechanisms which could serve as distinct treatment targets. Although the underlying pathophysiology of schizophrenia remains unknown, leading theories to date suggest it is associated with disruption of dopamine or glutamate systems (Rich and Caldwell, 2016; Steiner et al., 2012). Recently emerging evidence suggests inflammation may play a role in this illness (Muller et al., 2015). For example, increased levels of cytokines in blood and cerebrospinal fluid in schizophrenia relative to controls have been reported (Upthegrove et al., 2014; Watanabe et al., n.d.) Other evidence suggests that maternal infections and inflammation result in higher risk of offspring with schizophrenia. Furthermore, autoimmune diseases have been associated with increased risk for the diagnosis for schizophrenia (Eaton et al., 2006). Some HLA genes are associated with schizophrenia suggesting the importance of antigen presentation in the pathogenesis of the disease (Purcell et al., 2009; Stefansson et al., 2009). In addition, some anti-inflammatory agents have shown promise in schizophrenia treatment (Keller et al., 2013; Sommer et al., 2014)

One specific group with high peripheral (Kelly et al., 2017) and central inflammation (Rowland et al., 2017) are those with schizophrenia having elevations in antigliadin antibodies (AGA IgG). Gliadin is a protein found in wheat, barley and rye (Hadjivassiliou et al., 2002;

* Corresponding author at: Maryland Psychiatric Research Center, University of Maryland School of Medicine, Box 21247, Baltimore, MD 21228, United States of America.
E-mail address: dkelly@mprc.umaryland.edu (D.L. Kelly).

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Hadjivassiliou et al., 2010; Jackson et al., 2012b). We (Cihakova et al., 2018) and others (Sidhom et al., 2012) have found these are present in about 1/3 of the schizophrenia population. This subgroup with AGA IgG elevations may be distinct in having lower positive symptoms (Jackson et al., 2014), high kynurenic acid levels (Okusaga et al., 2016), and may benefit from a gluten free diet (Jackson et al., 2012a). It remains unclear, however, how these elevations in AGA IgG and immune activation in this subgroup contribute to the illness and possibly to schizophrenia psychopathology.

Tight junction permeability at the level of the gut and brain may play a role in schizophrenia pathophysiology (Banks and Erickson, 2010). Several studies in people with schizophrenia have found that some patients have increased permeability of the blood brain barrier (BBB) (Bauer and Kornhuber, 1987; Hanson and Gottesman, 2005; Kirch et al., 1992; Torrey et al., 1985) as well as the gut. This may allow the passage of immune cells and antibodies (Hanson and Gottesman, 2005) into the brain, leading to altered neuronal-glial function that in turn may lead to inflammation and schizophrenia psychopathology. A post mortem study of ultrastructural abnormalities of capillaries and of the pericapillary cellular environment suggests that blood brain barrier (BBB) dysfunction contributes to the pathogenesis of cortical lesions in schizophrenia (Uranova et al., 2010). Also, Severance et al. (2012) suggest that blood brain permeability may be present in schizophrenia as they report that AGA IgG antibodies are highly correlated in the blood and the cerebral spinal fluid, a phenomena not seen in healthy controls. Our group has also recently shown in a very small sample that gene expression of tight junction proteins may be disrupted in severe mental disorders such as schizophrenia, as evidenced by a trend in expression differences in claudin-5 in autism spectrum disorders (Fiorentino et al., 2016).

Another mechanism as to how elevated AGA IgG may mechanistically play a role in the pathophysiology of schizophrenia is the concept of mimicry. With the notion that AGA IgG may cross the BBB, it is possible that AGA IgG may bind to other proteins besides the intended antigen, gliadin, if they had a similar structure to gliadin. For example, if B cells and perhaps also gliadin-reactive T cells are entering the central nervous system, they potentially may recognize proteins that have a sequence similar to gliadin and subsequently leading to AGA IgG targeting other receptors or structures in the brain. The human *Glutamate Ionotropic Receptor NMDA type Subunit Associated with protein 1* (GRINA) has recently been shown using BLASTP analysis to be a molecular mimic to the 33-mer gliadin fragment, a part of gliadin that is responsible for the adaptive immune response against gluten (Garcia-Quintanilla and Miranzo-Navarro, 2016). Thus, AGA IgG may lead to targeting of GRINA (also known as TMBIM3) which is known to be mainly expressed in the central nervous system (Lisak et al., 2015; Rojas-Rivera et al., 2012).

