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**Unifying diseases from a genetic point of view: the example of the genetic theory of infectious diseases**

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**Abstract:** In the contemporary biomedical literature, every disease is considered genetic. This extension of the concept of genetic disease is usually interpreted either in a trivial sense or in a genocentrist one, but it is never taken seriously as the expression of a genetic theory of disease. However, a group of French researchers defend the idea of a genetic theory of infectious diseases. By identifying four common genetic mechanisms (Mendelian predisposition to multiple infections, Mendelian predisposition to one infection, major gene and polygenic predisposition), they attempt to unify infectious diseases from a genetic point of view. In this article, we will analyze this explicit example of a genetic theory relying on mechanisms and applied only to a specific category of diseases, what we call “a regional genetic theory”. We have three aims: to prove that a genetic theory of disease can be devoid of genocentrism, to consider the possibility of a genetic theory applied to every disease and to introduce two hypotheses about the form that such a genetic theory could take by distinguishing between a genetic theory of diseases and a genetic theory of Disease. Finally, we suggest that network medicine could be an interesting framework for a genetic theory of Disease.

**Keywords:** *Geneticization. Genetic disease. Genocentrism. Causal Selection. Disease mechanisms. Disease explanation. Disease theory.*

## **Introduction**

The concept of genetic disease has gone through several shifts [1-2]. In the 1960s, a paradigmatic example of genetic disease was phenylketonuria, a rare, monogenic Mendelian, hereditary disorder, for which the equation one mutation-one gene-one phenotype was explicitly assumed. But the following years

witnessed three major changes resulting in the collapse of this model. First, the core of the concept of monogenic Mendelian disease [3] was called into question by different scientific discoveries such as allelic heterogeneity (several allelic mutations of the same locus can cause the disease), locus heterogeneity (several genes can cause the same disease) and modifier genes [4] (most monogenic disorders are also influenced by the intervention of other genes). Secondly, there has been an increasing interest in the genetics of common, non-hereditary and polygenic disorders such as cancer or diabetes. Finally, the development of bioinformatics and rapid DNA sequencing techniques, such as recombinant DNA technology, sequencing by hybridization and whole-genome sequencing, together with “big science” projects such as the Human Genome Project, has led to an extraordinary upsurge of genetic data and of gene-disease correlations. So, while the concept of genetic disease originally designated a very restricted class of rare, Mendelian, hereditary, monogenic disorders, it nowadays encompasses common, non-Mendelian, non-hereditary polygenic disorders to the point where every disease seems to be genetic. Abby Lippman [5] has coined the word “geneticization” to describe this phenomenon of understanding all diseases as being the result of genes.

Two related but distinct issues arise here: what is a genetic disease and is the geneticization of diseases legitimate? A common strategy for addressing these questions, shared by several philosophers [6-9], is to begin by approaching the project of defining the concept of genetic disease as an instance of the causal selection problem [10], which consists in picking out the main cause of an event occurring in a multicausal context. Applied to the problem of genetic disease, this means that labeling a disease “genetic” implies that genes are the most important cause in disease explanation. If we understand the concept of genetic disease in the context of the causal selection problem, geneticization can then be understood as an expansion of the concept of genetic disease to all diseases. In that case, geneticization amounts to an acceptance of genocentrism – the belief that genes are the most important causal factor in explaining any biological phenomenon. Genocentrism, however, has already been heavily criticized [6-9]. We will not review here the numerous arguments against genocentrism: it is enough to say that genocentrism seems to be both scientifically unjustified and ethically

questionable. Since geneticization, on this causal selection understanding of the term, is identifiable with genocentrism, it follows that geneticization cannot be an acceptable approach to disease. These philosophers therefore attempt to give a more restricted account of genetic disease whereby it still addresses the causal selection problem without leading to the pervasive geneticization of disease. They do this by defining the concept of genetic disease in a strict way in an attempt to distinguish between diseases that are “true” genetic diseases, where genes are necessary and sufficient to cause the disease (usually the Mendelian monogenic diseases) and diseases where gene-environment interactions are more difficult to assess (usually the polygenic disorders).

