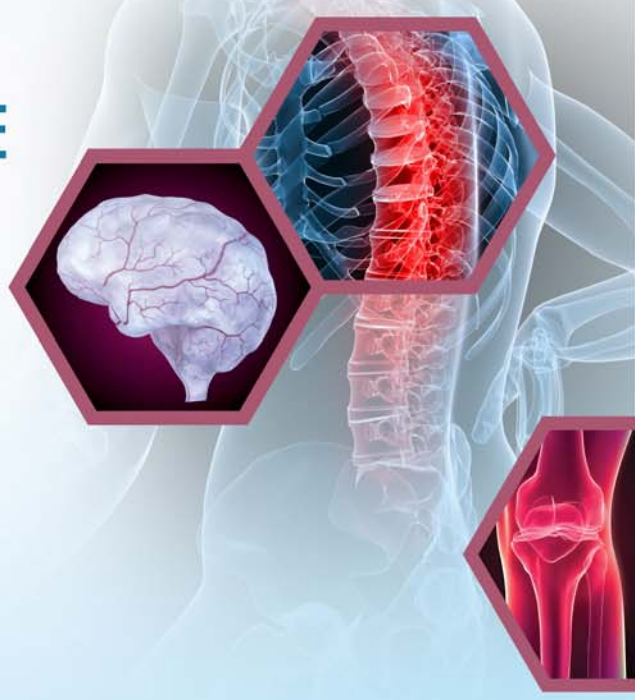
CLINICAL APPLICATION GUIDE

ARRAY 5

ARRAY 5 – Antibody

MULTIPLE AUTOIMMUNE REACTIVITY SCREEN™



CYREX™ Laboratories

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MULTIPLE AUTOIMMUNE REACTIVITY SCREEN™

OVERVIEW

Less than 10 years ago, the recognition that antibodies against self-tissue, a primary mechanism in the development of autoimmune disease, were present years before any recognizable symptoms, gave rationale and validity to the study of predicting vulnerability to developing autoimmune disease.[1] This field has advanced in the last decade to the point of identifying the Positive Predictive Value (PPV) of many antibodies as biomarkers to the development of specific autoimmune diseases.[2] [3]

The word "auto" is the Greek word for self, and autoimmunity is defined as an innate or adaptive immune response directed against a self-antigen. Autoimmune disease is a pathologic condition caused by an acquired or adaptive autoimmune response. Furthermore, chronic inflammation in lack of evidence of self-reactive CD4+ lymphocytes has been referred to as an auto-inflammatory condition. It is estimated that approximately one of four Americans has some sort of dysfunction of the immune system, including autoimmunity.[4] Studies have shown that autoimmunity is sex biased and tends to develop in females far more than males.[5] [6] [7] [8] [9] [10] [11] [12] [13]

Autoantibodies
Autoantibodies are present when the human body reacts against its own tissue antigen. Their presence can be a clue to autoimmunity. The measurement of autoantibodies is the first, and usually the best, step to recognize and prognose many autoimmune conditions.

Autoimmunity
Autoimmunity is defined as an innate (non-specific) or adaptive (specific) immune response directed against a self-antigen. An autoimmunity that results in tissue and organ damage leading to a certain pathologic condition, and subsequent system malfunction is usually referred to as an autoimmune disease. Innate autoimmunity is sometimes referred to as an auto-inflammatory condition.[14]

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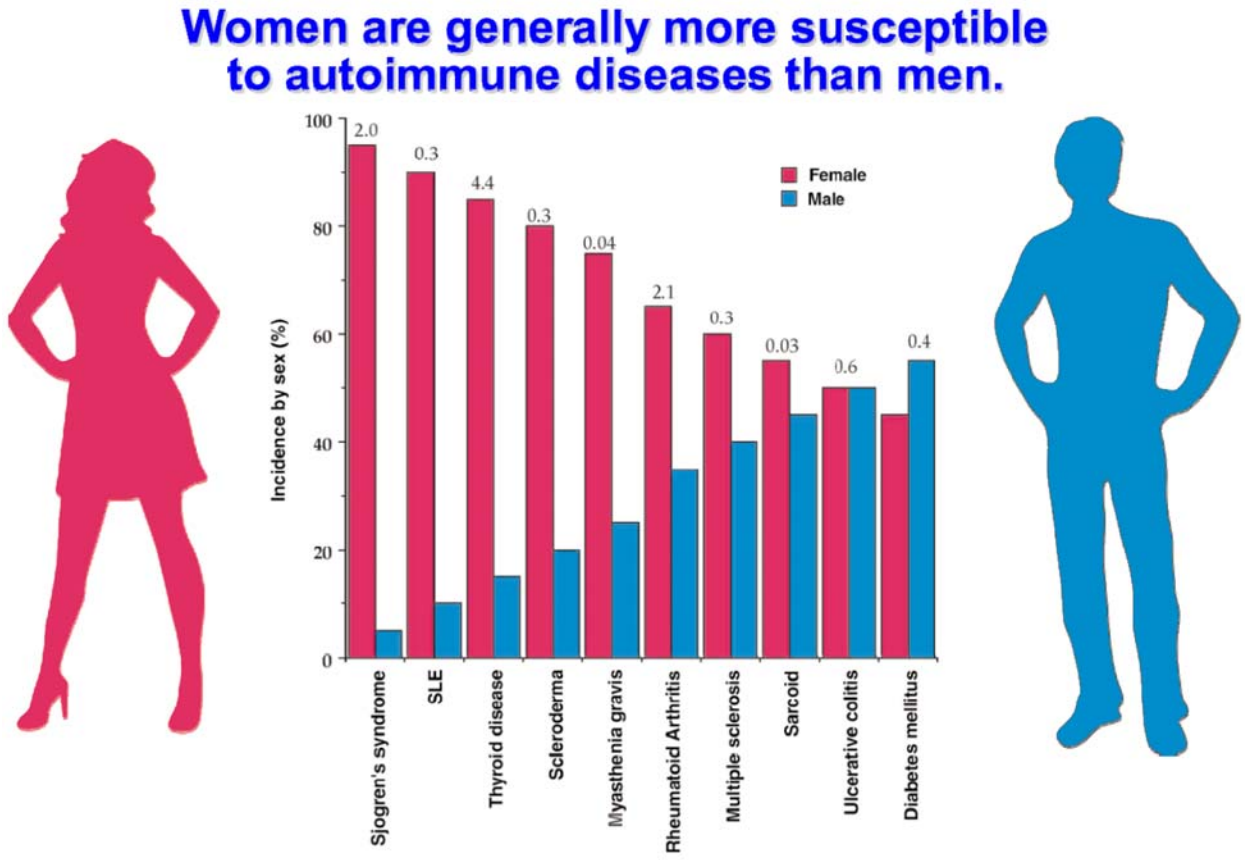

Figure 1 *- The sex distribution of the major autoimmune diseases. The numbers above the bars refer to the total number of disease cases (x1,000,000) in the USA.*[15]

The development of an autoimmune disease may be influenced by a triad of factors: genetic vulnerability, immune system response to environmental exposures (toxic chemicals, antigenic foods, infectious agents, etc.), and intestinal permeability.[16] There is a higher chance for developing autoimmunity with intestinal inflammatory conditions.[17] [18] [19] Proposed mechanisms of autoimmune endocrine disease involve a sequence of immune, inflammatory events in a genetically susceptible individual. In most cases, the immune response to the target cell progressively destroys the tissue, and hypofunction is the main clinical manifestation.[20]

Moreover, the close relationship of intestinal integrity with the immune system plays an important role in maintaining oral tolerance, which if compromised, can lead to autoimmunity.[21] [22] [23] [24] [25] [26] [27] [28] [29] [30] Oral tolerance is a complex immune phenomenon that eventually helps the body identify friend from foe, and therefore, not react against antigens found, for example, in regular dietary foods.