The mechanisms related to high AGA IgG antibody levels, and their role in schizophrenia, may be related to inflammation, gut permeability and potential self mimicry at the glutamate receptor site leading to antibodies against GRINA that may lead to irregularities in the structure, action or function at the glutamate receptor 1 protein subunit. Glutamate is believed to play a role in schizophrenia pathophysiology (Coyle, 2006; Jackson et al., 2012b; Matute, 2003; Samaroo et al., 2010). This interesting convergence at the glutamate site may explain illness pathophysiology particular to a subgroup with high AGA IgG. Here we specifically examine the relationship of antigliadin antibodies (AGA IgG) in schizophrenia patients to gut permeability (using *Anti-Saccharomyces Cerevisiae* antibodies; ASCA) and to the presence of GRINA antibodies.

2. Methods

2.1. Patients

In a previously published study we replicated findings that about 1/3 of people with schizophrenia compared to healthy controls had elevated AGA IgG levels (Cihakova et al., 2017). Here we analyzed stored serum to examine the relationship of AGA IgG to ASCA and GRINA antibodies. The sample consisted of people with a Diagnostic and Statistic Manual-IV-Text Revised (DSM-IV-TR) diagnosis of schizophrenia as well as a group of healthy controls for comparison. After signing informed consent all participants completed a blood draw and supplied basic demographic information. Blood samples were then processed and stored at −80 °C and sent to the Johns Hopkins University Immunologic Disorders Laboratory (CLIA and CAP certified clinical laboratory) for AGA IgG testing and blood storage. For a control group, the same serologic analyses were measured on a healthy control repository of people who had no major DSM-IV-TR psychiatric diagnosis. All work in this study was approved by Institutional Review Boards at the Johns Hopkins University, University of Maryland, and the State of Maryland Department of Health and Mental Hygiene.

2.2. Serological analysis

Sera were previously analyzed for AGA, IgG using the INOVA Diagnostics kit 708655 (Cihakova et al., 2017). For these AGA IgG, negative was defined as <20 U, positivity as >20 U. We also examined separately those >30 who were considered to have strong positivity to AGA IgG.

In this analysis we measured ASCA IgA and IgG using the INOVA Diagnostics 708,870 and 708,865 kits and in-house developed GRINAIgG ELISA (see below). Results were interpreted according to the manufacturer guidelines as follows: ASCA IgG and IgA (INOVA Diagnostics) normal levels were defined as <20 U, equivocal as 20–24.9 U, and positive as 25 U or higher. The results were expressed semi-quantitatively in arbitrary units (U). All samples were run in duplicate.

For the GRINA assay, the plates were coated with GRINA protein from ProSci (cat# 7147P) in carbonate-bicarbonate buffer, pH = 9.6 and incubated overnight at 4 °C and then washed. Pre-diluted sera and controls were added to the plate, and incubated for 30 min, allowing the antibodies from the sera to bind to the antigen present on the plate. Excess unbound samples were washed off and an enzyme-labeled anti-human IgA or IgG conjugate was added to the plate for another 30-minute incubation. Excess conjugate was washed off and the enzyme activity was measured by the addition of TMB chromogen. The enzymatic reaction was stopped after 30 min and the intensity of the color was measured spectrophotometrically at 450 nm using the Dynex Technologies ELISA reader. GRINAIgG results are reported as optical density (OD 450 nm) and GRINA IgG positivity was defined by us as OD > 0.615, which corresponds to the sum of the mean of GRINA OD and the standard deviation of GRINA OD of the healthy controls.

2.3. Statistical analysis

Simple comparisons were made using the Fisher exact test (Stata software). Quantitative antibody levels of all tests, as well as differences in demographic variables such as age, race, and gender were compared using two-tailed *t*-tests. Multinomial logistic regressions with age, sex and race as covariates were implemented to test for correlations of AGA IgG and ASCA IgG and IgA and GRINA. Multinomial regression (Stata software) was used to analyze the relationship between AGA, and ASCA or GRINA positivity.

3. Results

3.1. Subject demographic information

The demographic information of the schizophrenia (N = 160) and healthy control (N = 80) samples are shown in Table 1. The schizophrenia subjects had a similar gender distribution and a wider age distribution, with a higher proportion of young people and African Americans. These variables were included in the multivariate analyses in testing the relationship for each antibody of ASCA and GRINA to AGA IgG. We

Table 1
Demographic and clinical characteristics.

