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Why is Gluten Only One of Six Unique Coexisting Physiological Changes Which are Required to Trigger Celiac Disease? Discovery of Celiac Disease Causes with a Novel Method of Finding Non-Infectious Diseases Causes Which Combines Multiple Research

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ABSTRACT

Celiac disease (CD) is an inflammatory disorder of the upper small intestine triggered by the ingestion of wheat, rye, barley, and possibly oat products. The triggered immune reaction damages the intestinal mucosal layer and causes inflammation, which may result in a spectrum of gastrointestinal symptoms, such as diarrhea, fatigue, weight loss, bloating, etc. The global prevalence of biopsy confirmed CD has been 0.7%. The frequency of Celiac disease has increased in developed countries over the last decades and this finding points out the causal role of possible environmental triggers additional to gluten.

The clinical feature of CD is characterized by a small intestinal mucosa with the absence of normal villi, resulting in a generalized malabsorption of nutrients.CD arises in genetically susceptible individuals with HLA-DQ2 or HLA-DQ8 alleles and is characterized by a CD4+ T lymphocytes driven inflammation in the proximal small bowel triggered by gluten ingestion. Gluten is delivered to CD4+ T lymphocytes and activates them causing the secretion of different pro-inflammatory and inflammatory cytokines such as interferon (IFN)-γ, interleukins IL-1, IL-6, IL-8, IL-15 and others. After this, CD4+ T lymphocyte interaction with B lymphocytes leads to the release of autoantibodies such as anti-tissue transglutaminase (TTG) and DGA (deamidated gliadin antibody) which is a marker for active Celiac disease. The HLA-DQ2 and HLA-DQ8 alleles encoded by approximately 30% of the general population. However, only approximately 1% of the population is diagnosed with Celiac disease which indicates additional factors may be involved in the progression of this complex disease. Also, while most individuals display improvement in Celiac symptoms and signs following institution of the gluten free diet, up to 30% continue to experience symptoms and/or have persisting intestinal inflammation. These individuals are classified as having non-responsive Celiac disease.

The first clear medical definition of Celiac disease was given by Samuel Gee in 1888. It has been almost 75 years since Dr. Willem-Karel Dicke and his colleguees identified gluten as the cause of the Celiac diseases symptoms in 1953. Since this time the only available treatment for Celiac disease continues to be a maintaining a strict gluten-free diet for life. This is despite the fact that approximately 17,806 studies related to Celiac Disease has been conducted until 2024 [1]. It seems a common sense that a new approach is required.

The goal of this study was to use a new approach based on a novel mathematically based method of finding non-infectious diseases cause and apply it to analyze the causes of Celiac disease. This method has been published [3]. and also applied to other non-infectious diseases such as Breast Cancer, etc. and has shown results which are consistent with existing medical facts. The method is using a special algorithm based in math and allows to find disease causes for a specific non-infectious disease using results of multiple researches regarding risk factors of the disease.

The method is based on a model presented in the article "A Connection between Factors Causing Diseases and Diseases Frequencies: Its Application in Finding Disease Causes" (Alan Olan, Journal of Clinical Trials, Vol.13, Issue 4.) which is confirmed by empirical data. This method allows to combine dozens of studies on risk factors together with dozens of studies on biochemistry and physiology to extract implicit information on the causes of non-infectious disease out this entire research.

The use of method requires to find number of causes for a specific non-infectious disease using a special formula and data on disease frequency (usually the incidence rate) in specific population. These disease causes are two or more physiological changes beyond approximately 1-sigma interval which if they are co-existing long enough must trigger the non-infectious disease (triggering is not optional). After that the method requires to find disease causation factors out of multiple risk factors found for the disease. Only some of risk factors are real disease-causing factors. This is achieved using a set of special disease causation criteria discussed in the article by Olan A above and provided here for a reference as well [3]. **The method often allows to find few dozen of disease causation factors and more for a non-infectious disease out of existing medical research. These disease causation factors all point to the same set of limited number of physiological parameters changes beyond 1-sigma. The number of these physiological changes usually vary depending on the non-infectious disease from a minimum of 2 to a maximum of 6 or very rare more. In this case the few dozens of disease causation factors make changes (we can say "point") to the same set of 3 physiological parameters(for example).The method then allows to find these physiological parameter changes (which are the real cause of the non-infectious disease) using a properties based in math.**

After this the method allows to determine which physiological parameter of these few discovered ones is impacted by each of the dozens of disease causation factors previously found. Then method allows to group these factors according to the physiological parameter they impact. The disease causation factors taken from each group of these factors and combined together will cause a change beyond 1-sigma to all required for disease triggering physiological parameters. These combinations of disease causation factors applied long enough will cause a non-infectious disease. The occurrence of the disease causation factors is random but once they act together the non-infectious disease triggering is a must unless the factors are removed fast enough.

Final step of the method is a validation of its results using other and not used by the method research or with the already discussed disease causation criteria in order to eliminate any errors in steps of the method which a researcher could potentially make. One set of studies is used to get a result. Another independent set is used to verify it.

Once the simultaneously taking place physiological changes causing a non-infectious disease has been found the method allows to build a hypothesis of the disease pathology by using them and "connecting the dots" using the existing medical research on physiology, immunology, etc. The example of this process shown in the work as well. The hypothesis of Celiac disease pathology is proposed as one example of this.

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This article introduces to the basics of this method, provides required formulas for calculations and then move to a detailed analysis of Celiac disease. As the method is novel the appendix has an analogy to explain the idea of the method at "high level". The author's introduction to the method will allow other medical researchers to use their own and existing research to determine the causes of non-infectious diseases as per presented model, using a simple algorithm.

Results

Using this method and applying multiple existing selected studies at the same time the research analyses Celiac disease and as a result the work gives the causes of Celiac disease as a set of 6 physiological parameters changes beyond 1-sigma interval (slightly less, actually) and also as a set of disease-causing external factors which combinations in an individual must cause Celiac disease as per presented model. The research has found that reduction of Bifidobacterium in the intestine beyond ~1 sigma, reduction of immunoglobulin IgA beyond ~1 sigma (homeostatic IgA), genetic predisposition - HLA-DQ2/DQ8 common haplotypes (already accepted factor), TNF-alfa increase beyond ~1 sigma along with known factors such as Gluten consumption, and an increased intestinal permeability beyond 1 sigma (a proposed factor) interval will cause the Celiac disease if all conditions coexist long enough (an estimate is within 10-12 months). If all of these physiological changes coexist long enough the disease triggering is not optional it is a must as per the model. The 5 of these physiological parameters (excluding genetic factors) can be changed by different combinations of factors some of which are found in this research. Because these combination of factors can vary greatly the causation of Celiac disease may look quite complex and random while the real underlying causes - the 6 unique physiological changes stay the same.

Some of the discovered in this research external causation factors such as the use of iron supplements at 18 months of age or intake of gluten before 2 years are found to be reducing Bifidobacterium levels below 1-sigma. Here we observe how 2 different factors are impacting the same physiological change - the Bifidobacterium level and which is only causing the disease if co-exist with 5 other required physiological changes.

Another discovered factor such as TNF-α -308 G>A polymorphism (AA+AG vs GG) was creating a TNF-alfa increase beyond 1-sigma in the affected individuals. The external factor such as 3 or more respiratory infections in the first 6 months of child life were also increasing TNF-alfa levels beyond 1-sigma. TNF alfa was increased beyond 1-sigma due to DDE, PFOS, perfluorooctanoic acid pesticides. In other words 3 different factors separately can increase TNF alfa beyond 1-sigma which is a required but not sufficient cause of Celiac disease as the current research showed there should be 6 coexisting physiological changes and TNF alfa beyond 1-sigma cannot cause the Celiac disease as standalone physiological change.

The research rediscover and confirm that HLA-DQ2/DQ8 common haplotypes is a cause of Celiac disease which is consistent with current understanding but at the same time it stresses this is only 1 of 6 causes and cannot cause the disease as standalone factor and this is also consistent with current research on Celiac disease.

This research strongly suggests that the reason we cannot cure the Celiac disease is that it is triggered by 6 coexisting physiological changes and we are only compensating one - by reducing the gluten levels; so because other changes are stay beyond 1-sigma the reintroduction of gluten in the diet satisfies again the coexistence of 6 physiological changes which are required to cause the disease (must haves). The solution would be at least to take care of one or more additional physiological changes (like TNF alfa or homeostatic IgA) which would give a fair chance to cure it and potentially reintroduce gluten in the patient's diet later. This would allow to have 2 or more disease causing physiological changes (like TNF alfa or homeostatic IgA) out of 6 required to be eliminated and would break the disease-causing physiological set more reliably.

The fact that triggering Celia disease requires a coexistence of 6 physiological changes explains the relatively low (but rising) incidence of 17.4 per 100,000 person per year (in women). The model the current research is based on states that **the more incidence rate of non-infectious disease the less number of coexisting physiological changes beyond 1-sigma (actually, slightly less) is required to trigger the disease**. This relationship connects epidemiologic data and physiological underlying causes of non-infectious diseases.

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Introduction

In article "*A Connection between Factors Causing Diseases and Diseases Frequencies*: Its Application in Finding Disease Causes" (Alan Olan, Journal of Clinical Trials, Vol.13, Issue 4.) we introduced a model of non-infectious disease. According to this model which is matching to empirical evidence, the non-infectious disease is caused by changes to multiple physiological parameters when their values go beyond 1-sigma interval, slightly less actually. This means a non-infectious disease must occur if 2 or more particular physiological parameters changes beyond 1-sigma exist for while at the same time. Also, based on the model the criteria were introduced to determine if a risk factor is causing a non-infectious disease or not. In order to be a cause of non-infectious disease the risk factor **K** calculated as (RR - 1) or (OR-1) to be **3.55+/-50%** (or 355%+/-50%) if the factor is causing a change in **1** physiological parameter, and should have value of **19.67+/-50%** (1967%+/-50%) if it is causing a change to 2 physiological parameters beyond 1-sigma.We call these conditions a **Disease Causation criteria**. The Disease Causation criteria determine whether a factor is one of multiple which are causing disease. The disease-causing factor cannot cause a disease as a standalone as per model in article because it is usually changing only 1 physiological parameter out of multiple required. Non-infectious disease, as per the model presented in article, is caused by multiple physiological parameters changed beyond 1-sigma. The article introduced a formula to calculate number of non-infectious disease causes if the disease rate (incidence rate usually) is known for the disease in a specific population. The formula is shown below (n is number of disease causes (as number of physiological parameter changed beyond 1-sigma) :

$$n = \frac{\log P(D)}{0.22}, \text{ where } P(D) \text{ is the frequency of the disease} \quad (1.0)$$

In this formula P(D) is usually represented by **incidence rate** of non-infectious disease (annual disease rate). Using formula 1.0 and Disease Causation criteria it was shown how to find physiological parameters changes which are causing some non-infectious diseases. In this article we introduce a method which is based on this model, which allow researchers to analyze an existing research about a specific non-infectious disease and determine a *full* set of disease-causing physiological parameters for a non-infectious disease in much more complicated cases. Also, a method would allow to map a found disease causing factor to a physiological parameter which is changed by the factor beyond 1-sigma interval. For example, if we know that Diabetes is a disease-causing factor for Hypertension there is a need to know which specific physiological factor impacted by Diabetes is really a cause of Hypertension. There are multiple physiological factors impacted by Diabetes and the method will allow to find a single one out of so many (allows finding "a needle in a haystack") which is really causing Hypertension.

The method we introduce is based in math and those who mathematically inclined can find its foundation in the chapters of this article below. Here we will introduce a basic idea of the method and steps on how to practically use it.

Explanation of the Method

A method is introducing an *algorithm* based in math (but *not requiring* to use it much) which allows to process data from results of existing medical research in few steps and produce a *new information* which consist of disease causes represented by a set of **physiological parameters changes beyond 1-sigma** (slightly less, actually) and also, a few **separate groups of disease-causing external factors**. These few groups of factors are such that if you take a disease-causing factor from each group as a standalone it will not cause a disease but combined together with factors from all other groups *must* cause a non-infectious disease.

Let's say using the formula for a number of Disease causes (1.0) we found the number of causes as physiological parameter changes beyond 1-sigma. We also found from an existing research a few factors which are really causing a specific disease using a Disease Causation criteria provided. Now we need to determine which specific physiological parameters are really causing a disease. We only know their number and don't know yet what they are. We know the factors which are causing a change to these physiological parameters and we can use them to find these unknown parameters.

In order to do this we need to list many physiological parameters related to the factor and we can find them from existing scientific research (for example, we can look for all biomarkers of Diabetes and list as many as we can find). Once we list the physiological parameters in the header of some table, we need to list the factors found to be causing the disease along a most left column (vertically) of the same table. Based on the researches' data we already know which physiological parameters are related to those factors causing disease and we mark the intersection between the factor and the related parameter with letter "R" (or another letter).