There is a close correlation between developing autoimmunity and the presence of inflammatory conditions in the gastrointestinal system.[17] [18] [19] Furthermore, in genetically susceptible individuals, certain dietary proteins and peptides (*e.g.*, gliadin, or casein from milk) can trigger the autoimmune process in the GI tract itself or in other tissues in the body, such as the bone, joints, heart, thyroid, brain, etc.[31] [32] [33] [34] [35]

[36] In this respect, data supports that gluten reactivity can increase the prevalence and incidence of many of autoimmune conditions,[37] such as Rheumatoid Arthritis,[38] [39]Juvenile Rheumatoid Arthritis (JRA),[40] Hashimoto Thyroditis,[13] [41] [42] Systemic Lupus Erythematosus (SLE),[43] [44] [45] Diabetes Type1 (DM 1),[46] [47]idiopathic dilated cardiomyopathy,[48] [49] [50] [51] [52] [53] neurological autoimmune issues,[54] [55] and more.[56]

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CLINICAL SIGNIFICANCE

More than 80 distinct autoimmune diseases have been identified. Since so many of these disorders share similar symtomatology, it can be difficult for the health care professional to pinpoint the specific disorder. Initial common symptoms of autoimmunity may include fatigue, aching tendons or muscles, inflammation and low fever. The majority of patients are not diagnosed until the level of organ damage from the autoimmune mechanism has advanced enough to cause clinical complaints and sub-optimal health. Early detection, identifying the initial stages of development in autoimmune conditions before extensive tissue damage, would allow a 'Window of Opportunity' to address, arrest, and even in some cases reverse the autoimmune condition.

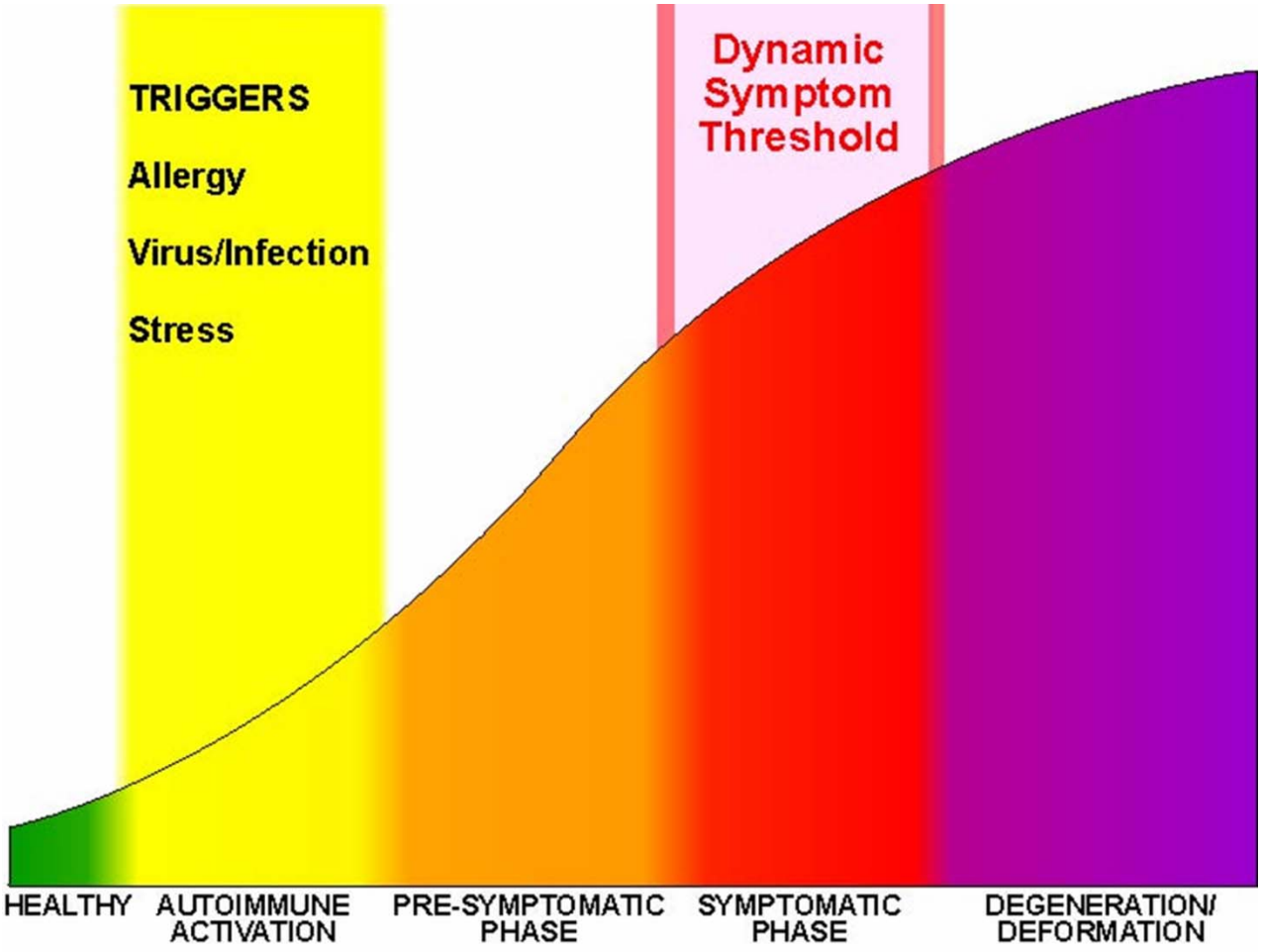

Figure 2 *– Autoimmune pathogenesis from healthy to degeneration or deformation.*

Autoantibodies are present when the human body reacts against its own antigen regardless of their causality value for specific conditions. Diagnosing an autoimmune disease can be difficult and a combination of clinical and laboratory data is often necessary;[57] however, the measurement of autoantibodies is the first and usually the best step in recognizing and prognosing of many autoimmunities and complex diseases.[58] [59] [60] Autoantibodies may be present several years before the diagnosis of autoimmune diseases such as SLE, rheumatoid arthritis, antiphospholipid syndrome, and DM 1.[61] [62] [63]

Whether an autoimmune disease will follow an autoimmune response depends upon both the severity of the response as well as the availability and the type of the antigen exposure. For example antigens on the surface of circulating blood cells are readily available to circulating antibodies versus zonulin which needs paracellular damage and antigen spillage in order to react to antibodies. The reason that antigen spillage can cause autoimmunity is that deletion of self-reactive lymphocytes is only effective for the systemically expressed antigens, such as those of the major blood groups and histocompatibility complex (MHC).[64] Examples for importance of the type of antigen would be interaction of antibodies to a receptor, such as stimulation in Graves' disease or blockage in myasthenia gravis. Autoantibodies can also be produced and directed against particular enzymes. As an example, antibodies against transglutaminase are biomarkers in the development of Celiac disease, and antibodies to the P450 enzymes are prominent in autoimmune hepatitis and primary biliary cirrhosis.[65] [66]

PATHOPHYSIOLOGY (MECHANISMS OF TISSUE DAMAGE)