At this point, some scientific issues with the concept of genetic disease that we already described [1-4] arise again: there are few, if any, “true” Mendelian monogenic diseases and the frontier between monogenic and polygenic diseases keeps getting blurrier and blurrier. So, while the problems of geneticization and genocentrism are avoided, the result is an overly restrictive and unclear meaning of the concept of genetic disease. One response at this point might be to abandon the concept of genetic disease. Is it truly useful? Pragmatism is sometimes invoked to explain this lingering attachment to the concept of genetic disease [11]. But, which pragmatic reasons and pragmatic for whom? We noted above the scientific difficulties encountered with the concept of genetic disease. From a clinical point of view too, it is unclear what purpose the concept serves. It does not guide genetic testing or genetic counseling (where the notion of “inherited disease” is more useful), nor does it define diseases that are targets for genetic therapy, as Caplan pointed it [12], nor does it pick out diseases that need special funding because of their rarity (“orphan” or “rare” diseases would be more useful concepts for this purpose).

We saw above how geneticization was abandoned in an attempt to salvage the concept of genetic disease, and that the key move in this analysis was approaching the matter through the causal selection problem. Since there seems to be little point in saving the concept of genetic disease, however, perhaps we can salvage the concept of geneticization. Of course, this should not be geneticization understood as essentially equivalent to genocentrism, which, as we noted is subject to significant objections. Rather, we suggest a meaningful interpretation of geneticization that bypasses the issue of causal selection. Rather than interpreting

geneticization as an expansion of the concept of genetic disease, we propose that geneticization be understood as the development of a common mechanistic explanation for the genetic side of diseases, what we call “a genetic theory of disease”. Our account is definitely not genocentrist – by no means do we want to suggest that genes are the most important factor in causal explanations of all diseases. Indeed, our account embraces interactionism and acknowledges a multicausal model of disease causation for every disease: no disease can be understood without appealing to both genes and environment.

But, if the theory stops there, it has moved only from genocentrism to weak interactionism, and that is not a very interesting achievement. Indeed, weak interactionism is probably true but certainly trivial: it does not tell us anything truly meaningful about causal explanations of diseases. Furthermore, there is still the lingering temptation to come back to the causal selection problem and to view diseases on a causal continuum where both genes and environment would play a part in causing every disease but where some diseases would still be “more genetic” or “more environmental” than others. That is why, in this article, we defend a first step towards a strong and meaningful interactionism. This strong interactionism asserts that diseases share some common genetic mechanisms in their development and tries to assess which types of genetic mechanisms are at play in disease explanation. In this kind of account, it does not make sense to consider some mechanisms “more genetic” than others. Rather, one can identify various mechanisms that could provide an interesting basis to reclassify diseases according to the type of mechanisms that they exhibit, thus providing a new way of understanding disease causation.

Since we aim to make sense of the evolution of contemporary biomedical science, the best method to test such an account is by taking the recent biomedical literature as our starting point. For this reason, we will focus on the genetic theory of infectious diseases, one of the rare examples of an explicit genetic theory [13]. This theory is defended by a small but renowned group of scientists and aims to unify infectious diseases through the identification of four common genetic mechanisms. Therefore, we will first describe the structure of this genetic theory of infectious diseases before discussing the benefits and limits of this approach. From this genetic theory restricted to a specific class of diseases (what we call a “regional” genetic theory), we will try to introduce two hypotheses about the form

that a general genetic theory could take by distinguishing between a genetic theory of *diseases* and a genetic theory of *Disease*. Finally, we will suggest that network medicine could provide an interesting framework for developing a genetic theory of *Disease*.

## **Section 1: The example of the genetic theory of infectious diseases**

### **From the germ theory to the genetic theory of infectious diseases**

Infectious diseases were born as an independent entity at the end of the nineteenth century with the development of the germ theory. This is best captured by the four Henle-Koch postulates [14], which state that for an agent to be considered the infectious cause of a disease, it must fulfill the following conditions:

1. The agent must be present in all cases of the disease.
2. The agent must be isolated from someone with the disease and grown in pure culture.
3. Inoculation into a susceptible organism of the agent—from a pure culture—must produce the disease.
4. The agent must be recovered from the infected—inoculated organism and grown again in culture.