Characteristics	Healthy controls (n = 80)	Schizophrenia patients (n = 160)	p value
Age (mean ± SD)	45.5 ± 4.3	41.2 ± 12.3	**0.003**
Gender (Male %)	51 (64%)	99 (62%)	0.646
Race Asian	2 (2.5%)	5 (3.1%)	0.63
Race Caucasian	40 (50%)	56 (35%)	**0.018**
Race African-American	38 (47.5%)	99 (61.9%)	**0.031**
Mean AGA IgG values (U)	9.1 ± 13.2	17.9 ± 21.4	**0.001**
Percent positivity of AGA IgG (>20 U)	8 (10%)	51 (31.9%)	**0.001**
Percent positivity of AGA IgG (>30 U)	5 (6.2%)	35 (21.9%)	**0.002**

P=<0.05 is consider significant and is shown in bold

found previously that 31% of this sample (N = 160) have elevated AGA IgG (>20 U) and 20% are considered highly sensitive (>30 U). As reported earlier, the level of AGA IgG was higher in the schizophrenia sample compared to healthy controls.

3.2. ASCA IgA and IgG antibodies

People with schizophrenia had a significantly higher prevalence of positive ASCA IgA, with 33.8% of patients positive and 16.3% of controls positive (Chi-square = 8.276, p = 0.004) (Fig. 1A). A similar and significant difference was observed for ASCA IgG, positive in 44.4% of patients and 20% of controls (Chi square = 13.9733, p < 0.001) (Fig. 1A). The mean values of ASCA IgG or ASCA IgA were also significantly increased in schizophrenia subjects compared to controls (p < 0.001) (Fig. 1B). Thus, schizophrenia patients have more prevalent positive ASCA IgA and ASCA IgG antibodies as compared to controls.

There was no meaningful correlation between AGA IgG and ASCA IgA or ASCA IgG antibody values in schizophrenia subjects (data not shown). However, multinomial logit regressions, controlling for age, sex, and race, reveal an association between AGA IgG positivity and ASCA IgG antibodies positivity for the people with schizophrenia (p = 0.05 for the estimated regression coefficient) but not for the controls (p = 0.13) (Fig. 2A,B). Thus, schizophrenia patients with AGA IgG antibodies positivity are more likely to be also positive for ASCA IgG than controls.

3.3. GRINA IgG antibodies

Persons with schizophrenia had significantly increased levels of GRINA IgG OD compared to controls (0.51 ± 0.38 v 0.36 ± 0.25, p < 0.001) (Fig. 3A). In addition, schizophrenia subjects with positive AGA IgG had a trend of a higher GRINA OD than subjects with negative

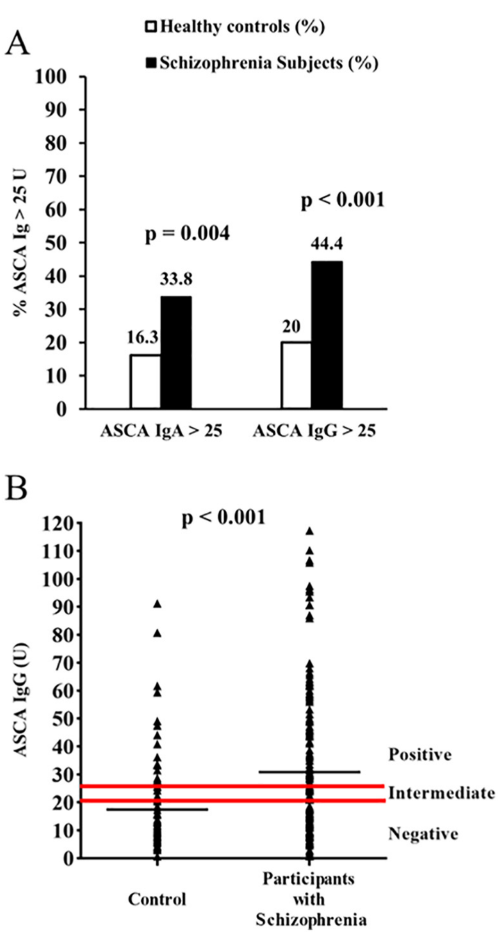

Fig. 1. The prevalence of ASCA IgA and ASCA IgG in the sera of people with schizophrenia and healthy controls. A) Comparison between the percentage of patients and healthy controls positive for ASCA IgA or ASCA IgG (>25 U). B) Quantitative levels of ASCA IgG in schizophrenia patients and healthy controls. Group differences were analyzed using Fisher's exact test. Differences with p values of <0.05 were considered significant.