Please note, we use a term "related" as it is unknown if the physiological parameter change is a cause a disease or not yet and all we know is that its change is present if the factor is present. Now we start analyzing which factors are having same parameter in common and we will call it **an *intersection* if unrelated disease-causing factors A and B both having the same physiological parameter changed**. We need to find all these intersections. Those intersections will be a superset of the physiological parameters which are causing a disease. The details of why this happens are provided in a detailed math explanation in this article. Here we can say that a match in just one physiological parameter changed (*important*: we looking for **a match by name**, not by value) between 2 different factors is not a random coincidence but a pattern. This pattern is determined by a fact that factors are causing a change of the physiological parameter beyond 1-sigma interval (or sometimes by other reasons explained later).

Here is a *simplified* explanation how the method works. Suppose there is a non-infectious disease with 2 unknown disease causes (quantity of 2 we have determined using formula 1.0). Suppose we determined already 2-3 disease causing factors (we can do it using Disease Causation criteria).Each disease-causing factor is changing physiological parameters randomly beyond their *original*(*or normal*) *range* which means a quantity of physiological parameters changes is random, the parameters' names, values are different as well, etc. The physiological parameters change for a disease-causing factors are random as they cannot be determined unless we do an experiment and determine what they have changed under influence of each of these disease-causing factors (we assume we do an experiment first time). Note, the physiological parameter changes are *random for a disease-causing factor but they may be almost the same for different people* impacted by this factor.

Suppose via the experiments we found that a disease-causing factor 1 has changed 20 different physiological parameters beyond their original (or normal) range and a disease-causing factor 2 has changed 50 different physiological parameters beyond their original (or normal) range. We just explained that *only 2 unknown* physiological parameters are really causing this disease. In order to determine **their names** we use a fact that due to random "selection" of physiological parameters out of so many (few thousands and more exist in human body) by **unrelated** *disease-causing* factors, a match by **their names** and values between these 2 groups of physiological parameters practically is not possible by accident (this is shown mathematically in this article). If we find **a match of physiological parameters by name it is a pattern** under these specified conditions, it is not random. For example, if one type of *disease-causing* factors (suppose a chocolate consumption) is causing a change in hemoglobin levels and a totally different *disease-causing* factor (suppose a long exercising) is causing a change in hemoglobin levels as well then it is a pattern *under these specified conditions*. It becomes a pattern which we are interested in because it happens between groups belonging to 2 different *disease-causing* factors. We know these 2 *disease causing factors* are impacting same physiological parameter, meaning a parameter with the **same name**. For this reason, in order to find a pattern (in our case a disease causation physiological parameter) we need to find a place where 2 physiological parameters change in both groups are the **same by name** (*important*: not by value) for these 2 different disease-causing factors.

This place where 2 disease causing factors have **the same name** of physiological parameter changed beyond original(or normal range) we call "an intersection". If we found such a match between physiological parameters **by name** (*important:* not by value) we found a pattern - a physiological parameter which is causing a disease. See a figure 1. Also, in Appendix 1 we provide a simple analogy which could help to clarify or visualize the explained concept further.

When we find all these intersections, we will find a list (or a matrix) of the parameters which are superset of physiological parameters which changes go beyond 1-sigma and are causing a disease. As there might be other patterns causing a match in parameters the number of parameters can exceed the number of parameters we determined via Number of Disease Causes formula (1.0). We will need to eliminate other parameters based on the methods provided in this article to get a final set of Physiological Parameters which changes go beyond 1-sigma (actually slightly less).These changes when they are present at the same time *must* trigger a disease.

The illustration of this process shown on figure 1. Once we know the final set of these physiological parameters and as we know up front which factor is related to which physiological parameter we can find which specific physiological parameter is impacted by the specific factor in such a way that a parameter goes beyond 1-sigma interval. In other words we get an understanding that a factor is impacting a specific physiological parameter. Now, if an individual is affected by a set of factors which are causing a change in ALL these physiological parameters required then the individual will get sick after sometime unless the harmful factors

are removed fast enough. This knowledge can help to prevent a disease in the individual or help potentially cure it or reduce severity of the disease.

Using a Method in Practice

In a nutshell, in order to use this method to find a set of physiological parameters which are causing a disease next steps should be taken:

- Find the number of causes (as physiological parameters changes) for the non-infectious disease using a formula for a disease causes (1.0) (*see also our article*: , "**A Connection between Factors Causing Diseases and Diseases Frequencies: Its Application in Finding Disease Causes**", *Alan Olan*, Journal of Clinical Trials, Vol.13, Issue 4.)
- Find as many as possible, the factors which are causing a disease using a Disease Causation criteria on existing experimental data or new research (*see our article*: "**A Connection between Factors Causing Diseases and Diseases Frequencies: Its Application in Finding Disease Causes**", *Alan Olan*, Journal of Clinical Trials, Vol.13, Issue 4.)
- For each factor found, you need to list as many as possible parameters related to it in some table. For example, if a factor is a consumption of some food, then include which nutrients, chemicals it contains including harmful ones as per existing researches. If a factor is a disease, then list which physiological parameters are known to be impacted one way or another as a symptom, a cause, etc. You need to place one factor vertically and appropriate impacted physiological parameters horizontally(in the table's header) in this table. The column where a factor is related to a physiological parameter can be marked with cross "X" or letter "R".

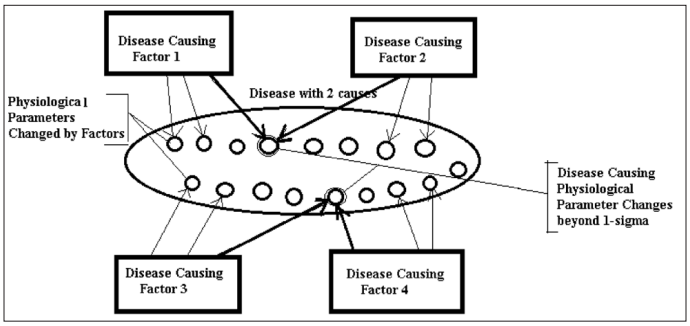


Figure1: (Disease with 2 causes, as per formula (1.0): Disease Causing Factors are Causing Multiple Physiological Changes. **Disease Causing** Physiological Changes are Common for Factors 1 and 2, for Factors 3 and 4. We Find Them By Determining an Intersection in a Physiological Parameter

- If the factor is by itself a physiological parameter it can be taken as one of the physiological parameters you are searching for during this step in the method. It can be corrected with next step if needed.
- Now, you need to find where the columns which contain physiological parameters are causing a crossing between factors. This means you need to **look for a cross ("X" sign) in the same column for 2 or more factors in the table**. We are basically finding which same (by name, not value) physiological parameter is changed by 2 disease causing factors.
- Build a list or a matrix **Pm** consisting of the parameters which are causing intersections. For example, like Pm: { r1, r19, r23, r45 }. In practice Pm can look like **Pm = { "Blood Pressure", "Estrogen Level Change", "Oxygen level", "ROS level" }**
- Eliminate redundant physiological parameters from matrix **Pm** if required (as per rules provided in this article). If the number of calculated parameters per formula (1.0) is less than number of parameters found via analysis of intersections then the redundant parameters need to be eliminated. The number of parameters found via analysis of intersection in a table should match to the number calculated via a formula (1.0) or be less if not all parameters can be found due to a lack of experimental data, etc. Also, if some physiological parameters found as result of analysis of intersection in a table are causing some disease-causing factors to change more parameters, than predicted by disease causing criteria, then some physiological parameters may need to be eliminated as well. The disease-causing factor can usually change only 1 or 2 physiological parameters beyond 1-sigma interval (slightly less than this interval, actually).
- Verify the results of using algorithm by checking if there are appropriate experimental data consistent with the physiological parameters found. Also, you can verify if a physiological parameter found satisfies a Disease Causation criteria above ***if*** there is any research on the risk of this parameter.

You can see that **a method allows to use a simple algorithm** on a set of existing experimental data in order to determine disease causes (as a set of physiological parameter changes beyond 1-sigma interval) and then verify the results using other research (which was not used doing steps of the algorithm) either by using Disease Causation criteria or by simply checking how this research is consistent with results of your findings.

Example of Method's Application for a Disease with 2 Causes

Let's look at hypothetical disease with 2 causes and apply to it the method described above. We created a **Table 1**. We can see in Table 1 that all physiological parameters are listed on the top and all found from the experiments Factors which are causing this hypothetical disease are listed on the left. Now, we can see that parameter **r20** is an intersection for Factor 3 and Factor 4, param **r12** is an intersection for Factor 2 and Factor 3 and Factor 4. A param **r17** is an intersection for Factor 1, Factor 2. We can build our matrix **Pm : { r12, r20, r17 }**. In practice, this matrix may look like a list **Pm : { 'Blood Pressure Change', 'Oxygen Level Change', 'Estrogen Change')**. This matrix contains physiological parameters which changes beyond 1-sigma are causing a disease if present at the same time.

Table 1: (areas in Gray are Where an Intersections Happen in Parameters r12, r20 and r17 Accordingly. Area Surrounded by Bold Frame is a Final set of Parameters for Matrix Pm)

Factors causing Disease	Physiological Parameters - Entire Set for ALL FACTORS as R1, R2, ... Rn													
	r12	r20	r2	r8	r17	r75	r34	r56	r39	r12	r55	r23	r78	r11
Factor 1			x		x				x	x		x		
Factor 2	x				x			x			x			x
Factor 3	x	x					x							
Factor 4	x	x				x							x	

Now, we see the matrix **Pm : { r12, r20, r17 }** has 3 elements but our disease only requires 2. We need to eliminate the incorrect one. We can notice that if we take a valid combination of 2 param as {r12, r17 } then a param r12 is showing that *Factor 2 is impacting r12 and r17 parameters but Factor 2 only can cause 1 parameter* impact (as determined by Disease Causation criteria) so the combination is not correct. If we eliminate r12 and take a combination of **{r20, r17 }** then both params are satisfying our requirement (assuming there is no info their changes are within 1-sigma). So from this table we can see that final physiological parameter's set which is causing this disease is {r20. r17 }.In this case Factors 3 and 4 are causing a change in parameters **r20**, Factor 1 and 2 are causing a change in physiological parameter **r17**. We have determined 2 physiological causes for a disease with 2 causes.

Criteria for Choosing Intersections of Physiological Parameters

The probability the single intersection has found a disease-causing physiological change is at least 96% and increases drastically with adding more intersections for the same parameter with other, **not related risk factor's studies**. As we can see there is a very small chance (at least less than 4%) of random intersection of physiological parameters belonging to 2 different factors and also, there are cases when more parameters found then determined by disease causation criteria, attributed mostly due to physiological dependencies. In order to select those parameters which are really causing a non-infectious disease we need to use these criteria below.

- We need to check if factors which are impacting physiological parameters found to be intersections are belonging to **same type of disease** or they are **very similar in nature** (like BMI impact and high weight impact) and we can ignore them as the intersection is most likely due to similarity.
- Make sure **a factor is causing a change the physiological parameter** which intersect (not opposite) As the factors should cause a change in physiological parameters.
- **Make sure both factors are causing change in the physiological parameter which intersect** or the intersection is not valid.
- If a **factor causing insignificant change (less 1-sigma interval) in physiological parameter then the parameters need to be ignored as a point of intersection** with this factor. The factors as we discussed need to make change in physiological parameter so its value will be beyond 1-*sigma* interval.
- Make sure the **physiological parameters changes in the point of intersection happen in the same direction** (either increase or decrease). If the changes move in different directions, then the parameters are considered as 2 different parameters and not as one.
- **The intersection of parameters for a similar factor is not considered correct** intersection (as it is the same factor, for example Increased Weigh and BMI over 30 are similar factors)
- If the experiment found that a factor which causing a disease is impacting 1 physiological parameter but the factor consists of combinations of 2 separate factors (for example observation was done for presence of diabetes or obesity together so they work as a factor) then **the combined factor can be allowed to have 2 intersections despite having impact on 1 physiological parameter** as one of the parts of the factor could be present at the time (for example either a diabetes causing 1 change in physiological parameter or obesity causing the change in another physiological parameter)
- **Element cannot cross itself**, for example if factor is IgA and physiological parameter IgA then they don't create a crossing. Usually, if a factor found as physiological parameter, then we already know this is a physiological parameter causing a disease.
- In many cases it is possible to **eliminate the redundant intersection by determining via a known research if the physiological parameter increases or decreases with the presence of specific factor**. For example, does lipoprotein level decreases or increases with diabetes as causation factor? **If same parameter where we see a intersection, increases in presence of one factor and decreases in presence of another** then the intersection is invalid.
- Once a set of physiological parameters was found **they can be also validated with already provided Disease Causation criteria to determine if the factor is a cause of disease** (a parameter should increase a risk of disease 3.5 +/-50% times) using an existing research. For example, if we find that an increased lipoprotein is causing a stroke and if some existing research confirms that a risk of its increase is **3.5 +/-50%** then it confirms a lipoprotein as a parameter was found correctly.
- In some cases biochemical analysis may help to eliminate an element from matrix Pm

Algorithm to Eliminate Redundancy

An approximate algorithm which can be used to eliminate redundant physiological parameters may look like this:

- Find out if all parameters which intersect in your table satisfy a hard condition that a factor only can cause as many changes to physiological parameters as determined via a disease causation criteria (which in most case is 1 and in some 2 or very rare 3).If some physiological parameters are causing not permitted number of changes by a disease-causing factor, then some parameters need to be eliminated (ignored as intersections).
- Check the factors which having intersections. If the factors are similar or related then their intersections can be due to similarity and ignored.
- Select a set of physiological parameters which from a common

sense will make most of factors intersect in them. Validate if your selection is following a rule number 1) above. If not use the elimination criteria provided in this article to help resolve conflicts.