In the years following the establishment of these postulates, several issues raised by the germ theory have been pointed out [15]. We will concentrate here on two specific difficulties. First, the third postulate cannot account for the problem of asymptomatic carriers. For example, it cannot explain the fact that of over one hundred people infected by the influenza virus, only ten of them will develop the flu. The “agent” of a given disease has been inoculated in an organism and yet fails to produce the disease in the infected organism. Secondly, these postulates do not address the question of the interindividual variability of the symptoms. The example of leprosy is particularly telling on this point [16]. Leprosy has two main clinical subtypes: the paucibacillary form and the multibacillary form. Whereas in the paucibacillary form there is a limited number of hypopigmented and

anesthetic lesions without any microscopically discernable bacteria, the multibacillary form exhibits numerous sensitive or anesthetic lesions with high bacillary loads. In the nineteenth century, G.A. Hansen identified the agent responsible for these two forms of leprosy as *Mycobacterium leprae*, thus giving leprosy its other name, “Hansen’s disease”. How can the same pathogen be responsible for two different clinical subtypes of diseases that receive two different types of treatment and do not have the same prognosis? To some extent, the first problem can be understood as a limiting case of the second one: the problem is to explain how the same pathogen inoculated in different organisms can produce so many different subtypes of the same disease, from completely asymptomatic forms to severe ones.

It is precisely in order to fill this explanatory gap that the genetic theory of infectious diseases has been designed: “The field of human genetics of infectious disease aims to define the genetic variations accounting for inter-individual variability in the course of human infections.” [13, p.915] Infectious diseases are then no longer understood as purely environmental diseases, but as also determined in part by genetic factors, thus stepping out of the moncausal model and advocating an explanation of infectious diseases in general that could fit both the individual and the population levels. The genetic theory of disease is not incompatible with and does not try to refute the germ theory. Nor does this theory claim to be a complete picture of the interindividual clinical variability. In fact, Casanova, Abel and Alcais acknowledged at least three other theories that contribute to a global explanation of the interindividual clinical variability:

In addition to microbial variation, three theories have been proposed to account for this heterogeneity. Non-microbial environmental factors may be involved, with air temperature or humidity, and the availability of an animal vector particularly crucial (the ecological theory of infection). Non-genetic host factors, such as age or, since the last century, personal vaccination history may have a key role (the immunological theory of infection). [17, p. 404]

Indeed, the genetic theory of infectious diseases does not even aim to provide a complete picture of the causal factors involved in the pathogenesis of infectious diseases: while acknowledging other possible factors at play, it only focuses on the genetic mechanisms of infectious diseases. To put it differently, the

genetic theory of infectious diseases only aims at providing an explanation of “the genetic side” of infectious diseases.

### **The proponents of a genetic theory of infectious diseases**

Evidence supporting the genetic theory of infectious diseases first came from observations of familial aggregations of both rare and common infections, and also from follow-up studies of adoptive children and twin studies. Nevertheless, with the exception of a few diseases, genetic susceptibility to infections was still poorly understood until the completion of Human Genome Project [18].

This may explain why, even if genes’ involvement in the host reaction to infectious diseases was implicitly recognized by every infectologist, only a small group of researchers explicitly theorized this involvement. These researchers are mainly Jean-Laurent Casanova, Alexandre Alcais and Laurent Abel. All of them worked in the laboratory of human genetics of infectious diseases at Necker Hospital Medicine School in Paris and they have written approximately thirty articles over the last thirty years to defend this theory. Our account of the genetic theory of infectious diseases will rest on two of their most recent and explicit articles [13,19] and on a chapter titled “Human Genetics of Infectious Diseases” that they published in a reference book on human genetics [17] in 2010. In these three papers, they attempt to unify infectious diseases from a genetic point of view by identifying four genetic mechanisms.

We will now describe these four mechanisms as they are detailed in the main articles to which we referred. Before that, however, we should note that the scientists who wrote these papers explicitly use the term “mechanisms”. We will discuss the use of this term later.

### **Description of four mechanisms**

*1. Mendelian predisposition to multiple infections:* mutations in one gene cause a susceptibility to multiple infections. For example, the X-linked agammaglobulinemia is caused by mutations in the Bruton’s tyrosine kinase gene. This gene plays an essential role in the maturation of B cells in the bone marrow. When mutated, immature B-lymphocytes cannot develop into functional B cells, thus causing a susceptibility to multiple bacterial infections at early stages of the

infected males' life. This is also referred to as "conventional primary immunodeficiency" ("conventional PID").