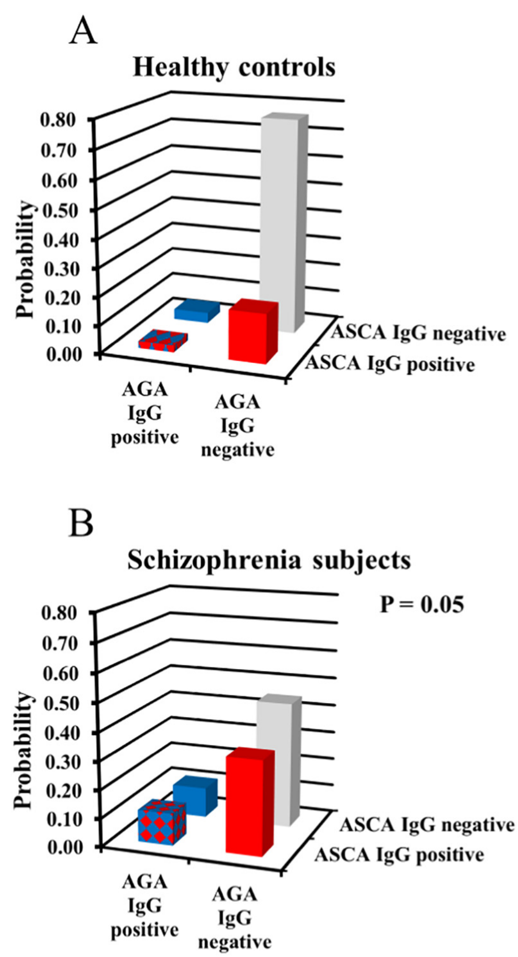

Fig. 2. The probability of positivity or negativity of ASCA and AGA IgG antibodies in the sera of healthy controls (A) and schizophrenia (B). Grey- negative for ASCA IgG and AGA IgG; red- ASCA IgG positive, AGA IgG negative; blue- ASCA IgG negative, AGA IgG positive; checker – AGA IgG positive, ASCA IgG positive. To test for an association between AGA IgG positivity and ASCA IgG positivity, controlling for demographic factors, we estimated a multinomial logistic regression of AGA IgG vs. ASCA IgG and IgA, controlling for the presence of schizophrenia as well as age, sex, and race. The estimated regression coefficient between AGA IgG and ASCA IgG was significant for people with schizophrenia (p = 0.05) but not for the controls (p = 0.13).

AGA IgG (Fig. 3B). We defined GRINA positivity as OD > 0.615, which corresponds to the sum of the mean of GRINA OD and the standard deviation of GRINA OD of the controls. Schizophrenia subjects had a significantly higher prevalence of positive GRINA IgG by this definition than controls, with 30.2% of the patients and 10.1% of the controls positive for GRINA IgG ($p < 0.001$) (Fig. 3C). Furthermore, logistic regressions, controlling for age, sex, and race, reveal an association between AGA IgG positivity and GRINA IgG antibodies positivity for the people with schizophrenia ($p = 0.016$) but not for the controls ($p = 0.471$) (Fig. 3D–E), suggesting a possible new pathogenic mechanism in people with schizophrenia having high AGA IgG.

4. Discussion

Recent research shows that GRINA (also known as TMBIM3) is a homolog to the gliadin 33-mer gliadin peptide (Garcia-Quintanilla and Miranzo-Navarro, 2016; Rothermundt et al., 2001). It is expressed in the brain with high levels in the hippocampus (Brand et al., 1993). We have shown in previous work (Cihakova et al., 2017) that AGA IgG positivity is prevalent in about 1/3 of schizophrenia patients and this relationship of AGA IgG to GRINA is of interest as the convergence of the glutamate story may help explain the illness, particularly in a subgroup of schizophrenia patients.