- If 3 factors which are not related intersect in the same physiological parameter then treat a physiological parameter as a high-priority intersection as it is extremely low probability that this intersection is not a pattern.
- If a physiological parameter is selected as a real intersection surround it with a bold rectangle to differentiate from original intersections.
- Remember that if 2 factors intersect it is a pattern which is determined by next facts 1) that factors are causing a same changes beyond 1-sigma to a physiological parameter or 2) the intersection occur due to dependency between related factors or related physiological parameters but the changes are not necessarily beyond 1-sigma. In other words in this case the intersection happens due to this relationships not necessarily due to 1-sigma change (but it can be both at the same time: due to relationship and also due to 1-sigma change).

Methodology

Analysis of Non-Infectious Disease Causes

Below we provide a discovery of Celiac disease causes as per method presented above. Using this example we demonstrate in more details how to use a method on a complex case of analysis of Celiac disease which requires elimination of redundant physiological parameters.

Celiac Disease

Celiac disease is a serious auto immune disease that occurs in genetically predisposed people where the ingestion of gluten leads to damage in the small intestine. The incidence of Celiac disease among women was 17.4 per 100,000 person, compared to 7.8 per 100,000 person among men. (https://celiac.org/about-the-foundation/featured-news/2020/02/incidence-of-celiac-disease-steadily-increasing/). Using a formula for number of disease causes let's determine a number of physiological parameter changes which are causing Celiac Disease.

For women:

$$N = \log_{0.22} 0.000174 = 5.71 =\sim 6$$

For men:

$$N = \log_{0.22} 0.000078 = 6.24 =\sim 6$$

As per calculations for both incidence rates Celiac disease happens due to 6 physiological parameters' changes.

Using a Disease Causation criteria provided in this article and developed in article "**A Connection between Factors Causing Diseases and Diseases Frequencies: Its Application in Finding Disease Causes**" (*Alan Olan*, Journal of Clinical Trials, Vol.13, Issue 4.) we are finding a list of factors based on existing research data which are really causing Celiac disease as they are changing some physiological parameter beyond 1-sigma. The list of found **Celiac disease-causing factors is below** with related explanation for each factor:

• "**having 3 or more respiratory infections in the first 6 months** of life **multiplied the risk by 2.8 (OR 2.79,** 95% CI; 1.03–7.54). " ("*Infections in early life as risk factor for coeliac disease*", Sandra Llorente Pelayo, Mirian Palacios Sánchez, Pablo Docio Pérez, et al, Annales de Pediatric (English Edition), Volume 94, Issue 5, May 2021, Pages 293-300). As per our criteria for one physiological parameter impact the Risk Factor K should be 3.5 (and OR = K + 1 = 3.55 +1 = 4.55) and we have this OR = 2.8 which is within **4.55 +/- 50%** (2.27 - 6.81) and this means this factor related to infection is one of 6 causes of Celiac Disease. We place this factor in Table 2.1, column 2. Please note that we use an alternate way to populate a table here as we put the factors on the top of the table.

• "**Intake of gluten before 2 years of age increases risk** of celiac disease at least 2-fold in children with genetic risk factors for this disease", also "...children who received amounts of gluten in upper tertile (i.e. high gluten intake) were at more than **2-fold higher risk for CD** than those consumed less (**OR=2.65**; 95% CI=1.70–4.13; p <.0001("*Effects of Gluten Intake on Risk of Celiac Disease: a case–control study on a Swedish birth cohort*", Carin Andrén Aronsson, MSc, Hye-Seung Lee, PhD, Sibylle Koletzko, PhD, et al, Clin Gastroenterol Hepatol. 2016 Mar 14(3): 403–409, doi: 10.1016/j.cgh.2015.09.030). **OR = 2.65** is within **4.55 +/- 50%** (2.27 - 6.81) so this factor is a one of 6 causes of Celiac Disease as per criteria developed in article ("**A Connection between Factors Causing Diseases and Diseases Frequencies: Its Application in Finding Disease Causes**", *Alan Olan*, Journal of Clinical Trials, Vol.13, Issue 4.) . We place this factor in Table 2.1, column 3.

• "Early clinical studies estimated a 10–**20-fold increased** risk for celiac disease (CD) **in IgA deficient subjects** [4-6]. This has recently been confirmed by several studies conducted on very large cohorts of IgA deficient patients" ("*Testing for IgG class antibodies in celiac disease patients with selective IgA deficienc.: A comparison of the diagnostic accuracy of 9 IgG anti-tissue transglutaminase, 1 IgG anti-gliadin and 1 IgG anti-deaminated gliadin peptide antibody assays*", Danilo Villalta , Maria Grazia Alessio, Marilina Tampoia, et al, Clinica Chimica Acta, Volume 382, Issues 1–2, July 2007, Pages 95-4) [7,8]. According to a Disease Causation criteria in article **the factor which is causing a disease and impacts 2 physiological parameters beyond 1-sigma should have a risk K = 19 +/- 50%** and so for **OR=20**, K = OR - 1 = 20 - 1 = 19 is within this range and it means the IgA related factor is one of the 6 causes a Celiac Disease and it is changing 2 physiological parameters. We place this factor in Table 2.1, column 4.

• "The HLA-DQ2*5 molecule is encoded by DQA1*05:01 and DQB1*02:01 alleles in cis-configuration in the DR3 haplotype. In general, up to 95% of patients with CD are positive to **HLA-DQ2** (DQA1*0501/DQB1*0201), and the remaining 5% are positive to HLA-DQ8 (HLA-DQB1*0302) haplotypes.31 **HLA-DQ2/DQ8 common haplotypes have been shown to elevate** disease risk **by 6-fold**. " ("*Understanding Celiac Disease From Genetics to the Future Diagnostic Strategies*", Carolina Salazar, Jennyfer M García-Cárdenas and et al, Clinical Medicine Insights: Gastroenterology, Volume 10, 2017). Taking **OR = 6** we determine **K = OR - 1 = 6 - 1 = 5** and it is within **3.5+/-50% range** and so the factor is one of 6 cause of Celiac Disease, impacting **1 physiological parameter** change. We place this factor in Table 2.1, column 5.

• "**Use of iron supplements reported at 18 months of age** was associated **with a threefold higher risk of celiac**" and more specifically the research shows that for child's use of dietary iron supplements at 6 and 18 months the risk of celiac disease OR = 3.1, 95 % CI ("*Maternal iron supplement intake during pregnancy and risk of celiac disease in children*", Ketil Størdal, Margaretha Haugen, Anne Lise Brantsæter, et al, Clin Gastroenterol Hepatol. 2014 Apr; 12(4): 624–631.e2). According to the Disease Causation criteria **K = OR - 1 = 3.1 - 1 = 2.1 and is within 3.5+/- 50% range** for a factor which is causing a disease by changing one physiological parameter. This means that High Iron supplementation factor above is **one of 6 causes of Celiac**

Disease. We need to remind that only if all 6 physiologial changes take place then this will trigger a Celiac Disease. One factor as stand alone should not trigger the disease. For more details please see the article "*A Connection between Factors Causing Diseases and Diseases Frequencies: Its Application in Finding Disease Causes*" (*Alan Olan*, Journal of Clinical Trials, Vol.13, Issue 4). We place this factor in Table 2.1, column 6.

• Another study says - " Polybrominated diphenyl ether (PBDEs), perfluoroalkyl substances (PFASs), and p,p'-dichlorodiphenyldichloroethylene (DDE) and HLA-DQ genotype category were measured in blood serum and whole blood, respectively." and its results are "After stratifying by sex, we found **higher odds of celiac disease in females with serum concentrations of DDE (OR = 13.0,** 95% CI = 1.54, 110), **PFOS (OR = 12.8**, 95% CI = 1.17, 141), **perfluorooctanoic acid (OR = 20.6**, 95% CI = 1.13, 375) and in males with serum **BDE153, a PBDE** congener (**OR = 2.28**, 95% CI = 1.01, 5.18)."("*Persistent organic pollutant exposure and celiac disease: A pilot study*", Abigail Gaylord , Leonardo Trasande, et al, Environmental Research, Volume 186, July 2020, 109439) so we can find that Risk Factor K = OR -1 will be **K= 12 for DDE, K = 11.8 for PFOS, K = 19.6 for perfluorooctanoic acid** which are all **within a 19+/- 50% range** and matching to a Disease Causation criteria which impact 2 physiological parameter changes. This means **DDE, PFOS, perfluorooctanoic acid found in serum concentrations in females are really one of the 6 causes of Celiac Disease impacting 2 physiological parameters**. For males, **OR • = 2.28** is in range between **4.55 +/- 50%** (2.27 - 6.81)and it mean **BDE153** is one of 6 causes impacting 1 physiological parameter. We need to notice here **these compounds are not causing the Celiac Disease as stand alone**. Only if 2 physiological parameters changes which are impacted by them present at the same time with other 4 out of 6 required to cause a disease changes only then Celiac Disease will be triggered as per mechanism described in article "*A Connection between Factors Causing Diseases and Diseases Frequencies: Its Application in Finding Disease Causes*"(*Alan Olan*, Journal of Clinical Trials, Vol.13, Issue 4).We place this DDE, PFOS, perfluorooctanoic acid related factor in Table 2.1, column 7.

• "A total of 11 studies with 1147 cases and 1774 controls were selected for this meta-analysis. The pooled **results indicated that TNF-α -308G>A polymorphism was associated with increased risk of celiac disease** (A vs G: OR=2.077, 95% CI=1.468-2.939, P=≤0.001; AA vs GG: OR=8.512, 95% CI=3.740-19.373, P=≤0.001; AA+AG vs GG: OR=1.869, 95% CI=1.161-3.008, P=0.010; **and AA+AG vs GG: OR=4.773**, 95% CI=3.181-7.162, P≤0.001" ("*ASSOCIATION OF TNF- α-308G>A POLYMORPHISM WITH SUSCEPTIBILITY TO CELIAC DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS*" , Arq. Gastroenterol. 56 (01) Jan-Mar 2019 • https://doi.org/10.1590/S0004-2803.201900000-20). As we can see combination of AA+AG vs GG increase risk of Celiac disease with **OR = 4.77** which is within a range of OR to be a cause of disease - **4.55 +/- 50%** (2.27 - 6.81). It means this combination is impacting 1 physiological parameter and, in this case, this is a TNF-Alfa and is one of 6 cause of Celiac Diseases. Additionally we can notice that according to an article "The frequency percentage of GG, AG and **AA** genotypes in TNF-α cytokines at -308A/G in Azeri population was 70.8%, **26.7%** and 2.5%, respectively"("*TNF-α gene polymorphism in Iranian Azeri population*", Mohammad Asgharzadeh, Manouchehr Fadaee, Hamed Ebrahimzadeh Leylabadlo, et al, Gene Reports, Volume 19, June 2020, https://doi.org/10.1016/j.genrep.2020.1006511) and we can see that probability of combination of AG is 26.7 percent or about 0.27 and interesting to notice that it is the probability which matching to **TNF-Alfa properties being beyond 1-sigma** interval and as we know to cause the disease the physiological parameter value should be beyond 1-sigma interval, slightly less (see article *Alan Olan, "A Connection between Factors Causing Diseases and Diseases Frequencies: Its Application in Finding Disease Causes*"). It means that a probability to have **TNF-α -308G>A polymorphism** is 0.267 which is required for a parameter to be beyond 1-sigma and be a disease-causing factor as well. We place this factor in Table 2.1, column 8.

Once we listed disease causing factors in Table 2.1, we are adding physiological parameters related to these factors and mark relationship between them and related disease-causing factors with letter "R" in the table. For brevity, we don't list here all but only few citations to the research which was used to populate these parameters.