In general, autoimmunity is a product of interaction of the body's immune system with environmental factors based on genetic background. Environmental factors such as infections can promote an adaptive immune response by cross-reacting, altering of self-antigens, causing antigen spillage, or even causing innate immune and inflammatory responses.[67] [68] [69] [70] [71] [72] [73] [74] [75]

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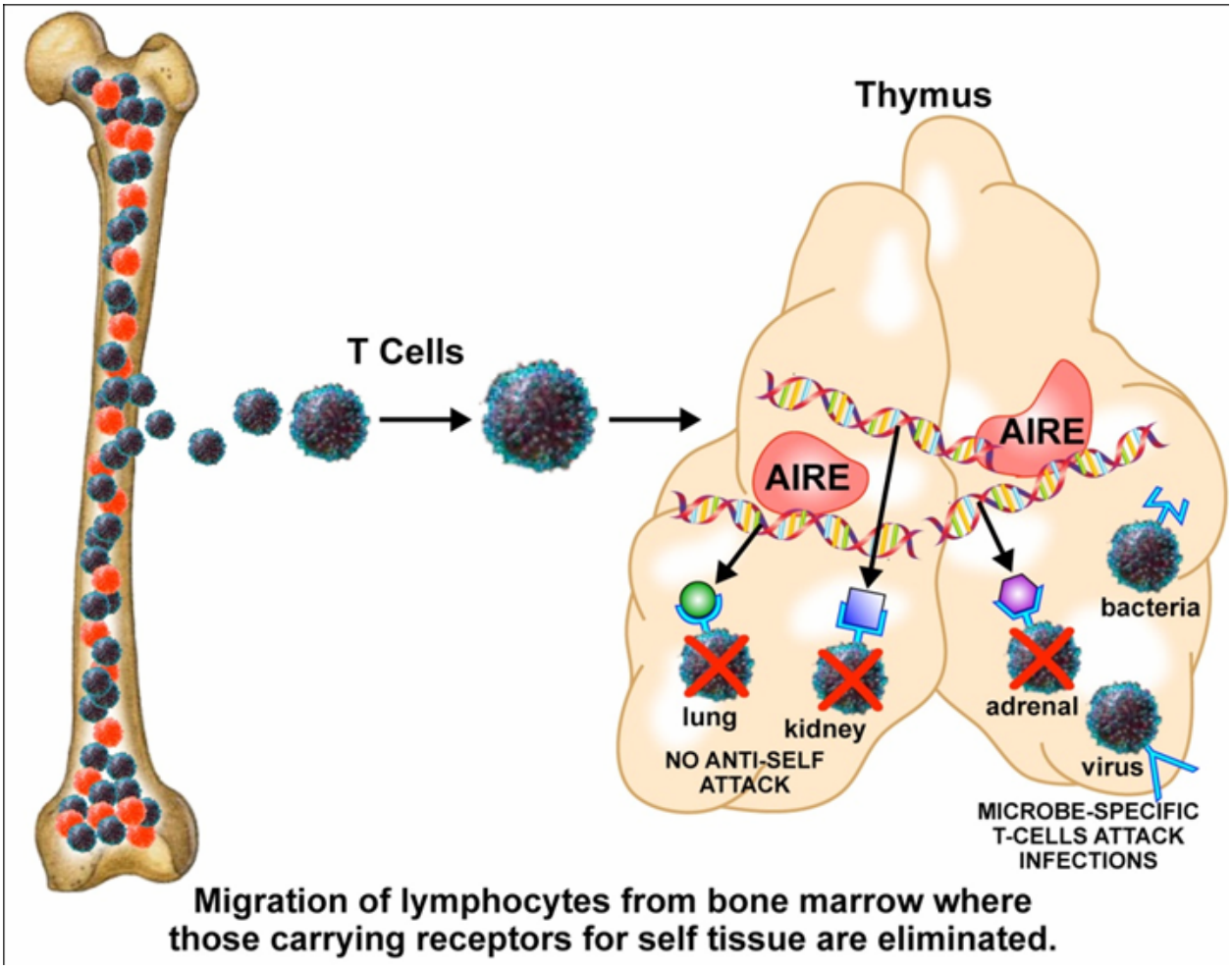

Figure 3 - The role of bone marrow and the thymus gland in the regulation of the immune system and the prevention of autoimmune disease.

Autoimmunity is strictly controlled by the genetic antigen recognition system as well as active regulatory mechanisms. Negative and positive selections in thymus and autoimmune regulatory (AIRE) genes are critical elements for normal T-cell commitment processes. Any defect in this system, can lead to autoimmune conditions.[76] [77] [78] In addition to AIRE genes, there are also certain active mechanisms involving subsets of T-cells (CD25, CD4) and fork head box protein P3 (Fox P3) that contribute to regulating of autoimmune responses.[46] [79] [80] [81]

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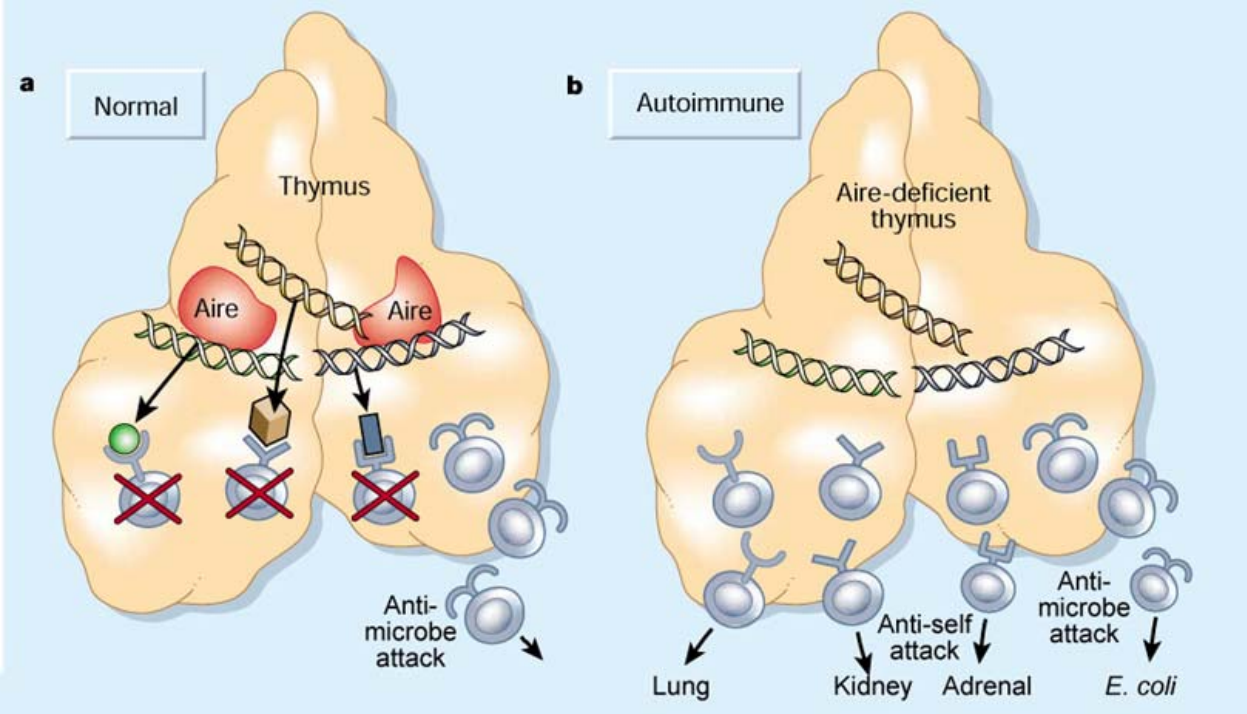

Figure 4 *-The autoimmune regulatory gene (AIRE) and autoimmunity.*

Interestingly, there are several defense mechanisms that can prevent the autoimmunity via slowing down the activation of self-reactive T-cells. These mechanisms include clonal anergy and peripheral self-tolerance. Anergy refers to an immune unresponsiveness due to a lack of certain co-stimulatory signals that are necessary for immune cells activation.[82] Peripheral self-tolerance is in fact an immunological ignorance due to an ineffective interaction between the T-cell and antigen presenting cells (APCs).[83] If these defense mechanisms malfunction, the chances for developing autoimmunity will increase.