GRINA is a member of a family of proteins with homology to BAX inhibitor (BI)-1 which have been shown to protect cells from apoptosis (Brand et al., 1993). GRINA's regulation of endoplasmic reticulum calcium homeostasis, and its interaction with IP3R have been linked to its protective role against ER stress-mediated cell death (Schwarz et al., 2001). Several studies have shown that apoptosis is altered in the neurons and sera of patients with schizophrenia (Banks and Erickson, 2010; Bersani et al., 2014; Chiappelli et al., 2015; Garcia-Quintanilla and Miranzo-Navarro, 2016; Plitman et al., 2016). Furthermore, the role of GRINA during endosome-to-Golgi retrieval has been investigated (Bagory et al., 2012), a process which has been suggested to be involved in the pathology of several neurodegenerative diseases. This process could be essential for membrane-trafficking, including the trafficking of the NMDA receptor in which hypofunctions may be essential in the pathology of schizophrenia (Kirov et al., 2013). In our study, we found higher GRINA IgG in schizophrenia subjects compared to controls. In addition, the GRINA IgG and AGA IgG positivity were correlated in regression analyses. Thus, we propose the presence of cross-reactivity between gliadin and GRINA which might disrupt the functions of the glutamate system and help explain the mechanism of the illness in those schizophrenia patients with high levels of AGA IgG. It remains unknown to what extent the GRINA measured in the periphery mimics brain GRINA, however it is plausible this protein can enter the periphery through an altered BBB.

We also find a relationship of ASCA to AGA IgG in the schizophrenia group and not the healthy control population. ASCA belongs to a group of anti-glycan antibodies. Glycan is a cell- wall carbohydrate of

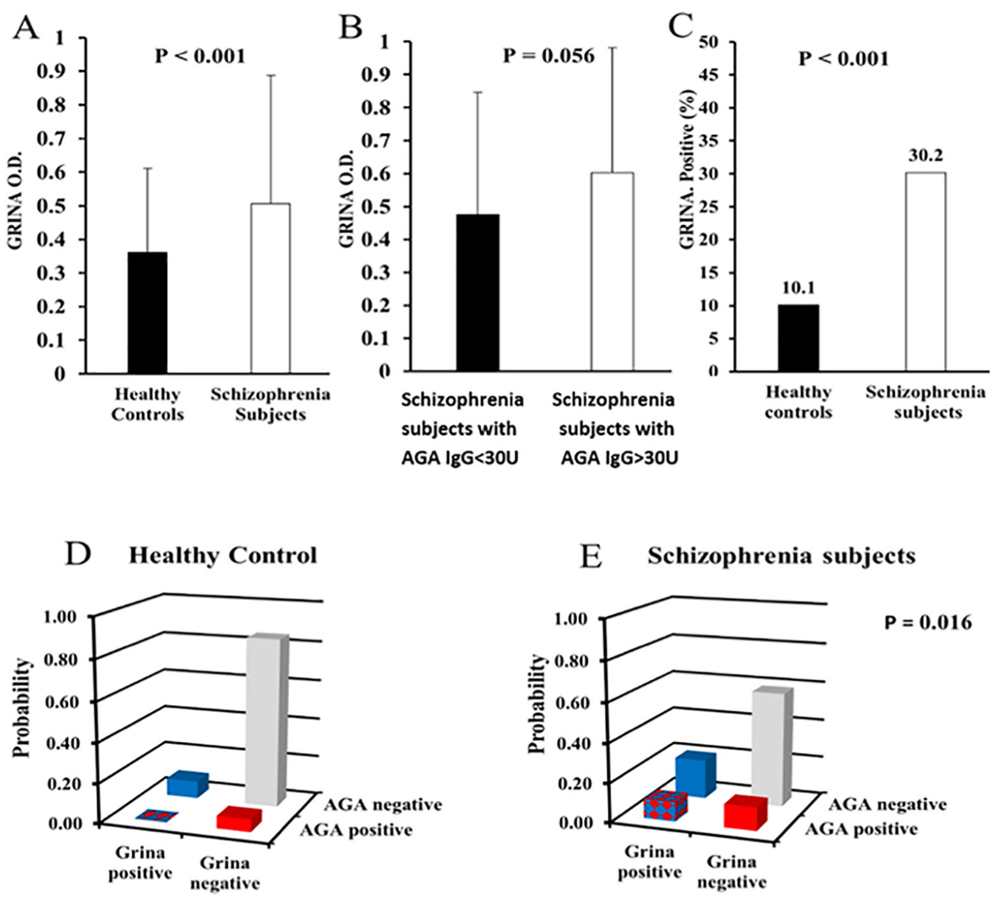

Fig. 3. The prevalence of GRINA IgG in the sera of people with schizophrenia and healthy controls. A) Quantitative levels of GRINA OD in schizophrenia and healthy controls. B) Quantitative levels of GRINA OD in people with schizophrenia with positive AGA IgG and schizophrenia with negative AGA IgG. C) Comparison between the percentage of people with schizophrenia and healthy controls positive for GRINA IgG (OD > 0.615). D) The probability of positivity or negativity of GRINA and AGA IgG antibodies in the sera of healthy controls. E) The probability of positivity or negativity of GRINA and AGA IgG antibodies in the sera of people with schizophrenia. (D and E) Grey- negative for GRINA IgG and AGA IgG; blue- GRINA IgG positive, AGA IgG negative; red- GRINA IgG negative, AGA IgG positive; checker – AGA IgG positive, GRINA IgG positive. We estimated multinomial logistic regressions of AGA IgG vs. GRINA IgG and IgA, controlling for the presence of schizophrenia, as well as age, sex, and race. The estimated regression coefficient for the relationship between AGA IgG and GRINA IgG antibodies positivity is significant for the people with schizophrenia ($p = 0.016$) but not for the controls ($p = 0.471$).