• "In a recent study, **an iron-fortified micronutrient powder provided to Kenyan infants ranging from 6 to 10 months of age** caused an increase of several taxa from Enterobacteriaceae family, especially the pathobiont *E. coli*, and **a decrease of Bifidobacterium in their intestine** [**95**]", "One of the oldest studies back in 1985, showed that **infants given an iron-fortified cow's milk preparation had lower *Bifidobacterium*** but higher counts of Bacteroides and E. coli than infants receiving an unfortified cow's milk preparation [92]" ("*Gut Microbiota and Iron: The Crucial Actors in Health and Disease*", Bahtiyar Yilmaz and Hai Li, Pharmaceuticals 2018, 11(4), 98; https://doi.org/10.3390/ph11040098). Based on this we add a Bifidobacterium as physilogical parameter change related to iron supplementation in Table 2.1 column 6 and put letter "R" to mark this relationship.

• "**Homeostatic IgA (which also functions as a natural antibody) is induced in the intestinal mucosa by continuous stimulation with commensal bacteria**, and is also detectable in circulation. Indeed, **little IgA is detected in the intestinal secretions and sera of germ-free** and neonatal mice and its production is restored soon after the colonization of commensal bacteria (2) "("*Regulation of IgA Production by Intestinal Dendritic Cells and Related Cells*", Front. Immunol.,Hiroyuki Tezuka,Toshiaki Ohteki, 13 August 2019, Volume 10 - 2019, https://doi.org/10.3389/fimmu.2019.01891). Another paper informs: "**Immunoglobulin A (IgA) is involved in the maintenance of gut homeostasis. Although the oral administration of bifidobacteria increases the amount of fecal IgA**", ("*Enhancement of IgA production by membrane vesicles derived from Bifidobacterium longum subsp. infantis*" , Atsushi Kurata, Shino Yamasaki-Yashiki, Tomoya Imai, et al Bioscience, Biotechnology, and Biochemistry, Volume 87, Issue 1, January 2023, Pages 119–128, https://doi.org/10.1093/bbb/zbac172). We see there is a relationship between commensal bacteria such as bifidobacteria and IgA. We mark this relationship with letter "R" in Column 4 of Table 2.1 for bifidobacteria.

• An article informs: "**The presence/absence of gluten in the diet can change the diversity and proportions of the microbial communities constituting the gut microbiota**. There is an intimate relation between gluten metabolism and celiac disease pathophysiology and gut microbiota; their interrelation defines intestinal health and homeostasis", and also "The **main bacterial strains described as related to this gluten metabolism are Rothia, Staphylococcus epidermidis**, Streptococcus pneumoniae, Streptococcus mitis, **and Bifidobacterium**. "("*Dietary Gluten as a Conditioning Factor of the Gut Microbiota in Celiac Disease*", Karla A Bascuñán, Magdalena Araya, Leda Roncoroni, et al, Adv Nutr. 2020 Jan; 11(1): 160–174, doi: 10.1093/advances/nmz080). We can see that consumption of gluten is related to the **Rothia, Staphylococcus epidermidis, Bifidobacterium** and we mark this relationship in Table 2.1, column 3 for "Gluten under 2 year" with letters "R" for each of these bacteria. We mark it as there

is dependency between these bacteria and gluten which impacts the bacterial diversity.

• Article informs regarding Influenza A: "An important finding in this study is **that TNF- levels and IL-8 levels manifest delayed peaks** in the nasal lavage fluid. Thus, as alluded to above, **while TNF- is already significantly elevated on day 2 of infection** at the time of peak symptom scores, and TNF- administration can induce the systemic symptoms we observed " ("*Local and Systemic Cytokine Responses during Experimental Human Influenza A Virus Infection*", Frederick G. Hayden, R. Scott Fritz, Monica C. Lobo, et al, J Clin Invest. 1998 Feb 1; 101(3): 643–649.10.1172/JCI1355). This and other researches support the fact that infections increase TNF-alfa cytokine production. We mark this relationship for TNF -alfa and infections with letter "R" in Table 2.1, column 2.

• "**Polymorphism in the TNF-α cytokine at position -308G/A affects the rate of production of this cytokine** so that the **AA genotype is associated with its high level. The GG genotype frequency was more abundant** in the present study than the other two genotypes, and because TNF-α is a pre-inflammatory cytokine, *its high level can be effective in susceptibility to inflammatory* and autoimmune diseases " ("*TNF-α gene polymorphism in Iranian Azeri population*.", Mohammad Asgharzadeh, Manouchehr Fadaee, Hamed Ebrahimzadeh Leylabadlo, et al, Gene Reports, Volume 19, June 2020, 100651). As per this study we see that AA genotype of TNF-α is associated with high level of this cytokine and we mark this relationship with letter "R" in Table 2.1, column 8.

• An article on DDT and DDE pesticides states: "Compared to women with the lowest **plasma concentrations of DDT and DDE, those with the highest concentrations of both compounds had higher levels IL-1β, IL6, and TNF- α**." ("Exposure to DDT from Indoor Residual Spraying and biomarkers of inflammation among reproductive-aged women from South Africa", Lea A. Cupul-Uicab, Riana Bornman, Janet I. Archer, et al, Environ Res. 2020 Dec; 191: 110088, Doi: 10.1016/j.envres.2020.110088). This relationship between DDE, etc. and increased TNF-Alfa we mark with "R" for TNF-Alfa in Table 2.1, column 7 (for a "**DDE, PFOS, perfluorooctanoic acid pesticide**" factor).We can see how the relationships between external factors causing Celiac disease and physiological parameters which are *related* to these factors are found and marked in the Table 2.1. In similar way we complete the rest of the Table 2.1 population.

As we can see the Table 2.1 lists the external factors on the top of the table which are causing Celiac disease and shows how they connected to the changes in specific physiological parameters (which are listed in the most left column).

Here and further below cs - stand for a cause. 1 cs, for example, means a factor is causing one physiological parameter change beyond 1 sigma interval. We use this abbreviation in Table 2.1.

R - means that an external factor located in the column is related to the change in physiological parameter which located in the specific row of the table. In other words some factor "XYZ" is related to the change in physiological parameter located in the row of the table and marked with letter "R".

Now we need to find intersections between physiological parameters related to disease causing factors and as we find out later, for Celiac disease this process is a bit complicated as the resulting list of physiological causes of Celiac disease has redundant physiological parameters which need to be eliminated... Let's find these intersections between physiological parameters related to the factors causing Celiac disease listed in the table in order to find the physiological parameters which are impacted by these factors and this way to determine the disease causing physiological parameters. The physiological parameters changes which we find are the real causes of Celiac disease . By looking at the table 2.1 we can see for example, that factors in columns 3,4,6 intersect as they all have a common physiological parameter change as **Bifidobacterium**.

Factors in columns 2 and 3 also intersect as they have a common physiological parameter change as **IFN-Gamma**, etc. We marked this intersection in gray color to separate them better from others. By looking at intersections in the Table 2.1 as explained we can build our matrix **Pm** which will at first contains all intersected physiological parameters and which will include next elements:

Pm = { **"Bacteria Rothia, etc","Low IgA", "IFN-Gamma", "TNF-alfa increase", "CD4+ T-cells"}**

which contains 5 elements so at least 1 to be found yet. We include "Low IgA" in the matrix as it was determined already via Disease Causation criteria that it is a valid disease-causing factor. "**Low IgA**" from studies here is **a homeostatic IgA** (not tTG-IgA!) the studies were not directly related to Celiac disease, not in Celiac disease patients.

Remember, the total number of physiological parameters causing Celiac was determined to be 6 using formula (1.0) in this article. Also, we need to check matrix **Pm** so *all physiological parameters where intersection happens assure that each factor is impacting only predicted number of physiological parameters*, not more not less. For example, if a factor is impacting 1 parameter (we mark it as 1cs in the Table 2.1 columns) then only one intersection for this factor should be observed. If we observe more intersections then some physiological parameters need to be eliminated from matrix Pm.

By looking at the table 2.1 we can notice that factor of "**Gluten before 2 years (1 cs)**" is intersecting in **Bifidobacterium** and **IFN-Gamma, CD4+ T-cell** physiological parameters but it is not correct because this factors should be causing only 1 (per 1cs) physiological parameter change not 3. We need to resolve this issue by eliminating incorrect crossings.

We can do it this way. "**Low IgA**" factor should be crossing 2 physiological parameters (**2 cs**) and one of them IgA itself and another is **Bifidobacterium**. This condition satisfies if intersection happen in physiological parameters "IgA" and "Bacteria **Rothia**, etc". In this case "IFN-Gamma" and "CD4+ T-cells" get excluded as Gluten can cross only in 1 parameter (1cs) and it was just determined to be **Bifidobacterium** and so cannot cross in these 2 parameters. So a matrix is now Pm = { **"Bacteria Rothia, etc","Low IgA", "TNF-alfa"}**. Now we notice that "Bacteria Rothia, etc" is a group of bacteria, which we grouped here for brevity. Let's take a look at this group. We can notice that factors in columns **3, 4,** 6 have intersection in **Bifidobacterium** and as there are 2 intersections it is a high priority pattern (it is highly unlikely, due to 2 intersections it is a random match).Factors in columns **3, 4** intersect 2 times (in bacteria Rothia and Staphylococcus epidermidis) and this can be ignored as intersection because a factor in column 3 and a factor in column 4 are already changing **Bifidobacterium** and were determined per Disease Causation criteria as factors changing only 1 physiological parameter (not more). Also, based on the intersection between factors "**Iron supplements at 18 months" and "Low IgA**" and the research this intersection is based on we can conclude the Bifidobacterium is reduced (not increased). The 3d study gives us only a fact of

change but did not provide a direction of it. But these 2 studies give us a correct result with probability at least 96% (see the Appendix) and new studies like this could increase this probability even more in this method.

Additional intersections in columns 3 and 4 *are patterns* too but it is likely that it happens due to relationship of dependent parameter (**Bifidobacterium** and these 2 bacteria). Based on this elimination we can write a final Pm matrix as
Pm = { "Bifidobacterium decrease, etc.", "Low IgA", "TNF-alfa increase"}

This matrix only has 3 physiological parameters changed **beyond 1-sigma** which are required to cause a Celiac disease if they coexist with other 3 (total must be 6). The physiological parameter number 4 is "Genetic Predisposition - **HLA-DQ2/DQ8** haplotypes"(and 5, 6 are unknown yet) which was determined directly per disease causing criteria. Strictly speaking HLA-DQ2/DQ8 haplotypes is a factor and not a disease-causing physiological parameter but for practical reasons as genetic hard to change we keep them as a "representation" of physiological parameter. It is not a physiological parameter in the sense that as we s have at least 2 factors **HLA-DQ2** haplotype or **HLA-DQ8** haplotype as options for MHC Class II receptor and they cause Celiac disease due to high affinity **(beyond 1-sigma)** to gluten peptides. So **the high affinity to gluten peptides [13] is the important physiological change here** and not the genetics itself. We have 2 different factors impacting the same physiological parameter the affinity to gluten (see Generic Disease Causation diagram on Figure 1).

The question may arise why do we see 2 intersections between 2 factors in columns 2 and 3 which intersect in **CD4+ T-cell** and **TFN-alfa**? As per our method a random intersection between 2 factors should be extremely rare and if it occurs it signifies a pattern with probability of at least 96%. But the pattern can be due to a fact that 2 parameters depend on each other, in this case a change **CD4+ T-cell** may indirectly cause a production of **TFN-alfa** cytokine and by knowing the possible relationship of these factors one crossing can be eliminated from matrix **Pm** as insignificant.

The **rows or columns in Table 2.1 surrounded by bold** rectangles represent the physiological parameters found as a final result of analysis and which are causing a disease.

Now we create Table 2.2 for final results of analysis where we consolidate only the physiological parameter which cause the Celiac disease based on **Pm** matrix and add Genetic Predisposition. The table can be used to validate the results of analysis by checking a match that factors are causing as many changes to physiological parameters as it was determined by Disease Causation criteria for the specific factor. For example, if a factor was determined to cause only 1 change in physiological parameter (**1 cs**) then we should observe this is the case in Table 2.2.
Now we can verify the results of analysis of Celiac disease completed above with existing research on Celiac disease below:

• An article says "report on children during and after the Swedish celiac disease outbreak showed that rod-shaped bacteria constituted a significant fraction of the proximal small-intestine mucosal microbiota (94). The presence of these bacterial groups conferred a **4-fold increased risk** for celiac disease in children aged <2 y"("*Dietary Gluten as a Conditioning Factor of the Gut Microbiota in Celiac Disease*", Karla A Bascuñá, Magdalena Araya, et al., Advances in Nutrition, Volume 11, Issue 1, January 2020) . Based on a disease cause criteria it means **this bacterial disbalance is a one cause of the Celial disease as the risk is K= 4 -1 = 3-fold** (K = RR -1) and within **3.5+/- 50%** range.
• Another research states "**The results of our study suggest a role for TNF-α in the pathogenesis of CD** [celiac disease - authors' note] and demonstrate that T cells are a source of this proinflammatory cytokine. This finding is in keeping with reports that monoclonal antibody anti-TNF therapy has been employed successfully in a patient with refractory CD."("*TNF-α production by intraepithelial T cells in celiac disease*", Conleth Feighery, Joan O'Keefe, Ph.D., Gastroenterology, VOLUME 125, ISSUE 5, P1560-1561, NOVEMBER 2003) . This is consistent with our results of analysis that TNF-alfa change beyond 1-sigma is a physiological parameter which is causing Celiac disease if a change beyond 1-sigma.

