

Array 3X – Part 3

TEST	RESULT			
	IN RANGE (Normal)	EQUIVOCAL*	OUT OF RANGE	REFERENCE (ELISA Index)
Array 3X - Wheat/Gluten Proteome Reactivity & Autoimmunity				
Wheat IgG			2.60	0.3-1.5
Wheat IgA	0.38			0.1-1.2
Wheat Germ Agglutinin IgG	0.93			0.4-1.3
Wheat Germ Agglutinin IgA	0.32			0.2-1.1
Non-Gluten Proteins A IgG	1.48			0.2-2.1
Non-Gluten Proteins A IgA	0.50			0.2-2.1
Non-Gluten Proteins B IgG		1.55		0.2-1.9
Non-Gluten Proteins B IgA	0.73			0.2-2.1
Gliadin Toxic Peptides IgG		1.54		0.2-1.9
Gliadin Toxic Peptides IgA	0.44			0.2-1.8
Native & Deamidated Gliadin 33 IgG	1.00			0.2-1.2
Native & Deamidated Gliadin 33 IgA	0.36			0.1-1.1
Alpha Gliadin 17-mer IgG		1.12		0.1-1.5
Alpha Gliadin 17-mer IgA	0.29			0.1-1.1
Gamma Gliadin 15-mer IgG			4.53	0.5-1.5
Gamma Gliadin 15-mer IgA	0.24			0.1-1.0
Omega Gliadin 17-mer IgG			3.55	0.3-1.2
Omega Gliadin 17-mer IgA	0.36			0.1-1.2
Glutenin 21-mer IgG	1.13			0.1-1.5
Glutenin 21-mer IgA	0.30			0.1-1.3
Gluteomorphin + Prodynorphin IgG		1.08		0.3-1.2
Gluteomorphin + Prodynorphin IgA	0.40			0.1-1.2



70-year old female

CC: Metabolic syndrome, Type II diabetes, asthma

Constipation, fatigue and cognitive decline

“Yo-yo dieter” not gluten free

This is a 70-year-old female, and she had metabolic syndrome, type 2 diabetes, and asthma. She had significant fatigue, cognitive decline, chronic constipation, and asthma. She reported feeling better when she was gluten-free but had a hard time sticking to it and would fall off the wagon often.

You can see that she has three markers out of range and a handful in the equivocal range. We have already discussed the significance of the positive wheat IgG, IgA markers, so I would like to focus on the nongluten proteins A IgG and IgA, and nongluten proteins B IgG and IgA as well as the gliadin toxic peptide results (*Note: the report on this slide is cut off, so tTTG values are not shown*).

Based on her results, we would suspect a wheat protein sensitivity and possibly celiac disease. We would advise her to be very diligent in avoiding wheat and gluten.

Non-Gluten Proteins (A and B)

Non-gluten proteins make-up the remainder of the **wheat proteome**.

Several non-gluten proteins, including **α -amylase/protease inhibitor, thiol reductase, serine protease inhibitor** (serpin), and **β -amylase** have been identified as potent allergens in IgE-mediated wheat allergy and/or baker's asthma.

Some research suggests involvement in the pathogenesis of **Irritable Bowel Syndrome (IBS)** and is often associated with triggers of allergic disorders.

Nongluten proteins make up the remainder of the wheat proteome. There are several nongluten proteins, including alpha amylase and protease inhibitor, thioreductase, serine protease inhibitor or SRPIN, and beta amylase. These have been identified as potent allergens in IgE-mediated wheat allergy and/or baker's asthma. Some research suggests involvement in the pathologies of IBS with these proteins and is often associated with triggers of allergic disorders.

Gliadin Toxic Peptides

A strong indicator of possible **Celiac disease, Crohn's disease** and other chronic inflammatory processes.

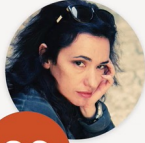
This peptide lies within the larger gluten protein and has proven to be exceptionally **resistant to digestion**.