microbiota. ASCA is found in 40–70% of people with Crohn's disease (Mallant-Hent et al., 2006; Zhou et al., 2016). In addition, celiac disease patients have been reported to have increased ASCA (Kotze et al., 2010). It was shown recently using normalized absorbance that schizophrenia patients have increased levels of ASCA IgG antibodies (Severance et al., 2012). It has also been reported previously that people with schizophrenia show increased expression of inflammatory markers such as haptoglobin-2 alpha and beta (Yang et al., 2006). Haptoglobin-2 is a precursor for an intercellular tight junction modulator zonulin (Tripathi et al., 2009). Interestingly, zonulin could be released by intestinal exposure to gluten bacteria (Fasano, 2011). Other antibodies against food associated antigens, such as bovine milk casein were also identified previously in schizophrenia patients (Severance et al., 2012). The fact that the presence of ASCA antibodies correlates with AGA IgG suggests that intestinal permeability may be part of the pathophysiology of this subgroup of people with schizophrenia.

In this subgroup of schizophrenia with an immune reaction to gliadin (AGA IgG positive), a population already known to have high inflammation (Kelly et al., 2017), potential mechanisms associated with AGA IgG role in schizophrenia may be related to gut permeability and mimicry at the GRINA site. The convergence of this hypothesis parallels well with the recent discovery that there is lymphatic vasculature in the CNS that allow leukocytes to migrate from the CNS to the draining cervical lymph nodes (Dissing-Olesen et al., 2015). If inflammation plays a critical role in the pathogenesis of schizophrenia then we can speculate that B cells and perhaps also gliadin-reactive T cells could be entering the CNS. On the other hand, antibodies that recognize CNS-derived self-antigens that act as a gliadin mimic in the CNS could potentially enter the periphery and recognize gliadin in the intestine. One limitation of our study was that the evidence of AGA and GRINA mimicry is only indirect since we showed that GRINA IgG and AGA IgG positivity were correlated in regression analyses. To obtain direct evidence we would have to isolate AGA specific antibodies from the schizophrenia subjects and show cross reactivity of these antibodies with GRINA. A second limitation is that we have not shown a pathogenic function of the GRINA antibodies in schizophrenia, which would be possible in the future by adoptive transfer of GRINA antibodies to an animal model. More work is needed to understand the role of AGA and GRINA antibodies in schizophrenia to evaluate if etiologies and treatment approaches may differ in this subgroup as this is important for personalized medicine. In addition, more work is needed to better understand the role of gut/brain permeability and protein mimicry to the role of inflammation in schizophrenia.

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Contributors

Daniela Čiháková conceived the idea of assaying GRINA1 antibodies, designed the study, oversaw all the assays, analyzed the data and wrote the manuscript. William W. Eaton and Deanna L. Kelly designed the overall screening study which provided the blood samples, oversaw all research procedures, blood collection and contributed to the analyses and manuscript writing. Deanna L. Kelly was the Principal Investigator of the clinical study and supervised all procedures and regulatory compliance. Monica V. Talor participated in the idea creation, developed the GRINA assay and ran all laboratory assays. Uasim H. Harkus conceived the idea of the GRINA 1 antibodies cross-reactivity with AGA antibodies with Dr. Cihakova and was involved in the analysis and the manuscript preparation. Haley Demyanovich and Katrina Rodriguez were the study coordinators and contributed to all sample collections and were involved in manuscript writing as well. Stephanie Feldman directed all study procedures and contributed to the manuscript.

Conflict of interest

Daniela Čiháková, William W. Eaton, Monica V Talor, Uasim H Harkus, Haley Demyanovich, Katrina Rodriguez and Stephanie Feldman have reported no financial interests or potential conflicts of interests.

Dr. Kelly has received honorarium for serving on an advisory board for Lundbeck and is a consultant for HLS Therapeutics.

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