As we can see the physiological parameters found to be cause of disease like bacterial change, TNF-Alfa increase as per method explained above are consistent with empirical data existing for Celiac disease causes. We also found that research on bacteria above suggests that bacterial change is one of the Celiac disease causes which consistent with the finding by our method. **We confirmed this result using a Disease Causation criteria** too. This confirmation is mostly needed to make sure we have no human errors during the processing by this method.

We came to conclusions about disease causing physiological changes with our method using *mostly unrelated* to these physiological parameters research. We have used a research on Celiac disease risk factors. We have used research on risk of gluten, respiratory infection and pesticides but *via a simple algorithm* this method uses to combine this studies with independent, not related to Celiac disease studies, we have produced **new data** that bacteria changes Bifidobacterium decrease, etc.) and TNF-alfa changes are causing Celiac disease which are consistent with related Celiac disease research. It shows how that method works.

Table 2.1: List of all Physiological Parameters related to Factors which Causing Celiac Disease Marked with "R" and Areas in Gray are where the Factors Intersect in Some Parameter. Areas Surrounded by Bold Frames are Final Disease-Causing Physiological Parameters which are part of Matrix Pm

Physiological Parameter s related to external factors	External Factors causing Celiac Disease						
	3+ respiratory infections in the first 6 months (1 cs) (2)	Gluten before 2 years (1 cs) (3)	Low IgA (2 cs) (4)	HLA-DQ2/ DQ8 common haplotypes (1cs) (5)	Iron supple-ments at 18 months (1cs) (6)	DDE, PFOS, perfluoro octanoic acid pesticides (2 cs) (7)	TNF-α -308G>A polymorphis m (AA+AG vs GG) (1cs) (8)
Gliadin		R					
glutenin		R					
alfa,beta, gamma,							
omega-gliading							
Rothia bacteria		R	R				
Staphylococcus epidermidis		R	R				
Bifidobacterium		R	R		R		
Alpha-gliadins 3 epitopes		R					
Trypsin		R					
Chymotrypsin		R					
Carboxype ptidase A , B enzyme		R					
Elastase		R					
IFN-Gamma	R	R					
IL-15		R					
IgA		R					
IgG		R					
IFN Type 1	R						
TFN -alfa increase	R					R	R
CD4+ T-cell	R	R					
Reovirus antibodies	R						
IRF-1	R						
Reovirus T1L	R						
IFN- beta	R						
Microbiota			R				
Proinflam matory IL-1beta,							
IL-6, TNF-alfa					R		
IL-8	R					R	
IL-6						R	

Overall according to the analysis done by a method explained above **Celiac disease is caused by simultaneous presence of these 6 physiological parameters changes beyond ~1 sigma interval** but due to lack of sufficient experimental data (regarding risk factors of Celiac disease, etc.) we could only determine 4 of them using the method:

- Bifidobacterium decrease, etc. in the intestine beyond 1-sigma
- Reduction of immunoglobulin IgA beyond 1-sigma (a homeostatic IgA)
- Genetic predisposition - HLA-DQ2/DQ8 common haplotypes
- TNF-alfa increase beyond 1-sigma
- Uknown yet
- Uknown yet

A Table 2.3 shows external factors which will cause Celiac disease if they are taken from each column and combined together. A combination of 6 factors from each column will cause Celiac disease in an individual. If the factors represent the 2 causes (means they are changing 2 physiological parameters beyond 1-sigma) then the number of factors can be less accordingly.

One of such set of factors causing Celiac disease is Iron supplements at 18 months (1cs) AND Low IgA (2 cs) AND **HLA-DQ2/DQ8 common haplotypes (1 cs) AND** 3+ respiratory infections in the first 6 months (1cs) AND Gluten consumption AND impact of PFOS pesticides (2cs). Another set is Gluten before 2 years (1cs) AND Low IgA(2cs) AND **HLA-DQ2/DQ8 common haplotypes AND** TNF-α -308G>A polymorphism (AA+AG vs GG) (1cs) AND Gluten consumption AND impact of PFOS pesticides (2cs). 1cs, 2cs stand for number of disease-causing physiological changes the particular factor impacts so they go beyond 1-sigma (slightly, less actually). Please note for simplicity we chose each factor from each column and in this case some total factors' power exceed 6 required as some factors have power of 2cs - mean they change 2 disease causing physiological parameters. There can be many other factors which combination could trigger Celiac disease but these factors will still impact this unique set of 6 disease causing physiological parameters. To trigger the Celiac disease at least one factor needs to impact each physiological parameters mentioned in the header of Table 2.3 so it goes beyond 1-sigma (slightly, less actually).

This table is built using a Table 2.2 for factors / parameters for a Celiac disease by creating columns for physiological parameters changes causing the disease and placing the factors found from former table to the new one in the column with the physiological parameters in which the factor either causing a change or related to the change.

Table 2.2: Short List of Physiological Parameters Found to be Causes of Celiac Disease and External Factors Impacting Them

External Factors	Physiological parameters which changes are causing Celiac Disease					
	Unknown physiological param 1	Unknown physiologi cal param 2	Bifidobacterium, etc	IgA reduction	HLA-DQ2/DQ8 common haplotypes	TNF-alfa increase
3+ respiratory infections in the first 6 months (1 cs)						x
Gluten before 2 years (1 cs)			x			
Low IgA (2 cs)			x	x		
Genetic predisposition (1 cs)					x	
Iron supplements at 18 months (1cs)			x			
DDE, PFOS, perfluorooctanoic acid pesticides (2 cs)						x
TNF-α -308G>A polymorphism (AA+AG vs GG) (1cs)						x

Note: the list of factors in Table 2.3 is obviously not complete and provided as per author's knowledge of specific research, other factors can be added in the future if new research finds them, etc. At the same time the future factors as the current ones will be related to the physiological parameters in the columns of the table as these parameters the real causes of a disease (the factors are only causing their change).

For example, a research shows that "Enterovirus and adenovirus infections were diagnosed by seroconversions in virus antibodies in longitudinally collected sera using EIA. **Enterovirus infections were more frequent in case children before the appearance of celiac disease-associated tissue transglutaminase autoantibodies** compared to the corresponding period in control children (**OR 6.3**, 95% CI 1.8–22.3; p = 0.005) "("Enterovirus Infections Are Associated With the Development of Celiac Disease in a Birth Cohort Study", Front. Immunol., Maarit Oikarinen, Leena Puustinen, Jussi Lehtonen, et al, 02 February 2021, https://doi.org/10.3389/fimmu.2020.604529). As we can see OR=6.3 and it means it is within a range of Disease-Causing criteria for OR 4.55 +/- 50% (2.27 - 6.81). So it means that *frequent Enterovirus infections in children is a disease-causing factor* for Celiac disease and it is changing 1 physiological parameter beyond 1-sigma. This parameter should be one of those 6 discovered. As we know now, it cannot cause a Celiac disease standalone but together with other 5 factors it must trigger it. The appropriate physiological parameter can be found using a set of already found physiological causes because all factors must change only this 6 physiological parameters. This can easily suggest that a potential candidate for this disease-causing physiological parameter could be TNF-alfa increase but the confirmation of this will be beyond the scope of this research. The important point here is that any other Disease-Causing factors should change these 6 unique disease-causing physiological changes beyond 1-sigma (slightly less, actually) so they coexist long enough in order to trigger Celiac disease.

Dual Role of Gluten in Celiac Disease Pathology

We have found 4 physiological causes of Celiac Disease using our method (MCMR) but the question is where is the role of gluten in this causation? We are going to discuss this here.

The modern research is well aware that gluten and more specifically its proteins gliadin / glutenin are the causes of Celiac disease. Our method also already found a gluten given before 2 years as a disease causation factor. Here is another study which was analyzing 1560 children and has stated: "The adjusted HRs for exposure to gluten at 0 to 3 months and 7 months or later (compared with 4-6 months) were 5.65 (95% CI, 1.19-26.78) and 2.39 (95% CI, 1.09-5.25) respectively, suggesting an increased risk of CDA for both early and late initial exposure to wheat, barley, and rye."("*Risk of Celiac Disease Autoimmunity and Timing of Gluten Introduction in the Diet of Infants at Increased Risk of Disease*", *Norris JM, Barriga K, Hoffenberg EJ, et al., JAMA*. 2005;293(19):2343–2351. doi:10.1001/jama.293.19.2343). From here we can see that HR = 5.65 and HR = 2.39 both within Disease Causation criteria for 1 physiological change - 4.55 +/- 50% (2.27 - 6.81). So this confirms that exposure to gluten at age 0-3 months or 7+ months is one of Celiac disease causation factors and this is consistent with current scientific evidence that gluten is a driving factor for Celiac disease.

The question is whether a gluten is a causation factor only or is it a disease-causing physiological parameter (see the Disease Causation Diagram - Figure 1) ? Let us suppose it is a factor. Now based on experience we know that there are many disease-causing factors which can affect the same physiological parameter (this method is using this property well and we've seen examples above). If a gluten is a factor than it can be replaced with other factor and the other factor can act on the same physiological parameter and cause a Celiac disease. But research shows if there is no gluten there is no triggering of Celiac Disease. Only introduction of gluten during Celiac disease remission (due to being on GFD) can trigger Celiac disease again, no other chemical compounds can do it. So there are no other factors to replace gluten [9,10]. It means **it is not a factor otherwise there would be at least a replacement of it so logically it is a physiological parameter**. In other words, if we state that there are many factors causing disease by acting on same disease Causing physiological parameter (which is based on experience is true) then gluten is not such a factor as there is no other factors which can replace gluten and cause the disease after the immune system has developed enough. So it means the gluten is a **disease-causing physiological parameter**.

Now we also know that Gluten given before 2 year (with enough doze) **is a factor** as it is impacting Bifidobacterium and other factors exist like Iron Supplementation before 18 years old which impacts same Bifidobacterium. We also know that gluten based on a disease causation criteria can act only on 1 disease causing physiological change to go beyond 1 sigma. This creates a conflict: how can Gluten be the factor in early childhood (2 years) in one case and the physiological parameter later if it can only change 1 disease causing physiological parameter? If a gluten was a factor which creates 2 physilogical disease's causes this would be possible (as we discussed in the beginning of article) but not if it creates 1 physiological cause.

The resolution of this conflict can be explained by timing: during early development gluten acts on undeveloped immune system as a factor and later it acts on more developed immune system as a physilogical parameter itself. Intestinal mucosal barrier is considered rather inadequate up to the second year of life [11]. The intestinal epithelial growth is intense during infancy, the transition to an adult-like bacterial microflora is incomplete before the third year. In other **words during early immune system development gluten is a factor which is causing a change in Bifidobacterim (and other factors can do the same) but during later immune system development it acts already as a unique disease-causing physiological parameter**, the one out of 6 causes of Celiac Disease and which should go beyond 1 sigma. So we observe a dual role of gluten in Celiac Disease causation mechanism: first it is a factor during early immune system development and second, it is a physiological parameter during later stages of immune development and when it becomes mature.

Because gluten is a physiological parameter once the immune system passes the certain development phase, we can add it to the list of physiological parameters and update our list. **The Celiac Disease is caused by combinations of 6 physiological changes beyond 1 sigma which present at the same time long enough** and one of these changes is a Gluten (gliadin / glutenin):

- Bifidobacterium decrease, etc. in the intestine beyond 1-sigma
- Reduction of immunoglobulin IgA beyond 1-sigma (this is a homeostatic IgA)
- Genetic predisposition - HLA-DQ2/DQ8 common haplotypes
- TNF-alfa increase beyond 1-sigma
- Gliadin / glutenin (Gluten)
- Unknown yet.

The 6th parameter is still yet unknown. To compensate for the missing parameter and demonstrate later hypothesis building process we will take a freedom to suggest that based on existing facts that 6nd unknown parameter could be (but not definite) **an intestinal permeability increase beyond 1 sigma**. The suggestion come from the fact that without the sufficient intestinal permeability it is practically impossible for gluten to reach lamina propria layer of intestine and be processed by transglutaminase and further be presented by Antigen Presenting Cells (APC) to CD4+ T lymphocytes. We can update the table 2.3 now with Gluten and a proposed intestinal permeability.