Regulatory T-cells (T-regs) control autoimmunity directly by cell-to-cell contact. When induced, T-regs assert their suppressive effects via interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β). Natural killer (NK) cells also play a role in regulating autoimmunity. However, eliminating regulatory cells alone may not necessarily initiate autoimmune diseases, which is an indication that other factors are involved.[51] [84] [85] [86] Autoimmunity may also result from immune cell hyper-responsiveness such as unchecked activity of cytotoxic T-cells and T-cell-induced activated macrophages.[87] [88]

Furthermore, Th1 (cell-mediated immunity) and Th2 (humoral immunity) pathways have a close connection with immune responses and thus, autoimmunity.[89] [90] There is evidence that a third T-cell subset, Th17, which has a reciprocal relationship with T-regs, is involved in several autoimmune conditions.[91]

There has been a better understanding of innate immunity and its role in triggering autoimmune conditions over the past few decades. The innate immune system uses sets of molecules known as pattern-recognition receptors such as Toll-like receptors, nucleotide oligomerization domain (NOD)-like receptors, and NACHT-LRR-PYD-containing protein (NALPs).[92] [93] For example NALP1 and NALP3 contribute to form cytoplasmic complexes called inflammasomes. Inflammasomes control the activation

of Caspase-1, which is responsible for activation of interleukins.[94] Interestingly, variants of NALPs are associated with certain autoimmunities and inflammatory conditions.[95] [96]

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INFLUENCING FACTORS

The triad concept of autoimmunity consists of three important components often present for the development of an autoimmune disease: 1) genetic background, 2) environmental components, and 3) intestinal permeability.

Genetic

Although genetic and environmental factors both play a central role in autoimmunity, many times it is not clear which one is the main link to heterogeneity of autoimmune prevalence. The importance of genes in autoimmunity became emphasized when it was noticed that the risk of autoimmunity is increased in twins and siblings of affected individuals.[97] Gene analysis studies thereafter have confirmed the genetic relevance and suggested different methods for predicting the development of autoimmune conditions such as SLE, RA, DM1, and MS on an individual basis.[98] [99] [100] [101]

HLA Typing

Data from studies on Human Leukocyte Antigen (HLA) has been suggestive of certain genetic connections of autoimmunity. HLA, in fact, represents the Major Histocompatibility Complex (MHC) Class I & II. HLA A, B, and C represent MHC class I and HLA DOA, DOB, DM, DP, DQ, and DR represent MHC Class II. Some of these classes are associated with higher risks of certain autoimmune conditions, for example, HLA-DR3 is associated with an increased risk of DM1, Autoimmune Hepatitis, SLE, and Sjogren while HLA-DR4 is more associated with RA and DM1. HLA-B47 has been linked to 21-Hydroxylase deficiency in congenital adrenal hyperplasia (CAH). The link between DQ2 and 8 with the classic form of Celiac Disease has also been well known. However, it is necessary to understand that a HLA typing neither can rule out nor be relied on for diagnosis and/or accurate prediction of autoimmune conditions.

Single Nucleotide Polymorphism (SNP)

Advances in genetic engineering over the past decade have made it possible for genome-wide-association scanning and identifying the Single Nucleotide Polymorphism (SNP), of which variations have been linked to different disorders including autoimmunity. For example, the PTPN22-R620w allele tends to be associated with RA, DM1, and SLE. This association has been controversial for Hashimoto throiditis.[102] [103] [104] However, a minor allele of a SNP (rs12730735) apparently has a significant association with the susceptibility of Hashimoto's thyroiditis in Korean population.[105]

Unfortunately, despite the huge and increasing information on SNP(s), there is still a lack of strong conclusive evidence in this regard.[106] [107] For instance, out of thousands of SNPs that have been studied in NIH, so far, none have found a solid association with RA.

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Familial History

Family history may also be of clinical importance regarding genetic susceptibility for increased risks of developing autoimmune disorders. Examples:

- the highest risk for first degree relatives for developing Crohn's disease is up to 20 percent;
- the risk for first degree relatives for MS is around 5 percent, increasing to around 40 percent for monozygotic twins;
- the chance for developing pernicious anemia for relatives is around 20 percent.
- Hashimoto thyroiditis tends to cluster in families with other immune disorders.
- Sjogren syndrome occurs 90 percent in women, of which half tends to cluster with other autoimmune disorders.

When genetic susceptibility is suspected from clinical information including gene analysis or family history, measuring auto antibodies may give further clues of possible ongoing and/or latent autoimmunity even in lack of presence of symptoms.

Environmental

The development of an autoimmune disease may be influenced by the genes a person inherits together with the way the person's immune system responds to certain environmental influences, such as toxic chemicals and infectious agents. The role of environmental factors can be better understood when one considers that 1) only 24-50 percent of identical twins develop the same autoimmune disease and 2) the fact that MHC differences are not the only factor contributing to the susceptibility to autoimmunity, but the toxin metabolism, lifestyles, and exposure rates which, in fact, are important factors that cause individuals to react differently to the same chemicals.

This concept is based on the fact that some autoimmune diseases are known to be more common in polluted environments or worsen by additional triggers such as bacteria or viruses. Furthermore, certain dietary proteins and peptides can trigger autoimmune disease in the gastrointestinal tract, as well as other tissues such as the bone, joints, heart, thyroid and brain.[31] [32] [33] [34] [35] [36] This interplay between genes and environmental factors is shown in Figures 5 and 6.