2. *Mendelian predisposition to one infection*: mutations in one gene cause a susceptibility to one infection. Let us take for example Herpes Simplex Encephalitis (HSE): *Herpes Simplex Virus-1* (HSV1) infects around 80% of the population, but only a small fraction will develop HSE, which still remains the most common form of sporadic encephalitis in Western countries. The diseased people have an autosomal recessive UNC93B deficiency. This deficiency impairs the recognition of RNA intermediates of HSV1 in the central nervous system, resulting in impaired interferon production and causing enhanced viral replication and cell death. This category of diseases is also called "novel primary immunodeficiencies" ("new PIDs"), as they were discovered later than the conventional PIDs, which were Mendelian predispositions to multiple infections.

3. *Major gene / Resistance to one infection*: the "major gene" or "major locus" concept was developed in the context of complex segregation analysis in order to understand the phenomenon of incomplete penetrance. Penetrance is the frequency of individuals carrying a particular allele that also express an associated trait. For a given disease-causing mutation, penetrance can be incomplete, meaning that only a portion of the people having the given allele will exhibit the corresponding disease. A "major gene" creates the immunodeficiency, but its penetrance may be lowered due to the combined effect of other genes and environment. The main assumption is that only one mutated gene causes the corresponding disease but other genes or environmental factors may influence the expression of this gene, thus explaining its variable penetrance. The concept of "resistance" mirrors the "major gene" concept: some specific mutations on a given allele confer resistance to a given pathogen because they result in the lack of expression of receptors needed by the invading microbes. For example, consider the case of malaria caused by *Plasmodium vivax*: *P. vivax* is one of the pathogens that cause malaria. To penetrate into the blood cells, it needs not only to fix on its receptor but also to a Duffy blood group chemokine coreceptor, also called DARC. A single nucleotide mutation on the promoter of the DARC gene prevents the expression of the DARC receptor at the cell surface, conferring a resistance to malaria caused by *P. vivax*.

*4. Polygenic predisposition to one or multiple infections:* Polygenic inheritance differs from the major gene concept: it implies that the global phenotype results not from one single gene influenced by other genes or environment, but from the combined effects of a large number of loci. Depending on the number and relative impact of the genes influencing disease, we may distinguish between oligogenic predisposition and “true” polygenic predisposition. Oligogenicity implies that the phenotype is dependant on two or a few major genes, while other genetic loci make a relatively lower contribution. In “true” polygenic inheritance, no major gene is involved and the occurrence of disease depends on a large number of genetic loci, each having a small contribution.

Table 1 summarizes these four different mechanisms.

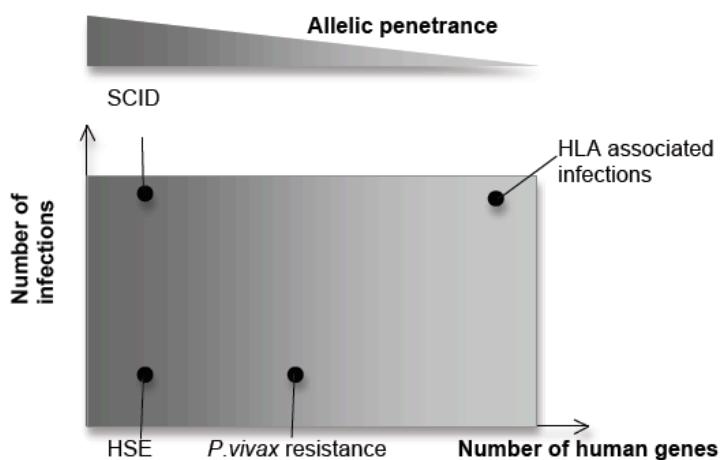
MECHANISM	DESCRIPTION	EXAMPLE
<b>Mendelian predisposition to multiple infections</b>	One gene, complete penetrance, multiple infections	<b>X-linked agammaglobulinemia:</b> Mutations in Bruton's tyrokinase gene ⇒immature B lymphocytes ⇒ multiple bacterial infections
<b>Mendelian predisposition to one infection</b>	One gene, complete penetrance, one infection	<b>Herpes Simplex Encephalitis:</b> Autosomal recessive UNC93B deficiency ⇒ impaired recognition of HSV1 by the CNS ⇒impaired production of interferon ⇒viral replication in the CNS
<b>Major gene/Resistance to one infection</b>	One major gene, high penetrance, one infection	<b>Malaria caused by P. vivax:</b> Mutations in the promoter of DARC gene ⇒ lack of DARC coreceptor of <i>P.vivax</i> ⇒ <i>P. vivax</i> cannot enter erythrocytes: resistance
<b>Polygenic predisposition to one or multiple infection(s)</b>	Multiple genes, low penetrance, one or multiple infection(s)	<b>HLA associated infections</b>