A Room for an Error

So far, we determined 6 physiological parameters changes beyond 1-sigma which must cause Celiac disease if they are taking place the same time long enough. From a practical perspective it gives us a room for an error in determination of these parameters. The disease cannot start unless 6 of them changed so if we determined 1 parameter incorrectly but 5 others correctly, we still should be able to prevent the disease by controlling these 5 (exempt genetics) physiological parameters to be within 1-sigma interval. We also should be able to use these 5 parameters to treat or possibly even cure a disease in early stages. But the success of it is not guaranteed as the disease already triggered and depends on the number of damages done, etc. For Celiac disease we are actually unknowingly following this strategy in practice by putting people on a Gluten Free Diet (GFD) and this way are removing one of 6 physiological causes which are triggering the disease and we get quite a good rate of success.

Celiac Disease Causation Diagram

Knowing the disease-causing physiological parameters and disease-causing factors acting on them we can create a Celiac Disease causation diagram. On the Celiac Disease causation diagram (Figure 2) we can see how multiple and different factors affect the same physiological parameter. All 6 physiological changes as we showed before are required to cause Celiac disease. We can see how factors as "gluten consumption before 2-year age" and "Iron supplements at 18 months" impact the Bifidobacterium levels. We can see that "3 and more respiratory infections" and "TNF Alfa polymorphism(AA+AG vs GG)" factors are impacting

changes in TNF alfa so it increases above 1-sigma (slightly less, actually required). Please note the factors have strength: **mostly factors impact only 1 physiological parameter** so it goes beyond 1-sigma approximately but more rarely **the factors have strength to impact 2 physiological parameters** as PFOS pesticides - they affect TNF alfa and affect the intestine tight junctions (intestinal permeability) . The fact that most factors can only impact 1 physiological parameter explains why Celiac Disease disease is still quite rare despite wide spread of genetic predisposition (HLA-DQ2/DQ8 common haplotypes). For example, in general Danish population, 47.7% were HLA DQ2/DQ8 positive and thus potentially at risk for CD ("*The distribution of HLA DQ2 and DQ8 haplotypes and their association with health indicators in a general Danish population.", Kårhus, L., Thuesen, B., Skaaby, T.,et al, (2018). United European Gastroenterology Journal, 6(6), 866–878*. https://doi.org/10.1177/2050640618765506) If the factor existed which was strong to affect all 6 causes (lucky, it does not exist for now !) we had an incidence rate of Celiac disease compared likely with a flu rate during flu epidemic (as we know flu is caused by 1 factor - 1 flu virus).

We have to stress here that once all 6 physiological changes of Celiac disease exist long enough the disease must start it is not optional. Once the disease has started **placing back the physiological parameter within 1-sigma not always will cure the disease** as the triggering of disease is launching a complex set of damaging processes (which depend on the specific non-infectious disease) and in this case we might need to take care of the consequences of the disease triggering and fix the damages as well in order to cure the disease. The success of curing the disease by placing back the physiological changes within 1-sigma will depend on the timing. The earlier it happened the better, the less damages has occurred. The more disease-causing physiological changes we placed back within 1-sigma the more chance of success as we restore the additional layer of natural protection and we take care indirectly of physiological functions which can help to restore mechanism which was preventing the disease originally.

Hypothesis of Celiac Disease Pathology

The method presented in this article allows not only find physiological disease causes of non-infectious disease but also allows methodically build a strong hypothesis of disease pathology. As we saw the method allows to find physiological changes required and coexisting during the triggering of non-infectious disease. Knowing them and having knowledge on biochemistry, physiology, etc from existing research it is possible to connect these physiological causes in such a way which clearly shows how the disease gets triggered. As the base of the hypothesis is built upon found disease causes the hypothesis found is highly likely to be correct or quite close to be correct. In this work we determined 5 disease causing physiological changes out of 6. The disease-causing factors, such as gluten and HLA-DQ2/DQ8 common haplotype are already well known to medicine (and the method confirmed them as a causation factor/parameter as well). To compensate the missing 6th parameter and demonstrate hypothesis building we will take a freedom to suggest based on the evidence it is an intestinal permeability increase beyond 1 sigma for a reasons we explained above in **"Dual Role of Gluten in Celiac Disease Pathology"** section. Of course this makes this hypothesis weaker as this 6th factor is not actually determined via a method.

As we already determined that a coexistence of Bifidobacterium reduction (beyond 1-sigma), IgA reduction (beyond 1-sigma), TNF alfa increase (beyond 1-sigma), HLA-DQ2/DQ8 common haplotype, and gliadin/glutenins and Increased intestinal permeability (beyond 1-sigma) would cause the Celiac disease if co-exists long enough we can connect this causes together using existing research.

The existing research shows that **reduction of Bifidobatcterium reduces the IgA levels** [18]. It also known the IgA plays a significant role in innate immune system response to non-commensal bacteria and supports **bacterial homeostasis in intestine** [19]. Reduction of IgA can lead to overgrowth of non-commensal bacteria in intestine. Gram-negative pathogens produce **LPS which can damage Tight Junction** (TJ) in intestine and increase intestinal permeability. The **increased intestinal permeability** allows gliadin/glutenins to reach lamina propria layer of intestine and creates immune reaction once presented with APC. The activated CD4+ T cells increase **TNF alfa** which is known [20] **to increase intestinal permeability**.

At the same time an increase in **intestinal permeability allows propagation of antigens** of different origin from the intestine to lamina propria and **induces more TNF alfa** production as a result. Also the **Bifidobacterium reduction** is causing **an increased level of TNF alfa** as well [12]. Now we connect our 6-disease causing physiological parameters with interactions we described here. All this connections are shown on Hypothesis of Celiac Disease diagram (Figure 2). This way we get a final hypothesis of Celiac disease. Please note the all-disease causation physiological parameter are already shifted beyond 1-sigma by external disease-causing factors which we discovered earlier in this work and the hypothesis explains what happens after this triggering condition of the disease has been reached.

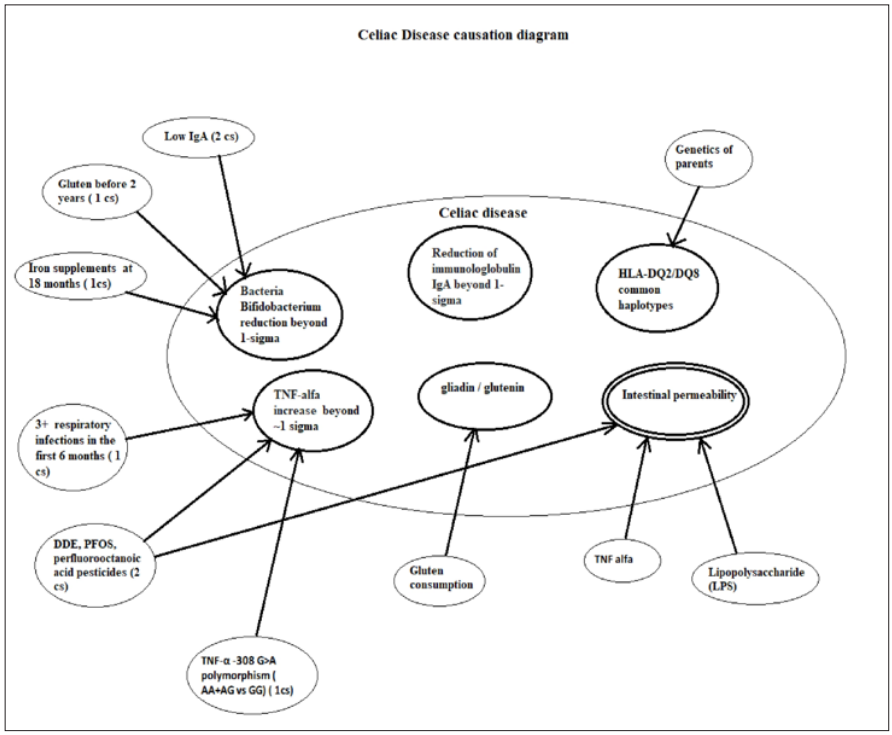


Figure 2: Celiac Disease Causation Diagram (=== - proposed parameter based on existing medical evidence, 1cs / 2cs - factor is impacting 1 or 2 physiological changes beyond 1 sigma)

Hypothesis of Celiac disease states (Figure 3): **A decreased beyond 1-sigma Bifidobacterium level is causing a decrease of IgA** (already decreased beyond 1 sigma level) **which leads to an increase of a permeability of intestine** (already increased beyond 1-sigma) **at least via non-commensal bacteria's LPS acting. This increase of permeability is growing more due to already increased beyond 1-sigma TNF alfa levels acting on it and allows gluten to reach lamina propria where the antigen presenting cells (APC) which are having HLA-DQ2/DQ8** (as part of MHC Class II receptor due to high affinity (**beyond 1-sigma**) to gluten peptides) **trigger CD4+ T cell induced inflammational process and this process increases the TNF alfa level even higher which in turn increases intestinal permeability more. This increase creates a positive and due to this self-supporting feedback loop by increasing the TNF alfa more**. This creates a kind of a vicious cycle: the more permeability the more TNF alfa production the more permeability. This is launching strong inflammation process observed in Celiac disease and is creating the large number of antigen out of gluten peptides by deamidation with transglutaminase.

We have demonstrated how the knowledge of 6 coexisting causes of Celiac disease and existing medical research helps us to build a hypothesis of non-infectious disease and in this case specifically the Celiac disease. As such a hypothesis is based on multiple physiological causes found with our *mathematically* based method and so we can treat them as a fact the chance of a hypothesis being built on the facts becomes higher. This hypothesis describes the mechanism of Celiac disease pathology long before the symptoms has started and IgA level (specifically tTG-IgA) while it is observed as high in many of Celiac patients during the active form of disease was normal before its triggering. The IgA levels (homeostatic IgA) in 1–2-year-old child are within range of **30–120 mg/dL**. (https://www.exeterlaboratory.com/test/immunoglobulins-iga-igg-igm/). When IgA in such a child reduces approximately below 52.5 mg/d it will be one of physiological changes required to cause Celiac disease. It will not cause Celiac disease as the other 5 physiological changes beyond 1-sigma required. This IgA level is not in any way IgA deficiency obviously. Currently we would consider this change as a norm so it gets unnoticed and ignored as cause of Celiac disease.

A non-infectious disease does not start from a non-normal physiological changes it starts when all physiological changes go beyond 1-sigma and coexist long enough. Celiac disease causation resembles a "padlock" with 6 numbered **scroll wheels**. which should be placed in a correct unique position for a long enough so it can be "unlocked" and thus the Celiac disease could only start. One-dimensional clinical trial cannot notice this as changing IgA, as example, will not cause the Celiac disease.

Now, out this hypothesis we can see that removal of the gluten reduces production of auto-antigen but it does not necessary stops the TNF-Alfa / Intestinal permeability positive feedback which is still also supported by lower than 1 sigma Bifidobacterium levels... This could be a potentially another reason why the approximately 30% of patients on gluten free diet still experiencing Celiac disease symptoms (non-responsive Celiac disease) .

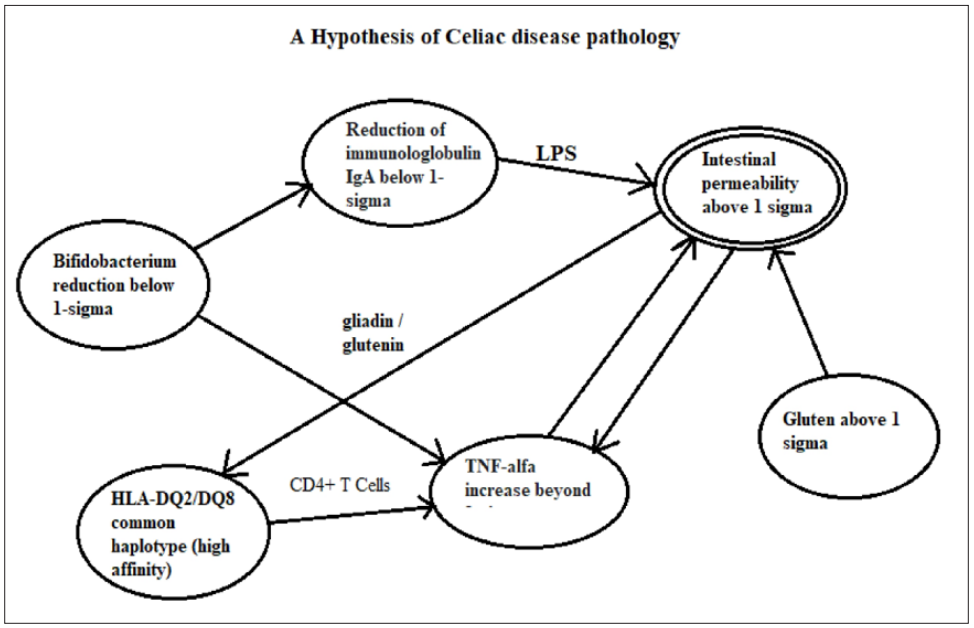


Figure 3: Hypothesis of Celiac Disease: === is proposed causation parameter

Principle of Indifference

As we discuss a method to find disease causes via experiments, we are proposing to use a simple principle which can be observed in physiological processes. **When regulating its own homeostasis separate physiological systems of the body are indifferent to the side effects of this regulation**. We can call this *a principle of indifference*.