The ability to identify a reaction to gliadin toxic peptide allows patients to **remove the trigger before the intestinal barrier becomes damaged** and causes serious long-term health issues.

Gliadin toxic peptides can be a strong indicator of possible celiac disease, Crohn's disease, and other chronic inflammatory processes. These peptides lie within the larger gluten protein and have proven to be exceptionally resistant to digestion. The ability to identify a reaction to gliadin toxic peptide allows patients to remove the trigger before the intestinal barrier becomes damaged and cause serious long-term health issues.

Okay, so here's another case study.

TEST	RESULT			
Array 3 – Wheat/Gluten Proteome Reactivity & Autoimmunity	IN RANGE (Normal)	EQUIVOCAL*	OUT OF RANGE	REFERENCE (ELISA Index)
Wheat IgG	0.35			0.3-1.5
Wheat IgA	0.46			0.1-1.2
Wheat Germ Agglutinin IgG	<0.40			0.4-1.3
Wheat Germ Agglutinin IgA	0.49			0.2-1.1
Native & Deamidated Gliadin 33 IgG	0.36			0.2-1.2
Native & Deamidated Gliadin 33 IgA	0.48			0.1-1.1
Alpha Gliadin 17-mer IgG	0.44			0.1-1.5
Alpha Gliadin 17-mer IgA	0.28			0.1-1.1
Gamma Gliadin 15-mer IgG	0.70			0.5-1.5
Gamma Gliadin 15-mer IgA	0.57			0.1-1.0
Omega Gliadin 17-mer IgG	0.68			0.3-1.2
Omega Gliadin 17-mer IgA	0.43			0.1-1.2
Glutenin 21-mer IgG	0.69			0.1-1.5
Glutenin 21-mer IgA	0.59			0.1-1.3
Gluteomorphin + Prodynorphin IgG			3.38	0.3-1.2
Gluteomorphin + Prodynorphin IgA	0.43			0.1-1.2
Gliadin-Transglutaminase Complex IgG	0.35			0.3-1.4
Gliadin-Transglutaminase Complex IgA	0.32			0.2-1.5
Transglutaminase-2 IgG	0.38			0.3-1.6
Transglutaminase-2 IgA	1.00			0.1-1.6
Transglutaminase-3 IgG	0.79			0.2-1.6
Transglutaminase-3 IgA	0.70			0.1-1.5
Transglutaminase-6 IgG	0.95			0.2-1.5
Transglutaminase-6 IgA	0.69			0.1-1.5



36-year old female

CC: depression, brain fog, acne, fatigue, gut issues, muscle aches

No noticeable reaction to gluten

This is a 36-year-old female with chief complaint of depression, brain fog, acne, fatigue, gut issues, and muscle aches. She had no noticeable reaction to gluten when she consumed it, but as you can see here on the slide, very significant antibody production to gluteomorphin, plus prodynorphin IgG.

Gluteomorphin + Prodynorphin

Gluteomorphin: opioid peptide formed from **undigested gliadin from gluten protein**

Prodynorphin (PDYN) is an **opioid polypeptide**; building block for endorphins

Exogenous PDYN can compete with endogenous PDYN for **receptor sites**

Gluteomorphin & PDYN **associated with** autism spectrum disorder, CD, NCGS, PANDAS

Cross-reacts with enkaphalin (peptide involved in pain sensation)

Gluteomorphin is an opioid peptide that is formed from undigested gliadin from gluten protein. Prodynorphin is an opioid polypeptide and a building block for endorphins. Exogenous prodynorphin can compete with endogenous prodynorphin for receptor sites, so gluteomorphin and prodynorphin are associated with autism spectrum disorder, celiac disease, non-celiac gluten sensitivity, and PANDAS, and it cross-reacts with enkephalin, which is a peptide involved in pain sensation.