Table 1: Four genetic mechanisms in the genetic theory of infectious diseases

## **Section 2: From common genetic mechanisms to the concept of genetic continuum**

### **Common genetic mechanisms**

With four genetic mechanisms at play in the interindividual clinical variability in infectious diseases, we might expect infectious diseases to be split into four mutually exclusive categories, each defined by its own genetic mechanism. In fact, however, the categories overlap to create a continuum. Indeed, the previously described mechanisms are said to be common, meaning that the same disease can combine two or three mechanisms. As an example, genetic predisposition to tuberculosis, which was considered to be purely polygenic, was recently shown, in addition, to reflect a Mendelian predisposition to one infection in some patients and a major gene effect in others [20, 21]. It is precisely because these mechanisms are not the property of a specific category of diseases that there are non-mutually exclusive classes of diseases and that we can talk about a mechanistic continuum and not of a simple typology. The term “continuum” must be understood here in its usual mathematical sense: it indicates that the genetic differences between infectious diseases are not discrete, but just a matter of degree. This concept of continuum is well represented in various figures in the articles of Alcaïs, Abel and Casanova [13, 17, 19], a version of one of which appears below (Fig. 1).



**Fig. 1: Schematic representation of the genetic continuum of infectious diseases.** The ordinate is the number of infections at risk of development. The abscissa is the number of genes at play. Allelic penetrance is represented by the triangle above the graph: when just one or a major gene is involved, penetrance is high. Conversely, when multiple genes are involved, each gene has a limited effect on the global phenotype and penetrance is lower. Finally, the shades of gray (from dark gray to light gray) represent the genetic continuum between infectious diseases and are also highly correlated with allelic penetrance as suggested by the common color code. Four diseases are represented on this graph exemplifying the four previously described genetic mechanisms in infectious diseases.

### A new concept of genetic continuum

This is a rather new way of representing the concept of genetic continuum. For example, in a textbook published by the National College of French Teachers and Practitioners of Medical Genetics (CNEPGM) [22] in 2004, genetic diseases are represented in a very different manner. The graph, entitled “joint action of genetic and environmental factors in diseases”, consists of a single line, made of three segments (black, gray and white), each one corresponding to a specific disease category. The black segment represents “the diseases that are mostly genetic”, whereas the white one represents “the diseases that are mostly environmental”. Between these two extremes, we find a gradation of gray indicating diseases where both genetic factors and environmental ones are at play but in different proportions. In other words, this is a typical representation of a genetic continuum as framed by the “causal selection problem”: some diseases are

more genetic than others and the main issue at stake is to determine the proportions in which genetic and environmental factors interact. In this kind of genetic continuum, the previous examples of infectious diseases will probably be on the “mostly environmental” side of the graph.

The genetic continuum represented in Figure 1 differs from the latter in two aspects. First, the causal selection problem is not an issue: there is no distinction between diseases based on how much genes and environment influence their phenotypes. Indeed, the continuous gradation of gray represents allelic penetrance, that is, the fraction of people having the gene(s) and the corresponding disease. A disease with lower penetrance is not a disease with less genetic influence. Indeed, polygenic inheritance does not suppose less genetic influence than Mendelian predisposition: it is only a difference in the way genes cause the disease. In Mendelian predisposition, one gene is responsible for the disease whereas in polygenic inheritance several genes are responsible together.

Second, whereas on the traditional representation of the genetic continuum it is impossible to distinguish between different causal mechanisms for the same disease, this distinction is completely possible in the kind of representations used by Abel, Alcaïs and Casanova. For example, tuberculosis should appear in at least three different points of Figure 1 since it can be caused by at least three different genetic mechanisms as we previously mentioned.