We can observe this principle in multiple cases. For example, if a brain needs to increase a blood pressure to improve a supply of nutrients and oxygen it is *indifferent* to the fact that a heart may not be able to sustain this high blood pressure.

Another example could be this. If an intestine is trying to regulate its homeostatis of bacteria it can pass the signals to the brain via different biochemical pathways to reduce appetite so in this case an intestine is indifferent to that its actions can eliminate some source of energy and needed nutrients to the brain and other systems and worsen their functioning.

This principle allows to explain that supporting a homeostasis in one physiological system of the body can and often does harm functioning of other systems and this way it can cause a non-infectious diseases. If we find a physiological system which is regulating its homeostasis with extreme steps and help it to fix the problems, we can address a non-infectious disease of another physiological system which can be caused by this indifference.

Results and Discussion

We introduced a mathematically based method how to find a non-infectious disease causes using a multiple researches which give estimates of risks (RR/OR) for different factors in regards to the same specific non-infectious disease. This method is a method of combining multiple research to find non-infections disease causes (MCMR). Method starts with finding a ***number of disease causes using a formula*** (1.0) when we know a rate of this non-infectious disease in a population (often we use an incidence rate for this to see annual probability of the disease).According to the method, once the risk factors were found using ***disease causation criteria provided above***, we need to find out physiological parameters which are changed when these factors are present.

Once we list all disease-causing factors vertically and physiological parameters related to them horizontally (or vice versa) we mark the relationship between related factors and physiological parameters changed with a letter “R”. Then we find so called intersections between 2 factors - the places where 2 or more different factors are having same physiological parameters marked as related with letter “R”. The parameter is same by name (not by value).

Table 2.3: External Factors Which are Causing the Celiac Disease. Any Factor Combination taken from all Different Columns Should Cause a Celiac Disease. Header: Physiological Parameters Changed Beyond 1-Sigma (Slightly Less Actually) 1cs - Factor Impacts 1 Physiological Cause, etc.

Bifidobacterium, etc.	IgA reduction	HLA-DQ2/DQ8 common haplotypes	TNF-alfa increase	Gliadin / glutenin (Gluten)	Intestinal permeability increase (proposed ONLY !)
Iron supplements at 18 months (1cs)	Low IgA (2 cs)	genetic predisposition(1 cs)	3+ respiratory infections in the first 6 months (1 cs)	The ingestion of wheat, rye, barley, and likely oat products	PFOS pesticides (2cs)
Gluten before 2 years (1 cs)			DDE, PFOS, perfluorooctanoic acid pesticides (2cs)		
Low IgA (2cs)			TNF-α -308G>A polymorphism (AA+AG vs GG) (1cs)		

We mark the column in gray or other color to indicate an intersection. We need to find all intersections like this. The physiological parameters where intersection are happening, we list as matrix **Pm**. This list or matrix **Pm** is a superset of the physiological parameters changes which are causing a disease if their changes go beyond 1-sigma interval (actually, slightly less than this interval) and are present at the same time.

We eliminate the redundant parameters from this matrix **Pm** by using *few rules of elimination* and following a recommended algorithm if the count of parameters found exceeds the count determined by formula (1.0) calculating the number of disease causes or if a strict rule that a factor should cause only 1 change(or as determined by Disease Causation criteria) is broken.

One of these elimination rules is to check if the factors where intersection happens are related to each other (for example the same type of disease, or similar experiment like BMI and weight impact on disease, etc) and ignore the intersection for this factors as they are likely due to similarity. Another rule is to check if the physiological parameters for the same factors are related and this causing a change in 2 parameters for the same factor as one valid parameter is changing a dependent one. The dependent parameter need be eliminated from matrix Pm. Remember that most factors in practice are impacting only 1 physiological parameter change which is causing a disease. If we see a factor with 1 calculated impact is found to be causing 2 or more changes in physiological parameters in our table then the redundant physiological parameters need to be eliminated using the elimination rules.

Once the redundant parameters were eliminated, we can check the final list of physiological parameters or matrix Pm using our criteria for disease causing factors (provided above for your reference) if there is an appropriate research regarding risks of these physiological parameters for the disease and confirm that we did not make any errors in steps of the described method. Also, we can use a related research regarding these found physiological parameters to see significance of their impact on the disease and this way to confirm the significance of the found physiological parameters found via the described method. In other words the method allows a verification of its results using a different studies, not used in the processing by the method.

As example of method's application we analyzed a Celiac disease. We determined that **Celiac disease happens due to 6 physiological parameters changes** beyond 1-sigma interval according to the method and a mathematical model it is using. We determined that **the physiological parameters which are causing Celiac disease are:**

- Bacteria Bifidobacterium decrease, etc. in the intestine beyond ~1 sigma
- Reduction of immunoglobulin IgA beyond ~1 sigma (this is a homeostatic IgA)
- Genetic predisposition - HLA-DQ2/DQ8 common haplotypes
- TNF-alfa increase beyond ~1 sigma
- Gliadin / glutenin (Gluten)
- Increased intestinal permeability beyond 1-sigma (proposed based on existing evidence)

The decreased beyond 1-sigma IgA here is a homeostatic IgA and it is *not* transglutaminase IgA (tTG-IgA). We are looking here at the moment of Celiac disease triggering. The disease has no started yet to increase transglutaminase IgA. HLA-DQ2/DQ8 common haplotypes is here more like a practical "representation" of disease-causing physiological parameter which must be unique (see Generic Disease Causation Diagram figure 1). These both haplotypes are 2 factors which are causing a change in this physiological parameter which according to research by Moustakas A.K, et al could be a high above 1-sigma affinity to gluten [13]. This is an important difference as we cannot easily change genetics but we could possibly chemically change the affinity to gluten in those having these haplotypes in order to treat Celiac disease.

By controlling 5 of these unique disease-causing physiological parameters (we cannot control genetics) we can prevent Celiac disease in an individual or possibly cure it (if a disease in early stages) or treat it. If all the required physiological parameters changes take place at the same time the **Celiac disease *must*** start after some time (we can estimate it as within 10-12 months based on gluten reintroduction research) [9,10]) unless they are taken under control by forcing them to be within 1-sigma interval. The **triggering of the disease if causation conditions are satisfied is not optional**. It is a must. The analogy of this process could be an electrical fuse in a house. We know that if we plug in an electrical iron, air conditioner, etc. and exceed the threshold for the fuse the fuse will burn out. The fuse must burn out, it is not optional. The only random facts here are the electrical appliances which will cause it, these electrical appliances are an analogy of factors causing diseases here. We can have different external

factors causing a non-infectious disease but as long as they impact the all required physiological parameters a "fuse" of the body will burn out and the disease will start.

The research also discovered some disease-causing factors for Celiac disease (see Table 2.3).Celiac disease according to Table 2.3 can be caused by multiple combination of factors chosen from each column of this table. One of such set of factors could be Iron supplements at 18 months (1cs) AND Low IgA (2 cs) AND **HLA-DQ2/DQ8 common haplotypes (1 cs) AND 3+** respiratory infections in the first 6 months (1cs) AND Gluten consumption AND impact of PFOS pesticides (2cs). Another disease-causing set is Gluten before 2 years (1cs) AND Low IgA(2cs) AND **HLA-DQ2/DQ8 common haplotypes AND** TNF-α -308G>A polymorphism (AA+AG vs GG) (1cs) AND Gluten consumption AND impact of PFOS pesticides (2cs). 1cs, 2cs stand for numbers of disease-causing physiological changes the particular factor impacts so they go beyond 1-sigma (slightly, less actually).

We have also stressed that once the non-infectious disease has started **placing back the physiological parameter within 1-sigma will not always cure the disease** as the triggering of disease is launching a complex set of damaging processes (which depend on the specific non-infectious disease) and in this case we might need to take care of the consequences of the triggering and fix the damages as well to cure the disease. The success of curing the disease by placing back the physiological changes within 1-sigma will depend on the timing. The earlier it happened the better, the less damages has occurred. This fact can explain why we have cases of Nonresponsive and Refractory Celiac Disease **after patients placed on GFD**.

The more disease-causing physiological changes we placed back within 1-sigma the more chance of success as we restore the additional layer of natural protection and we take care indirectly of physiological functions which can help to restore mechanism which was preventing the disease.

Now, we need to notice that when we say the factors are causing a physiological change which trigger the non-infectious disease and, in our case, a Celiac disease this causation is in some cases is **logical not a physical causation**. Logical causation means that the presence of this factor means the presence of physiological change required (important, not a correlation but as a fact) but it is not always the same as physical causation where the factor directly or indirectly causing biochemical change. If we state that if there is **A** condition means there is **B** condition it does not always mean that A causes B. What important for us is that A and B conditions **coexist**.

We need to notice here that multiple medical researches **often find risk factors for a specific disease which have values close to RR/OR = 4.6 or RR/OR = 20.6**. These are not just a statistically significant risks but these numbers indicate that 1) the **factors are really disease-causing factors** 2) the factors are **causing a change in 1 physiological parameter beyond 1-sigma** (for RR/OR = 4.6) or **2 physiological parameters beyond 1-sigma** (for RR/OR = 20.6). Examples of these cases were shown in this article for gluten or pesticides researches for Celiac disease. In some rare cases the risk factors can have **RR/OR=93**+/-50% and this means the disease-causing factors are impacting 3 **physiological parameters beyond 1-sigma**. The disease causation criteria provided in article "*A Connection between Factors Causing Diseases and Diseases Frequencies: Its Application in Finding Disease Causes*" (*Alan Olan*, Journal of Clinical Trials, Vol.13, Issue 4) allows to determine more precisely if the risk factors are causing a disease or not and allows to expand validity for these risks beyond the 2 examples of RR/OR above. The referred article is using a risk factor **K** but it is easily converted for RR/OR as **RR = K + 1** (same for OR) and the RR/OR can be used as the theoretical values for RR/OR +/-50%. A short reference of these criteria was provided in this article as well.

In this article we have shown that **disease causation factors can be separated into few groups** according to a physiological parameter they change beyond 1-sigma. **Any combination of factors** taken as one from each of these groups **must cause a non-infectious disease** (one example is Table 2.3 for Celiac disease). For example "Iron Supplementation at 18 month"(1cs) factor AND "Low IgA"(2cs) AND "TNF alfa AA+AG polymorphism"(1cs) + "HLA-DQ2/DQ8 common haplotypes"(1cs) AND Gluten AND Gluten consumption AND impact of PFOS pesticides (2cs) *must* trigger the Celiac disease after some time. Please note that the factors are having a symbolic name and for their precise meaning refer to the research citation provided in this article.

In this research we also showed that **method of combining multiple researches (MCMR)** we used to analyze Celiac disease also allows to build a strong hypothesis of non-infectious disease pathology by connecting the found disease-causing physiological changes with known biochemical and physiological interactions between them. As example we have created a Celiac disease pathology hypothesis which states:

A decreased beyond 1-sigma Bifidobacterium level is causing a decrease of IgA (already decreased beyond 1 sigma level) **which leads to an increase of a permeability of intestine** (already increased beyond 1-sigma) **at least via non-commensal bacteria's LPS acting. This increase of permeability is growing more due to already increased beyond 1-sigma TNF alfa levels acting on it and allows gluten to reach lamina propria where the antigen presenting cells (APC) which are having HLA-DQ2/DQ8** (as part of MHC Class II receptor due to high affinity (**beyond 1-sigma**) to gluten peptides) **triggers CD4+ T cell induced inflammational process and this process increases the TNF alfa level even higher which in turn increases intestine permeability more. This increase creates a positive and due to this self-supporting feedback loop by increasing the TNF alfa more**. This creates a kind of a vicious cycle: the more permeability the more TNF alfa production the more intestinal permeability increase. If this hypothesis is correct this **positive self-supporting feedback loop is likely the cause of non-responsive Celiac** Disease as the removal of Gluten is not destroying this loop and the intestine continues to get damaged.

We also have introduced **a principle of indifference** which we find as a useful tool in understanding of disease causes as well. The principle of indifference states: **when regulating its own homeostasis separate physiological systems of the body are indifferent to the side effects of this regulation**.

The principle allows to understand that human body is not a perfect creation where every system absolutely works in harmony with others but a set of physiological systems where homeostatis regulation of one does not care of effect (possible negative) this regulation has on other physiological systems and this way can create changes of physiological parameters so they go beyond 1-sigma and can be part of disease causation physiological set.