Gluteomorphin + Prodynorphin

Antibodies to gluteomorphin & PDYN indicate **gut permeability**; sign of undigested gluten molecules entering bloodstream

In brain: gluteomorphins bind to opioid receptors and block binding of endogenous opioids

Gluteomorphins also bind to lymphocytes and alter messages they send to brain; cause **cognitive/mood abnormalities**


PDYN **affects** pain sensation and has opioid effect due to interference with receptors

Patients with these antibodies may **feel “addicted” to wheat**

Antibodies to gluteomorphin and prodynorphin indicate gut permeability, because they're a sign of undigested gluten molecules entering into the bloodstream. So in the brain, gluteomorphins bind to opioid receptors and block the binding of our own endogenous opiates, the ones we produce ourselves. Gluteomorphins also bind to lymphocytes and alter messages that they send to the brain, and all of this together can cause cognitive and mood abnormalities, which as you recall, this patient that was producing antibodies to them was suffering from. Prodynorphin affects pain sensation and has an opioid effect due to interference with receptors, and this could explain why some patients with these antibodies can feel kind of addicted to wheat or wheat products. And when this patient eats wheat, this 36-year-old female, the primary effect was changes in her cognitive function, mood, and pain sensation. That's what you would expect by seeing the antibodies to prodynorphin and gluteomorphin, and if you look at her chief complaints, which are depression, brain fog, muscle aches, then that makes a lot of sense, and in her particular case, a strict gluten-free diet improved most of her symptoms significantly.

We often get the question from patients, if I had no noticeable reaction to gluten, and then I remove it from my diet and I feel a lot better and then I add it back in and I feel worse, and I have a noticeable reaction, did you just make me gluten-intolerant? Maybe you've heard that from a patient before, and our answer is no, that's not what happened, but instead there was masking going on, where we sometimes describe it as the clean windshield effect, so if your windshield is full of dirt and you have another little speck of dirt, you're not going to notice it, but if you have a clean windshield and a little speck of dirt gets on there, it's going to be noticeable, and that's kind of what happens with gluten. Our bodies have a pretty remarkable capacity to protect us from toxins that we're exposed to that insulate us from the effects of those toxins, which means that if we're eating something like gluten that we're intolerant of continuously, the reaction might subside over time or become less noticeable, but of course the question is, what's happening in the background that isn't noticeable but could be really dangerous for the body, like production of antibodies to the myelin sheath, which could progress to multiple sclerosis in 10 or 20 or 30 years, or cerebellar proteins, which could cause problems with GATE, or antibodies to islet cells or glutamic acid carboxylase, it could lead to diabetes later on down the line, so there's clearly a cost even if that cost isn't noticeable symptoms. In some cases, patients ask to completely remove it from their diet and then add it back in to even be aware of reaction, so don't let a lack of reaction to gluten convince you that there isn't a problem.

TEST	RESULT			
Array 3 – Wheat/Gluten Proteome Reactivity & Autoimmunity	IN RANGE (Normal)	EQUIVOCAL*	OUT OF RANGE	REFERENCE (ELISA Index)
Wheat IgG	0.56			0.3-1.5
Wheat IgA			1.27	0.1-1.2
Wheat Germ Agglutinin IgG	0.55			0.4-1.3
Wheat Germ Agglutinin IgA		0.93		0.2-1.1
Native & Deamidated Gliadin 33 IgG	0.81			0.2-1.2
Native & Deamidated Gliadin 33 IgA			1.28	0.1-1.1
Alpha Gliadin 17-mer IgG	0.68			0.1-1.5
Alpha Gliadin 17-mer IgA	0.70			0.1-1.1
Gamma Gliadin 15-mer IgG		1.14		0.5-1.5
Gamma Gliadin 15-mer IgA	0.65			0.1-1.0
Omega Gliadin 17-mer IgG		0.93		0.3-1.2
Omega Gliadin 17-mer IgA	0.49			0.1-1.2
Glutenin 21-mer IgG	0.61			0.1-1.5
Glutenin 21-mer IgA		1.05		0.1-1.3
Gluteomorphin + Prodynorphin IgG	0.55			0.3-1.2
Gluteomorphin + Prodynorphin IgA	0.62			0.1-1.2
Gliadin-Transglutaminase Complex IgG	0.44			0.3-1.4
Gliadin-Transglutaminase Complex IgA			1.51	0.2-1.5
Transglutaminase-2 IgG	0.63			0.3-1.6
Transglutaminase-2 IgA		1.33		0.1-1.6
Transglutaminase-3 IgG	0.58			0.2-1.6
Transglutaminase-3 IgA			3.28	0.1-1.5
Transglutaminase-6 IgG	0.52			0.2-1.5
Transglutaminase-6 IgA	1.01			0.1-1.5