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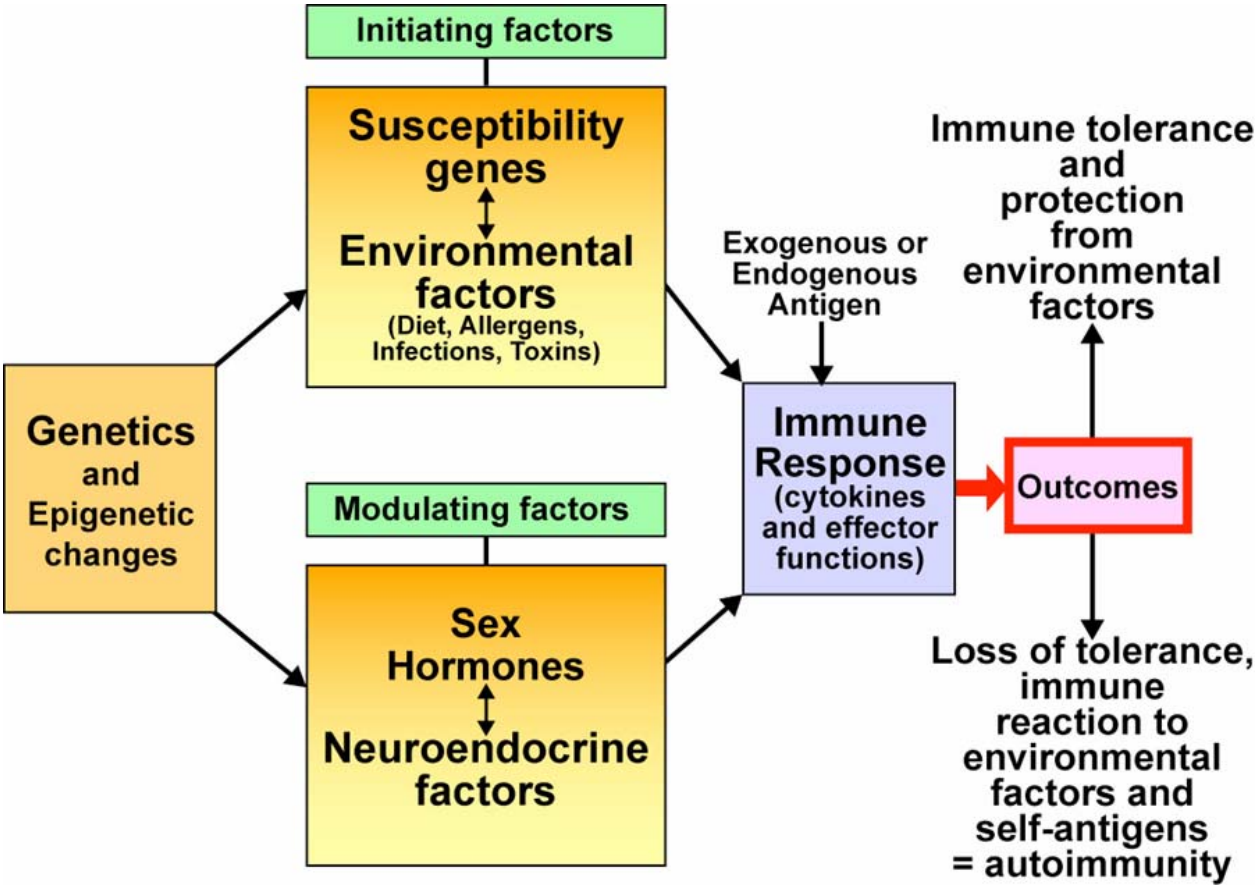

Figure 5 *- The role of susceptibility genes plus environmental factors such as diet, allergens, infectious agents and environmental toxins in the development of autoimmune disorders.*[36]

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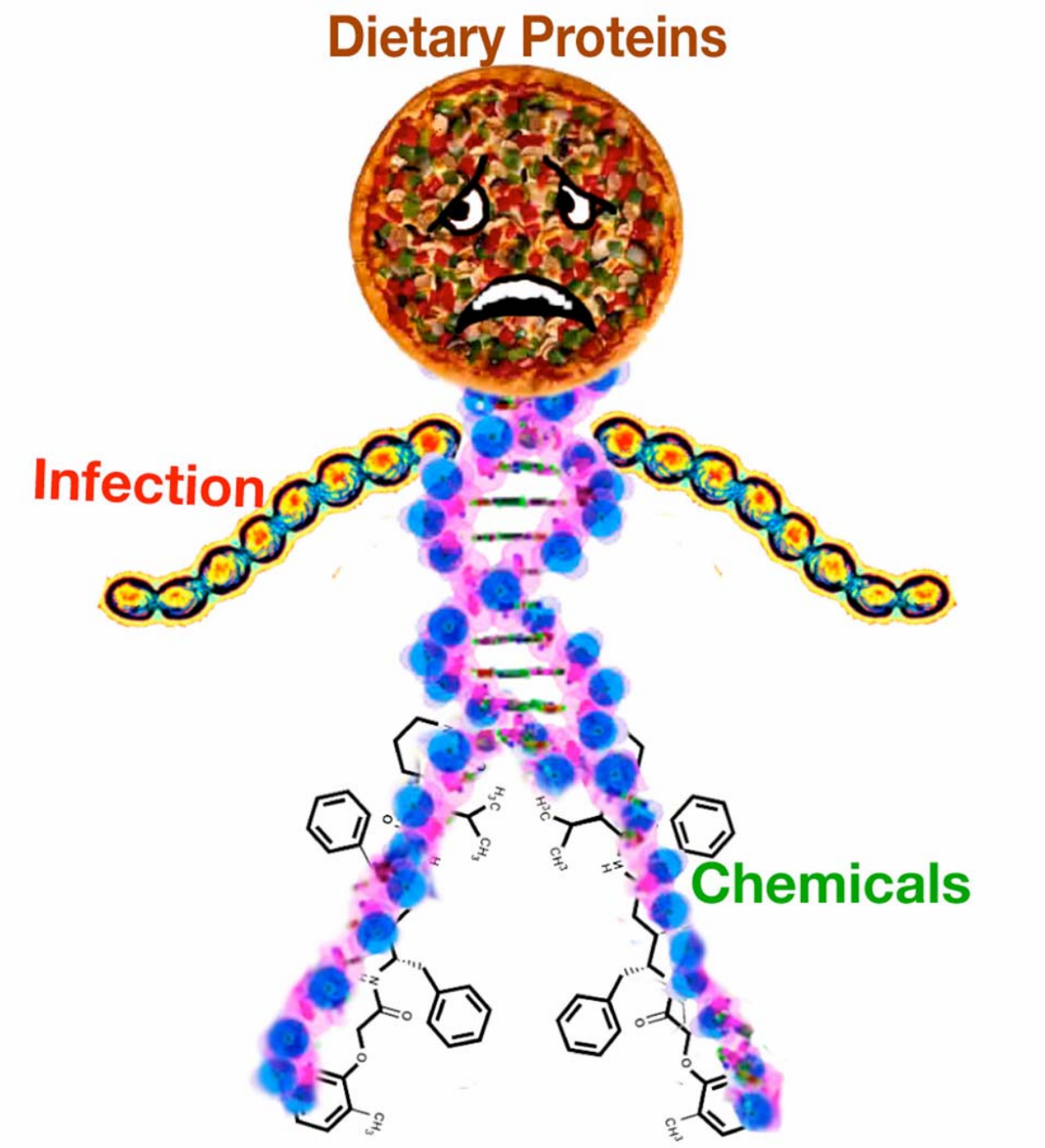

Figure 6 - Genes plus environmental factors are responsible for the development of autoimmune diseases.