As we discussed a non-infectious disease always has a minimum 2 physiological causes which triggers it and then it develops and modifies other physiological parameters creating an enormous complexity which the modern research is observing but the triggering point of the disease is just 2 to 6 physiological changes... The analogy of this could be a button on the TV set - once you press it all the complexity of modern TV technology takes place ! If we don't need the TV to be ON, we usually do not press the button, we are not looking to find how complex the internal working of it unnecessary... The introduced method is basically allowing to find this "button" for the non-infectious disease.

There will be definitely a question of how to additionally validate the result of this research via clinical trials? Unfortunately at this time we may have a difficulty doing this as the clinical trials in majority of cases are one dimensional - we modify one parameter while other we are trying to keep the same. As this mathematically based method showed that the non-infectious disease require multiple physiological changes coexisting and Celiac disease in particular has 6 physiological causes this would require a special mechanism of clinical trials so we can observe 6 physiological changes at the same time. A classical clinical trial where we would observe one physiological change required for Celiac would just give us a risk but cannot show the triggering of the disease.

The nature has already made a multidimensional trial for us - HLA-DQ2/DQ8 common haplotypes which about 30% of population has is required physiological parameter but we do know this is not enough to cause the Celiac disease without 2nd dimension - gluten. The model our method is based on states that a non-infectious disease requires at least 2 disease causing physiological changes which coexist long enough for its triggering. In this sense the Celiac disease is quite a good example how the disease triggering of non-infectious disease is working: it clearly shows that we need to have at least **HLA-DQ2/DQ8 common haplotypes** (affinity beyond 1-sigma) **AND gluten** and even in this case only about 1% of population is sick with Celiac and not 30% as we would expect if the 30% of population is having HLA-DQ2/DQ8 common haplotypes and unknowingly consumes gluten. The part we were missing are those 4 other physiological causes which we have discovered using the method or proposed in this research.

The Celiac disease this way can give us a clear example of how other non-infectious disease are following the same pattern: **all of them require a combination** of disease-causing physiological changes beyond 1-sigma which must coexist long enough.

Conclusion

In this article we have showed how a research which estimate a risk of non-infectious disease can be used to determine disease cause as a set of disease-causing physiological parameters changes beyond 1-sigma (actually, slightly less than this interval). We showed how to determine which disease-causing physiological parameter is impacted by specific disease-causing external factors. It was shown how certain different combinations of external disease-causing factors can cause a non-infectious disease if they act together and coexist long enough and how to determine these disease-causing factors combinations.

The application of the method presented here has shown that Celiac disease has total 6 coexisting physiological causes which trigger it and that a gluten and genetic predisposition are just two of these six physiological causes. There can be many combination of factors which make these physiological changes and this creates an effect of random causation and its high complexity while underlying cause of Celiac disease is always the same unique set of 6 coexisting physiological changes beyond 1-sigma.

Overall a method presented here allows to increase efficiency of existing medical research in finding non-infectious disease causes and also stresses that non-infectious disease is having a multi-factorial coexisting causes. These causes are multiple physiological parameters changes beyond 1-sigma coexisting at the same time and happening due to actions of external disease-causing factors.

Disclaimer

This work is not intended to be used in diagnosing and treatment of any disease in any patient, those actions should be done by qualified professionals only. The work is intended as a reference for the researchers only. The author is not responsible for any issues created by unintentional usage or consequences of this work.

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Appendix

Analogy to Clarify a Method

A simplified analogy which explains why we looking for a match between physiological parameters could be this.
Imagine a large town. We observe it from the top. A person arrives to downtown for some personal business on a regular day. How likely this person meets *a friend* or colleague in a totally random place of the downtowns. Very unlikely. We observe this person is going to downtown for few days to different places and he never meets a friend or a colleague.

Now, we observe from the top that some rare folks meet someone in downtown often and sometime in the same location. We know **there is a pattern explaining these meetings**, they are not random in most cases. There might be someone they have agreed to meet with before (a colleague they travel together with, a friend, etc.). If we find these folks meeting, we know we found very likely some pattern.

In this analogy, we can treat a downtown as a human body, a person arriving to downtown as a physiological parameter change caused by some disease-causing factor. People which meet each other in the downtown are an analogy of physiological parameters which "meet up" as they cause a disease and not just a random meeting. If we find those folks who meet up we know there is some cause there. In the method presented, these "meetings" between physiological parameters are represented by "intersections".

Mathematical Foundation of the Method

Here we will go into a mathematical foundation of the method in details. Let's look at the simple case of a disease where it was prior determined via experiments that multiple factors are

causing changes in only 2 physiological parameters of human body (parameters further).

Let the factors be **F1, F2, ... Fn** and the parameters be **C1, C2**. Now, let's look at the case where *F1, F2,..., Fn factors separately causing **only 1*** change in physiological parameters either C1 or C2 beyond 1-sigma (this actually often takes place in practice). That means that only C1 or C2 changes by some factor Fj (j E {1,2,..n }). Let's **P1**, ..., **Pn**, where n > 2 be *the sets of all physiological parameters which are related to factors F1, F2, Fn* accordingly. For example, P1: { r12, r15, r29, 43 }, P2: { r15, r28, r34, r89, r34, r12, r98 }, etc.

Let's look at standalone factor **Fj**. As we know, a factor **Fj** (where *j is some integer from 1 to n*) impacts the specific physiological parameters either **C1** or **C2** then we know that this params C1 or C2 should be part of its set of **Pj** as **it contains ALL the related to Fj parameters (a complete set)**. *Let's take a factor F1 such that its set P1 contains C1, and choose some F2 such that its set P2 contains C2 (it is possible as we know factors impact either C1 or C2), then if we choose any other factor as F3 then its set of P3 must contain either C1 or C2 (as F3 also impacts these physiological parameters - either C1 or C2 and P3 is a complete set). If P3 contains C1 then it intersects with P1. If P3 contains a C2 it intersects with P2. So **P3 must intersect with either P1 or P2 (either in C1 or C2).** In similar way we can apply this to P4, P5, Pn. So this brings us to conclusion that **a set of physiological parameters Pn, where n > 2 must intersect with either P1 or P2 either in C1 or C2**. This means parameters Pn intersect with each other either in C1 or C2. We can see representation of this set's behavior on the figure 4. **All sets Pj, Pk,... matching to Fj, Fk,.. on the figure 1 are crossing and only in C1 or C2 but not both**.*

We don't know the values of C1 and C2 but if *we can find where parameters Pn intersects with each other we can determine **a subset** of physiological parameters **Pm***: { Ry, Rx, Rz, , Rt } which contains values of C1 and C2. This subset of Pm will be much smaller than set of all possible params included in P1, P2, . Pn (as it is a subset and similarities in params of P1, Pn are not very probable and that is addressed below) but may contain more than 2 parameters and *only 2 parameters of this subset **Pm*** can be real physiological parameters causing a disease as they are C1 and C2.

In order to eliminate the incorrect parameters from subset **Pm** we need to notice:

- That the params C1 or C2 should ***be such so all P1, P2, ..., Pn intersect in them*** and if some parameters of Pm: { Ry, Rx, Rz, Rt } don't fit this rule *their need to be eliminated*. Practically it means this. We take random (or using a common sense) a combination of some 2 parameters **Rk** and **Rm** from a set of **Pm** *and check if the P1, ... P2 all intersect in them if not then the Rk and Rm combination is not a valid set of C1, C2 and we may need to check another set of 2 parameters **Rk** and **Rg***
- if some parameter of set **Pm**: { Ry, Rx, Rz, Rt } ***is known as not changed beyond 1-sigma it should be eliminated*** as disease is caused by change in param beyond 1-sigma (as per our model).
- if some parameter of **Pm**: { Ry, Rx, Rz, Rt } ***is causing some set Pn intersect 2 times with some other set Pk then it should be eliminated*** as factors F1, F2, . Fn can *only* impact 1 physiological parameter in this case and cannot impact / intersect 2 or more due to this.

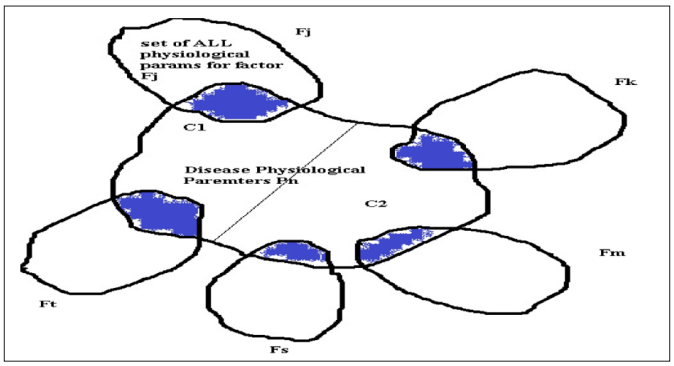


Figure 4: (Blue areas are area where Pj, Pk, etc. for factors Fj, Fk, etc. intersect with a set of physiological parameters C1, C2 which are part of set Pn and which are causing disease)

The method above was described for a case of factors F1, ..., Fn impacting only 2 parameters but it can be extended to 3 and more parameters.

How Likely are Random Matches Between Physiological Parameters?

As we discussed above the set of physiological parameters Pm: { Ry, Rx, Rz,.. , Rt } where we observe intersections may contain more parameters then needed (more than 2 in our case and due to other reasons). We need to be concerned with a question such as if we find one intersection of sets P1 and P2 in a physiological parameter belonging to 2 different external factors how likely it can be a random intersection? To answer this question let's formulate the problem mathematically.

Let's have a set A of integers from k = 1 to very large N. Let's randomly select n numbers in set of P1 = {Ak, Ag, .., At } and then randomly select n numbers into set P2 = { Af, As, ... Al } from our original set A (k= 1 to N) such that each element repeats only once in set P1 and only once in P2 (it is a unique element to sets P1, P2). For example, if we chose a number 3 as part of the set P1 then it only exists one time in the set P1. What is a probability that we find element **Ai** in set P1 and P2 ?

To answer this question let's do next steps. Let's limit set A by some top element enumerated by t (so set is not infinite).

- We can take **n** elements from **t** elements of set A with number ways **tCn**
- Number of ways to take **n** elements with an element Ai equals the number of ways to select **n-1** elements (we exclude Ai) from **t -1** (set of **A** elements) and is **t-1Cn-1**
- Then probability to take **n** elements which include element **Ai** in set P1 (or P2) is P(Ai E Psel) = **t-1Cn-1** / **tCn**, where Psel is P1 or P2 sets
- The probability that element Ai will be in P1 and P2 is P (Ai E P1 and Ai E P2) = P (Ai E P1) * P (Ai E P2) as events independent.
- So probability P (Ai E P1 and Ai E P2) = P (Ai E P1) * P (Ai E P2) = (**t-1Cn-1 / tCn) ^ 2**
- Or finally, the probability that element Ai will be in P1 and P2 is P (Ai E P1 and Ai E P2) = (**t-1Cn-1 / tCn) ^ 2**

Using a formula above let's calculate a probability of match in element Ai if we take randomly elements from a sequence of numbers from 1 to 1000 (t = 1000, assuming so many physiological parameters exist) and take only n = 10 element into sets P1 and P2 accordingly. P(Ai E P1) = $_{999}C_9$ / $_{1000}C_{10}$ = (2.63 * 10^21) /(2.63 * 10^23) = 1 / 10^2 = 0.01 the same is fare for P(Ai E P2) = 0.01 and so the probability of getting element Ai in sets P1 and P2 is

(t-1Cn-1 / tCn) ^ 2 = 0.01 ^ 2 = 0.0001

This is a probability of random match. **The probability of non-random match is 1 - P (Ai E P1 and Ai E P2) = 1** - 0.0001 = 0.9999 ~= 1 so very close to 1. It means ***if we see a match between set P1 and set P2 in some element Ai it extremely likely it is not random***. This is an important conclusion. The only matches we find practically are not random but are caused by some reason and in our case, it is due to same physiological parameter impacted by 2 different factors. We need to notice that number of parameters actually much more as most agree that there are around 20,000 different proteins in our body and each is a potential physiological parameter. So the probability of the match selecting 10 of 20,000 will be much smaller!

In practice there are about over **t=150** physiological parameters known to medicine and for a single factor we usually find about n=30 related parameters. Doing calculations for this case we get P(Ai E P1) = $_{149}C_{29}$ / $_{150}C_{30}$ = (6.43 * 10^30) /(3.2 * 10^31) = 0,2 and so the probability of getting element Ai in sets P1 and P2 is

(t-1Cn-1 / tCn) ^ 2 = (0.2)^2 = 0.04

We see the probability of random match is higher in practice (4%) and so in practice we can see more random matches. The probability of at least one random match will also increase as we find intersections for dozens of different causation factors.

This random matches still can be eliminated with methods described in this article by applying other restrictive conditions, including using our criteria for disease causes.

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