50-year old
male

CC: anxiety/worry, tremors
in hands, tinnitus, rosacea

No digestive symptoms

Next patient is a 50-year-old male.

Chief complaint of anxiety and worry, tremors in hands, tinnitus, and rosacea, and this man had no digestive symptoms, which is another patient with no digestive symptoms, but he was producing antibodies to several peptides that we've already discussed, so wheat, IgA we're out of range, deamidated gliadin we're out of range, and then he had equivocal antibodies to wheat germ agglutinin, gamma-gliadin, omega-gliadin and glutenin. But he also was producing antibodies to some that we haven't discussed, like gliadin-transglutaminase, he's out of range on that, transglutaminase-2 he was equivocal, on transglutaminase-3 he was well outside of the range.

Gliadin- transglutaminase complex

Transglutaminase is the enzyme that **deamidates gliadin in the gut**

Tissue transglutaminase (tTG) **forms covalent tTG-peptide** complexes with gliadin

These complexes can **adhere to intestinal walls**, where recognized by antigen-presenting cells and trigger immune response

This results in **autoantibodies** produced against the complex and pro-inflammatory response

Associated with CD, Crohn's disease

The gliadin-transglutaminase complex, let me start with just transglutaminase. It's the enzyme that deamidates gliadin in the gut, and then tissue transglutaminase forms a covalent tissue transglutaminase peptide complex with gliadin, so it's a complex or a bond between transglutaminase and gliadin, and those complexes can then adhere to the intestinal wall where they're recognized by antigen-presenting cells and can trigger an immune response. This then results in production of antibodies against the transglutaminase-gliadin complex and a subsequent pro-inflammatory response. Gliadin-transglutaminase complex antibodies are associated with celiac disease and Crohn's disease.

Tissue- transglutaminase 2

Transglutaminases are **structural enzymes** important to barrier formation

Transglutaminase 2 (tTG-2) found in gut; **converts glutamine to glutamic acid**, deamidation of gliadin

Food processors use transglutaminases to **bind proteins together in processed meats** (aka “meat glue”)

Associated with CD, Crohn’s disease, dermatitis herpetiformis, ulcerative colitis

Tissue transglutaminase 2. Transglutaminases are structural enzymes which are important to barrier formation, and transglutaminase 2 is primarily found in the gut. It converts glutamine to glutamic acid. It is involved in the deamidation of gliadin, as I mentioned before. Food processors, companies that make processed food, use transglutaminases to bind proteins together in processed meats. This is AKA meat glue, and transglutaminase 2 is associated with celiac disease, Crohn’s disease, dermatitis herpetiformis, and ulcerative colitis.

Tissue- transglutaminase 2

Together with alpha-gliadin, **used to diagnose CD**

If tTG-2 antibodies present without antibodies to alpha-gliadin, indicates **autoimmunity not mediated by gluten** (investigate other causes)


Transglutaminases present in other tissues; **antibodies** to tTG-2 can cross react with tTG in skin, brain, elsewhere

Known to **cross-react** with fibrinogen in addition to tTG-3 & tTG-6

I mentioned this before, together with alpha gliadin, transglutaminase 2 is typically used to diagnose celiac disease, so if tGT 2 antibodies are present without antibodies to alpha gliadin, then it indicates autoimmunity that's not mediated by gluten. That's important to understand. If you just see elevated tGT 2 antibodies, and there is no antibody production to wheat or the gluten peptides, it is indicating some kind of autoimmune process, but it's not triggered by gluten, and you'd want to investigate other causes. Transglutaminases are present in other tissues. Antibodies to tGT 2 can cross react with tGT in the skin, the brain, and elsewhere, and tGT 2 antibodies are known to cross react with fibrinogen in addition to the other transglutaminases 3 and 6.