Association of certain xenobiotics, including mercury, iodine, vinyl chloride, canavanine, organic solvents, silica, l-tryptophan, particulates, ultraviolet radiation, and ozone have been implicated in initiation and progression and even, exacerbation of human autoimmune disease.[108] [109] [110] [111] [112] [113] [114] [115] [116] [117]

Therefore, taking a complete detailed history (i.e. setting up a questionnaire) of all possible autoimmune related environmental toxins and chemicals that a person may have encountered can be of great clinical importance. **Top**

History

Clinical manifestations of autoimmune disorders can present at any age. It is important to consider:

A) The patient's environment:

- Work
- Home
- School

B) To what toxins is the person exposed on a daily basis? Common toxin-filled work environments include:

- Autobody repair shops
- Nail salons
- Dental offices
- Janitorial services
- Moldy buildings
- Lead paint
- Diet
    - Gluten
    - Dairy

C) Current medications and medical procedures and medical history:

- NSAIDS
- Hormone replacement therapies
- Breast implants
- Joint replacement
- Organ transplant
- Blood transfusion
- Infections
- Viruses
- Bacterial overgrowth
- Diagnosed with gluten-reactivity
- Diagnosed with an autoimmune disorder
- Family history of autoimmunity
- Known increased intestinal permeability

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MEASURING AUTOANTIBODIES

Considering the huge number of antibodies against specific human body antigens, screening for all available antibodies is neither necessary nor cost-effective, if possible at all. Therefore, a reasonable clinical approach to autoimmunity and autoimmune diseases may be performed by narrowing down the screening test based on appropriate and relevant criteria including:

- **Background condition** - screening for autoimmunities that are commonly associated with the background condition, for example gluten reactivity, or chemical exposure.
- **Tend to cluster** - for example, a single person will experience multiple autoimmune diseases, or members of a family may share the same, or even other, autoimmune diseases. The association of one disease of unclear etiology with another of authentic autoimmune etiology strengthens the possibility that the former is also an autoimmune disorder.[53] [118]
- **Prevalence** - screening for epidemiologically common autoimmunities, such as autoimmune thyroiditis.
- **Sensitivity/Specificity** - measuring antibodies that have highest sensitivity for detecting autoimmune responses.
- **Predictive Autoantibodies** - screening antibodies that are present before, or independent of, symptoms.
- **Cost-effective** - Avoiding the expensive measurements when there is no clinical advantage between the two.

Individuals with gluten immune reactivity, and compromised mucosal integrity, are at greater risk than the general population for developing one or more autoimmune conditions. However the associated autoimmune conditions may not be resulted directly from gluten reactivity. It is believed that genetic factors and cross-reactivity of antigens play an important role in this regard. Important examples of such autoimmune conditions may include:

Diabetes Mellitus Type-1 (DM 1) - DM 1 is an autoimmune condition with relatively high incidence in those with CD. This disorder can be caused by islet cells damage and lack of insulin synthesis (islet cell autoantibody) or ineffective insulin (genetic or autoimmune). The predictive autoantibodies against insulin and islet cell antigen (ICA), may assist in foreseeing this condition in those with CD.[119] [120]Moreover, antibody against the enzyme glutamic acid decarboxylase (GAD65), which may be detectible in 60% of celiac patients,[121] has been implicated in DM 1,[122] particularly if associated with certain neurological issues.[123] [124] The common symptoms of DM 1 include polydipsia, polyphagia, polyuria, and, if left untreated, vascular damage and ophthalmopathy. DM 1 is not typically associated with truncal obesity due to low insulin levels.

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Latent Autoimmune Diabetes in Adults (LADA) - Data suggests that some adults with DM 1 and with apparent type 2 diabetes (7.4% of all diabetic patients diagnosed at 30-74 years of age) may have increased levels of ICA and GAD65 antibodies.[125] [126] [127] Patients with this autoimmune condition (LADA)[128] carry genes for both types of diabetes, such as **HLA-DQB1** genotype (similar to DM 1) and **TCF7L2** gene (similar to DM 2).[129] [130] [131] Although these patients may not need insulin initially, they may progress to insulin dependent or independent states within years or even months, depending on levels of circulating antibodies and the body mass index (BMI).[128] [132] [133] [134] For example, compared to those who have lower levels of GAD65 antibodies, those with higher levels have a lower BMI which progress to insulin dependent condition faster.[134] [135] Therefore, testing for GAD65 and ICA antibodies may help clinicians to identify patients with LADA and provide appropriate management, including immune modulation.[132] This can especially be important in patients who are resistant to oral anti-diabetic drugs or are at higher risk of developing DKA.[127] [128] [134] [135] [136]

Musculoskeletal - Patients with musculoskeletal autoimmune conditions including rheumatoid arthritis typically present with severe inflammation in joints, bone and muscles. Arthritic peptide autoantibodies and collagen complex antibodies are found to be increased in autoimmune arthritic conditions[137] [138] [139] and recommended to be measured in those with CD due to increased prevalence of such autoimmunities.[140] Antibodies to Fibulin and osteocyte may also be implicated in the pathogenesis of osteoarthritis, arthritis,[141] osteoclastogenesis,[142] and osteoporosis.[143] Osteoporosis and the bone antibody levels in celiac patients improve in response to the gluten-free diet.[144] Furthermore, 40% of patients with stiff man syndrome (SMS) are associated with antibodies against GAD as well as DM1.[145] [146] [147] SMS is a rare disorder of the CNS presented with chronic, progressive, fluctuating muscle rigidity with painful spasms as well as epilepsy.

Cardiovascular - The risk for autoimmune heart disease is increased in CD, and thus, patients presenting with CD are recommended to be assessed for cardiovascular wellness, and vice versa.[53] Myocardial peptides autoantibodies may have predictive value for heart muscle damage,[148] [149] [150] [151] while Alpha-Myosin antibodies may be considered as a marker of predisposition and do not support the concept of playing a primary pathogenic role.[152] Furthermore, since Fibulin binds to fibrinogen,[153] it is considered as a coagulation component of coronary artery atherosclerotic lesions.[154] Moreover, antiphospholipid syndrome and autoimmune thrombocytopenia, which are associated with abnormalities in blood coagulation, can lead to target tissue infarction and or bleeding.

Inflammatory Bowel Disease (IBD) - IBD includes Crohn's disease and ulcerative colitis. These are autoimmune conditions with an increased prevalence in gluten sensitive enteropathy patients. Anti-*Saccharomyces Cerevisiae* antibodies (ASCA) tend to be elevated in patients with Crohn's disease as well as Behçet's syndrome (if associated with gastrointestinal symptoms), both of which share similar symptoms including gastrointestinal mucosal damage, arthritis and uveitis.[155] Anti-neutrophil cytoplasmic antibodies (ANCAs), on the other hand, have more predictive value in ulcerative colitis.[156] ANCA is also positive in conditions such as Wegner's Granulamatosis,[157] respiratory disease,[158] and also, long-term use of antithyroid medications.[159] Furthermore, a clue to autoimminity in stomach can be found via detecting antibodies against parietal cells and ATPase.[160] [161] [162]

Neurological Issues - Celiac disease can be associated with neurological manifestations such as peripheral neuropathy or autonomic dysfunction. Pathogenesis can be either gluten-dependent (such as gluten ataxia) or without having a direct relation to typical celiac pathophysiology (such as Guillain Barré

syndrome). Neurological issues may not be reversible, even on a gluten free diet,[163] therefore, it would be of clinical significance to screen for autoimmunities in advance. Autoantibodies against the asialogangliosids (GM1) have been shown to elevate with conditions that involve the nervous system such as: Multifocal motor neuropathy,[164] [165] Guillain Barré syndrome, and myasthenia gravis. Elevated Cerebellar antibodies (against Purkinje's cells) are also an indication of neuroautoimmunity.[166] Furthermore, Anti-GAD autoantibodies may result in an excess of excitatory neurotransmitters, which can lead to seizures, anxiety, and insomnia.[167] [168] [169]

It is believed that cross-reactivity, with environmental antigens such as microorganisms, plays an important role in this respect. *Campylobacter jejuni*, for example, has been identified frequently in association with Guillain Barré and Miller Fisher syndromes.[170] Similarly, a cross-reactivity between gliadin and cerebellar antigens (peptides) can lead to autoimmunity[31] and perhaps, neurodegeneration.[171] Cross-reactivity between milk, gluten, and cerebellar peptides has been implicated in autism spectrum disorders.[172] There is also evidence that the similarities of peptide sequences between Streptococcal proteins and myelin basic protein (MBP) can result in pediatric autoimmune neuropsychiatric disorder associated with group A streptococcal infection (PANDAS), and Obsessive Compulsive Disorder (OCD).[173] MBP and synapsin are often target tissues in the demyelination process in various neuroimmune disorders including multiple sclerosis.[174] [175]