### **Consequences of the genetic continuum**

What are the epistemological consequences of this mechanistic continuum? First, it provides a unifying explanation of interindividual clinical variability from a genetic point of view. It is assumed that for each infectious disease, one or more of these mechanisms can be instantiated to explain why a fraction of the infected individuals exhibit symptoms while others will stay asymptomatic. So, the mechanistic continuum exhibited by the genetic theory of infectious diseases represents an important gain in understanding the pathogenesis of infectious diseases, compared to the previous germ theory, which did not provide any explanation for this phenomenon of interindividual clinical variability and could not account for the problem of asymptomatic carriers or for some variations in the symptoms exhibited by the individuals.

Not only does the genetic continuum of infectious diseases give a unifying background to account for interindividual clinical variability, it also provides a satisfactory explanation of infectious diseases both at the individual and at the population levels. The germ theory could only provide an explanation for sick individuals: these individuals have tuberculosis because they have been infected by *Mycobacterium tuberculosis*. On the other hand, the genetic theory of infectious diseases allows two kinds of explanations. At the population level it allows a general account of every genetic mechanism implied in the predisposition to a given disease: in this population, some individuals get tuberculosis because they have either a Mendelian predisposition to *Mycobacterium tuberculosis*, or a major gene effect. But at the individual level it would be theoretically possible to distinguish between these different mechanisms to explain why in this particular case this individual got tuberculosis.

## **Section 3: Is this genetic theory a real mechanistic explanation?**

### **Preliminary comments on the concept of “mechanism”**

Now that we have presented the main content of the genetic theory of infections diseases, we will comment on the term “mechanisms,” which is explicitly used by Abel, Alcaïs and Casanova but may raise some justified concerns for those who are familiar with the recent debates about the definition of mechanisms and their relevance to biological explanations [23]. In these debates, we use Machamer, Darden and Craver’s definitive characterization of mechanisms, which comes from their classic 2000 paper “Thinking about Mechanisms”. The so-called “MDC account” of mechanisms has become the received philosophical view of mechanisms in recent years, superseding other attempted definitions. The account has even crossed over into the scientific community, making the original MDC paper the most-cited paper ever published in *Philosophy of Science*. The MDC account characterizes biological mechanisms as “entities and activities organized such that they are productive of regular changes from start or set up conditions to termination or finish conditions”.[24, p.3]

The genetic theory of infectious diseases does, to an extent, have the entities called for here, in the form of genes or diseases. It also seems that a regular organization between entities and activities is definitely assumed in each mechanism between genes and diseases' development. Still, these are not the entities and forms of organization expected when talking about "genetic mechanisms". When talking about "genetic mechanisms", we expect to be confronted with molecular activities such as DNA replication and transcription, regulatory networks of gene expression and so on. Do the mechanisms described above really deserve to be called "genetic" mechanism? Indeed, are they even specific enough to be considered mechanisms at all?

### **Imprecise activities, missing entities and problematic concepts**

There are three specific critiques we can see as expanding on the questions raised in the last paragraph. First, as we pointed out, the described mechanisms are imprecise. For a genetic mechanism, we may expect a detailed molecular description. For example, the description of the fourth mechanism, that is, the polygenic predisposition to one or multiple infections, clearly remains vague. Indeed, the identification of a truly polygenic predisposition requires a large number of individuals, both because of the small-expected effect attributable to each gene and because of the additive nature of these genetic effects. That may explain why evidence of such genetic mechanisms at both the population and individual levels has not yet been provided by human studies but only by studies of susceptibility to infectious diseases in animal models of experimental infectious diseases. The description of the third mechanism, "major gene/resistance to one infection", suffers similar shortcomings. Very little is said about how other genes and environment may affect the expression of the major gene.

Secondly, we could argue that the genetic theory of infectious diseases does not take into account some entities involved in the interindividual clinical variability of infectious diseases, especially the genetics of the microbiome and the genetics of the pathogen [25]. On the one hand, the microbiome is the complex community of bacteria, archaea, eukarya and viruses that infect humans and live permanently in our body. It is firmly believed that the genetics of this microbiome interacts with our immune system, thus modulating its response to infections. On the other hand, the genetics of the pathogen itself are probably of

great importance to understanding the interindividual clinical variability: different individuals of the same pathogen species do not necessarily carry the same type of resistance to antibiotics, the same genes of virulence, etc. It is not that the genetic theory of infectious diseases developed by Casanova, Abel and Alcais is not incompatible with these theories; it just does not mention them.