Okay, next case, 33-year-old male.

TEST	RESULT			
Array 3 – Wheat/Gluten Proteome Reactivity & Autoimmunity	IN RANGE (Normal)	EQUIVOCAL*	OUT OF RANGE	REFERENCE (ELISA Index)
Wheat IgG	0.75			0.3-1.5
Wheat IgA	0.45			0.1-1.2
Wheat Germ Agglutinin IgG	0.61			0.4-1.3
Wheat Germ Agglutinin IgA	0.62			0.2-1.1
Native & Deamidated Gliadin 33 IgG	0.47			0.2-1.2
Native & Deamidated Gliadin 33 IgA	0.59			0.1-1.1
Alpha Gliadin 17-mer IgG	0.90			0.1-1.5
Alpha Gliadin 17-mer IgA	0.37			0.1-1.1
Gamma Gliadin 15-mer IgG	0.94			0.5-1.5
Gamma Gliadin 15-mer IgA	0.42			0.1-1.0
Omega Gliadin 17-mer IgG	0.63			0.3-1.2
Omega Gliadin 17-mer IgA	0.61			0.1-1.2
Glutenin 21-mer IgG	0.63			0.1-1.5
Glutenin 21-mer IgA	0.59			0.1-1.3
Gluteomorphin + Prodynorphin IgG	0.37			0.3-1.2
Gluteomorphin + Prodynorphin IgA	0.55			0.1-1.2
Gliadin-Transglutaminase Complex IgG	0.32			0.3-1.4
Gliadin-Transglutaminase Complex IgA	0.69			0.2-1.5
Transglutaminase-2 IgG		1.34		0.3-1.6
Transglutaminase-2 IgA	0.58			0.1-1.6
Transglutaminase-3 IgG	0.69			0.2-1.6
Transglutaminase-3 IgA	0.47			0.1-1.5
Transglutaminase-6 IgG	0.45			0.2-1.5
Transglutaminase-6 IgA	0.63			0.1-1.5



33-year old
male

CC: hives, poor sleep, poor digestion

Gas, bloating, loose stool

Mostly gluten-free, but occasional gluten "binges"

Chief complaint was hives, poor sleep, and poor digestion. He had gas, bloating, and loose stool. He was mostly gluten-free, but he did go on what he described as occasional gluten binges. As you can see here, he was producing antibodies to transglutaminase 2 in the high normal range, equivocal, but there were no antibodies to any of the epitopes of wheat, so whatever autoimmune process was going on here. His case was not related to wheat or gluten, and he was happy to hear that, even though I wasn't a big fan of his occasional gluten binges. There wasn't a reason at least according to this panel not to do that. Of course, there are other reasons not to do that, but this panel is not indicating gluten intolerance or wheat intolerance for him.

Tissue- transglutaminase 3

tTG-3 expressed primarily in **epidermis**, to lesser degree in placenta and brain

tTG-3 **upregulated** in several degenerative diseases

tTG-3 **antibodies** common in dermatitis herpetiformis; also found in Huntington's disease, CD, esophageal cancer

Cross-reacts with tTG-2 & tTG-6

Transglutaminase 3 is expressed primarily in the epidermis, skin, to a lesser degree in the placenta and the brain, and tGT 3 is upregulated in several degenerative diseases. tGT 3 antibodies are common in dermatitis herpetiformis. They're also common in Huntington's disease, celiac disease, and esophageal cancer, and they cross react with transglutaminase 2 and 6.