Autoimmune Hepatitis **-** An inflammatory disease of the liver, autoimmune hepatitis, typically afflicts young females. The patients may present with gastrointestinal symptoms including abdominal distension, pale stool, nausea, and vomiting, as well as, dark urine and jaundice. Liver inflammation may also occur along with other autoimmune diseases such as Graves' disease, Crohn's disease, ulcerative colitis, rheumatoid arthritis, and DM 1. Conventional testing for autoimmune hepatitis includes Anti-liver kidney microsome type 1 antibody (anti LKM-1), anti-nuclear antibody (ANA), anti-smooth muscle antibody (SMA), and serum IgG. However, increased anti-hepatocyte antibodies may also indicate a pertinent pathogenic process, and can be used in conjunction with conventional markers.[176] [177]

Endocrine / Reproductive **-** There is an increased prevalence of reproductive abnormalities including later menarche, earlier menopause, and recurrent miscarriage in women, as well as infertility in both genders amongst the untreated celiac population.[178] [179] [180] In females, premature Ovarian Failure (POF) is frequently associated with autoimmune disorders, such as SLE, Myasthenia Gravis, and particularly, autoimmune thyroid disease, during which the antibodies to ovary is increased.[181]

Testis antibodies can appear with trauma, polyendocrine syndrome and male infertility.[182] [183] [184]

Endocrine / Thyroid **-** Thyroiditis or thyroid inflammatory condition involve immune responses such as subacute thyroiditis, infectious thyroiditis, radiation thyroiditis, drug-induced thyroiditis, and fibrous thyroiditis (not autoimmune). However, autoimmune thyroiditis (Hashimoto thyroiditis aka chronic autoimmune thyroiditis) has been reported as the most common cause of hypothyroidism involving almost 10 percent of population with an increasing frequency with age.[185] The clinical presentation of autoimmune thyroiditis occurs within a wide range of symptoms; from symptoms of Goiterous (growing in size without iodine deficiency) and atrophic (shrinking in size) thyroiditis[186] to symptoms that are related to thyroid activity and hormonal output, including euthyroid (no symptom), thyroid hypofunction symptoms, and in many cases with symptoms of thyroid hyperfunction due to release and not synthesis of thyroid hormones. Autoimmunity in thyroid is far more common in women than men and tends to be

associated with other autoimmune conditions, including Vitiligo,[187] which may precede the thyroid hypofunction.[188] Increased levels of antibodies including TPO[189] and anti thyroglobulin [190] [191] [192] [193] antibody can also be seen in Graves' disease, another thyroid autoimmune condition with hyperactivity due to TSH receptor stimulating Immunoglobulin (TSI). These antibodies are all polyclonal [194] (mostly IgG1 or IgG3) meaning that they can be any class of antibodies. Although thyroglobulin and TPO antibodies can cause thyroid cells lysis,[195] it is the T-cell-induced apoptosis that apparently plays the main role in thyroid tissue damage. The clinical setting plus hormonal and immune tests are necessary to evaluate the condition. Radioactive iodine uptake (RIU) sometimes is required to differentiate the acute initial phase of Hashimoto from true hyperthyroidism.

Causality of Autoantibodies

It should be noted that predictive importance of autoantibodies is different than their causality. The causality of an autoantibody in respect to a specific autoimmune disease has to be evidenced through direct,[196] [197] [198] [199] [200] [201] indirect, [11] [61] [62] [202] [203] [204] [205] [206] [207] [208] [209] [210] and circumstantial evidence.[211] [212] The presence of autoantibodies is considered as circumstantial evidence and could be suggestive of current or future autoimmune conditions. As mentioned earlier, the major advantage of screening for autoantibodies is that they can detectably appear in the system long before the symptoms force the patient to clinics. Clinicians should be aware that the detection of antibodies does not necessarily mean that a patient will become ill, but rather gives a percentage of risk for autoimmune disease over subsequent months or years.[58]

CLINICAL USES OF ANTIBODY ARRAY 5

Clinical autoimmune disease is preceded by complicated autoimmune changes that are usually under way for many years before diagnosis. In autoimmune diseases, the immune system manufactures antibodies that target the body's own tissues. When an autoimmune condition (such as a gluten sensitive enteropathy) is diagnosed early, it is possible that gluten has not caused serious damage yet and only findings may include mild histological damage associated with subclinical or silent disease. Thus, identifying the presence of these antibodies becomes an early-warning system as to what tissue damage may be developing for the patient allowing the development of an intervention protocol, which may reverse the development of the autoimmune disease.

Array 5 is clinically beneficial for patients who:

- present with any idiopathic condition
- have been diagnosed with gluten reactivity
- have chronic increased intestinal permeability
- have been diagnosed with an autoimmune disorder
- have chronic toxin exposure

CLINICAL INTERPRETATION OF ANTIBODY ARRAY 5

Array 5 test results are not diagnostic for any clinical condition or disease. These reports may be used in conjunction with other pertinent clinical data for the purposes of diagnosis.

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Array 5 Antigens, Associated Conditions and References.

Antigen	Associated With	Table References
Parietal Cell	• Gastric Autoimmunity • Chronic Atrophic Gastritis • Pernicious Anemia	De Block *et al. J Clin Endocrinol Metabolism*, 1999; 84(11):4062-4067 (161). Greenwood *et al. Eur J Pediatr*, 2008; 167:917-925 (162). Varis *et al. Dig Dis Sci*, 1979; 24(3):187-191 (213).
Intrinsic Factor	• Autoimmune Gastritis • Pernicious Anemia	Goldkorn *et al. J Bio Chem.* 1989, 264(31):18768-18774 (214). Shackleton *et al. J Clin Pathol*, 1989; 42:210-212 (215). James *et al. Brit Med J*, 1974; 4:494-496 (216).
ASCA + ANCA	• Beçhet's Syndrome with GI Involvement • Crohn's Disease • Ulcerative Colitis	Fresko *et al. Clin Exp Rheumatol.* 2005; 23(Suppl.38):S67-S70 (156). Gómez-Puerta *et al. Chest* 2009; 136:1011-1111 (159). Nisihara *et al. Dig Dis Sci.* 2010; 55(8):2309-2315 (157).
Tropomyosin	• Ulcerative Colitis • Colon Autoimmunity • Inflammatory Bowel Disease	Das *et al.J Immunol*. 1993, 150:2487-2493 (217). Koike *et al.Bone Marrow Transplantation*. 2001, 28:619-621 (218). Mirza *et al. Inflamm Bowel Dis*, 2006; 12(11):1036-1043 (219).
Thyroglobulin	• Autoimmune Thyroid Disease • Hashimoto's Thyroiditis • Graves' Disease	Saboori *et al. J Immunol*, 1999; 163:6244-6250 (192). Muixí*etal. J Immunol*, 2008, 181:795-807 (191). Carayanniotis and Rao. *Immunol Today*, 1997; 18(2):84-89 (190).
Thyroid Peroxidase	• Autoimmune Thyroid Disease • Hashimoto's Thyroiditis • Graves' Disease	Guo *et al. J Immunol*. 2001, 166:1327-1333 (220). Roddiger *et al. J Molec Endocrinol*, 2002; 29:287-295 (221). Kaczur *et al. Clin Chem*, 1997; 43(8):1392-1396 (222).
21 Hydroxylase (Adrenal Cortex)	• Adrenal Autoimmunity • Adrenal Insufficiency • Autoimmune Endocrine Disorders	Nigam *et al. Clin Endocrinol*, 2003; 59:593-598 (223). Laureti *et al. J Clin Endocrinol Metab*, 1998; 83:3507-3511 (224). O'Leary *et al. Q J Med*, 2002; 95:79-82 (225).
Myocardial Peptide	• Autoimmune Myocarditis • Rheumatic Heart Disease	Cleutjens *et al. J Clin Invest*, 2008; 118:2979-2985 (226). Engle *et al. Circulation*, 1974; 49:401-406 (151). Frustaci *et al. Circulation*, 2002; 105:2611-2618 (53).
Alpha-Myosin	• Autoimmune Myocarditis • Rheumatic Heart Disease	Goldman *et al. Br Heart J*, 1995; 74:598-603 (227). Faé *et al. J Immunol*, 2006; 176:5662-5670 (228).
Phospholipid	• Antiphospholipid Syndrome • NIDDM • Systemic Lupus Erythematosus	Caponi *et al. Clin exp Immunol*, 2007; 150:140–143 (229). Petri. *Lupus.* 2010; 19:419-423 (230). Shigeta *et al. Diabetes Care.* 1997; 20(12): 1896-1899 (231).
Platelet Glycoprotein	• Autoimmune Thrombocytopenia • Cardiovascular Disease • Systemic Lupus Erythematosus	Lipp *et al. Eur J Haemotol.* 1998; 60:283-288 (232). Bussel *et al. Am Soc Hematol.* 2000; 2000(1):222-240 (233).
Ovary/Testis	• Autoimmune Endocrine Disorders • Autoimmune Polyendocrine Syndrome Type 1	Fénichel *et al*. Human Reproduction, 1997; 12(12):2623-2628 (182). Novosad *et al.* BMC Women's Health, 2003; 3(2):1-7 (234). Luborsky *et al*. Human Reproduction, 2000; 15(5):1046-1051 (235). Tung and Teucher. Human Reproduction Update, 1995; 1(1):35-50 (185). Sakamoto *et al*. J Urol, 1995; 153:1316-1320 (184). Reimand *et al*. Int Immunol, 2008; 20(1):39-44 (183).

Antigen	Associated With	References
Fibulin	• Osteoarthritis • Atherosclerotic Lesions	Xiang *et al. J Immunol*, 2006; 176:3196-3204 (142). Argraves *et al. Histochem Cell Biol*, 2009; 132:559-565 (155).
Collagen	• Lupus Erythematosus • Arthritis • Goodpasture's Syndrome	Fujii *et al. Br J Dermatol*, 1998; 139:302-306 (139). Arends *et al. J Immunol*, 2006; 176:1252-1258 (236). Khare *et al. J Immunol*, 1995; 155:3653-3659 (140).
Arthritis Peptide	• Mixed Connective Tissue Disease • Rheumatoid Arthritis • Osteoarthritis	Basu *et al. J Immunol*, 2000; 164:5788-5796 (138). Bourne *et al. Ann Rheum Dis*, 1985; 44(9):592-598 (237). Francis *et al. Eur J Gastroenterol Hepatol*, 2002; 14:1355-1356 (141).
Osteocyte	• Osteoporosis • Osteopenia • Osteoclastogenesis	Takayanagi. *Nature Rev*, 2007; 7:292-304 (143). Sugai *et al. J Clin Immunol*, 2002; 22(6):353-362 (144). Mora. *Rev Endocr Metab Disord*, 2008; 9:123-130 (145).
Cytochrome P450 (Hepatocyte)	• Autoimmune Hepatitis Type 2 • Liver/Microsomal Autoimmunity • Heptocellular Carcinoma	Rigopoulou *et al. J Autoimmune Dis*, 2007; 4(2):1-6 (238). Czaja *et al. Am J Gastroenterol*, 2002; 97:413-419 (239). Chaves *et al. J Pediatr Gastroenterol Nutr*, 1991; 12(2):288-290 (240). Wood *et al. J Cutan Pathol.* 2009; 36:262-266 (241). Zachou *et al. J Autoimmune Dis.* 2004; 1:2 doi:10.1186/1740-2557-1-2 (177).
Insulin + Islet Cell Antigen	• Insulinoma • Type 1 Diabetes • Unexplained Hypoglycemia • Latent Autoimmune Diabetes of Adults	Borg *et al. Diabetes.* 2002; 51:1754–1762 (119). Ismail AAA. *Clin Endocrinol.* 2011; Accepted Article:doi: 10.1111/j.1365-2265.2011.04259.x (242). Schölin *et al.J Intern Med.* 2004; 255:384-391 (243). Tuomi T, et al. Australia Diabetes. 1993 Feb; 42(2):359-62 (128).
Glutamic Acid Decarboxylase (GAD65)	• Cerebellar Ataxia • Type 1 Diabetes • Celiac Disease • Stiff Person Syndrome • Latent Autoimmune Diabetes of Adults	Ellis and Atkinson. *Nat Med.* 1996; 2:148-153 (123). Hadjivassiliou *et al. Lancet Neurol.* 2010; 9:318-330 (121). Honnorat *et al. Arch Neurol.* 2001; 58:225-230 (124). Tuomi T, et al. Australia Diabetes. 1993 Feb; 42(2):359-62 (128).
Myelin Basic Protein	• Demyelinating Diseases • Autism • PANDAS / OCD	Ponomarenko *et al. PNAS*, 2006; 103(2):281-286 (244). Berger *et al. N Engl J Med*, 2003; 349:139-145 (175). Vojdani *et al. J Int Med*, 2003; 254:363-374 (245).
Asialoganglioside	• Chronic Inflammatory Demyelinating Polyneuropathy • Multiple Sclerosis • Guillain Barré Syndrome • PANDAS / ANDAS / OCD	Baba *et al. J Neuroimmunol.* 1989; 25:143-150 (165). Bansal *et al. J Clin Pathol.* 1994; 14:300-302 (166). Jacobs *et al. J Infect Disease.* 1997; 175:729-733 (246). Vojdani A. *Latitudes.* 6(2):1-6 (174).
α + β Tubulin	• Demyelinating Diseases • Early Onset Type 1 Diabetes • Thyroid Disorders	Kirvan *et al. J Immunol*, 2007; 178:7412-7421 (75). Rousset *et al, Clin Exp Immunol*, 1983; 52:325-332 (247). Rousset *et al, Diabetologia*, 1984; 27:427-432 (248).
Cerebellar	• Celiac Disease • Gluten Ataxia • Paraneoplastic Cerebellar Degeneration Syndrome	Vojdani *et al. Nutr Neurosci*, 2004; 7(3):151-161 (31). Balegno *et al. Anticancer Res*, 2005; 25:3211-3214 (249). Blaes *et al. Ann Neurol*, 2005; 58:313-317 (250).
Synapsin	• Inhibited Neurotransmitter Release • Demyelinating Diseases	Gitlits *et al. J Invest Med*, 2001; 49(3):276-283 (251). Bustos *et al. J Cell Sci*, 2001; 114:3695-3704 (252). Bitsch *et al. J Neurol*, 2004; 251:1498-1501 (176).

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