Thirdly, we may question the concepts chosen for describing these mechanisms. Indeed, concepts such as “Mendelian predisposition” or “monogenic” are borrowed from classical human genetics. But, as has already been suggested above, these concepts are not as straightforward as they may seem, since several of them have been challenged recently. Indeed, non-Mendelian modes of inheritance [26] have been discovered and monogenic disease [27] is no longer considered a simple category.

### **Mechanism sketches?**

These objections are not so much obstacles to a mechanistic description of the genetic theory of infectious diseases as a problem of explanatory level: molecular mechanisms are not so much absent here as implicit. What the proponents of the genetic theory of infectious diseases propose is neither the explanation of a specific case of genetic susceptibility for a given infectious disease (in which case the described entities and activities would be more specific), nor is it a complete general description of the molecular level of each mechanism (in which case we could expect some general schema to describe each mechanism). As the theory itself is a work in progress, (some of these mechanisms such as “Mendelian resistance” have been only recently described), the description is necessarily incomplete. It still constitutes, however, what Craver would describe as a “mechanism sketch”:

A sketch is an abstraction for which bottom out entities and activities cannot (yet) be supplied or which contains gaps in its stages. The productive continuity from one stage to the next has missing pieces, black boxes, which we do not yet know how to fill in. [24, p.18]

Thus, the mechanisms of the genetic theory of infectious diseases seem closer to mechanism sketches than to a complete mechanistic description of genetic susceptibility in infectious diseases. However, even mechanism sketches have a purpose: they constitute heuristic tools designed to indicate what further

work needs to be done to get a better mechanistic explanation. More importantly, the incompleteness of this theory does not weaken our main argument, as we are not so much interested here in the genetic theory of infectious diseases itself as in the conclusions that we can draw from such an example of a regional genetic theory.

## **Section 4: What about the genetic theory of diseases in general?**

### **What about a genetic theory of disease in general?**

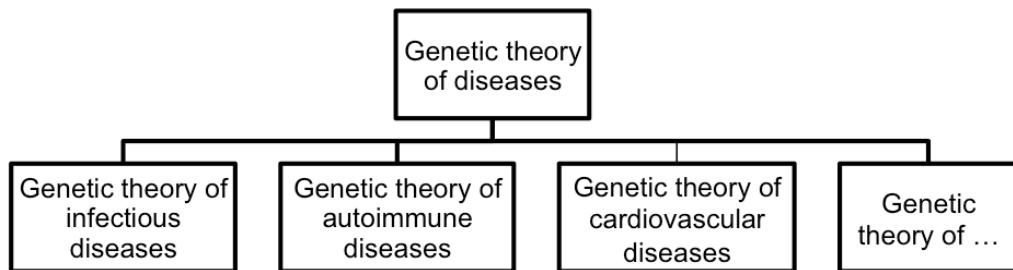
The genetic theory of infectious diseases is an example of what a regional genetic theory, that is, a genetic theory that applies only to a specific group of diseases, could look like. With the genetic theory of infectious diseases, we considered the example of a genetic theory devoid of genocentrism that relies on four common genetic mechanisms to unify infectious diseases from a genetic point of view. However, our starting point was not the extension of the concept of genetic disease to the infectious diseases but its extension to any disease. That is why what we are ultimately interested in is a genetic theory of disease in general, which could apply to any category of disease. We can consider two ways to progress from this example of a regional genetic theory to a more general theory. One is to progress to a genetic theory of *diseases*, and the other is to move on to a genetic theory of *Disease*.

The distinction between a genetic theory of *diseases* and a genetic theory of *Disease* derives from Paul Thagard's history of medical theories [28]. In this history, Paul Thagard makes a clear distinction between "ancient" medical theories and modern ones. Every ancient theory, such as humoral medicine, traditional Chinese medicine or traditional Indian medicine, relies on a general definition of Disease as an imbalance (even if the nature of this imbalance differs from one ancient theory to another). Conversely modern medicine emerged with the development of the microbial theory that identifies a specific cause for a specific class of diseases. Later, other specific theories for other classes of diseases arose, giving birth to our current medical theory, which is a collection of different theories for different classes of diseases. So there is a clear opposition

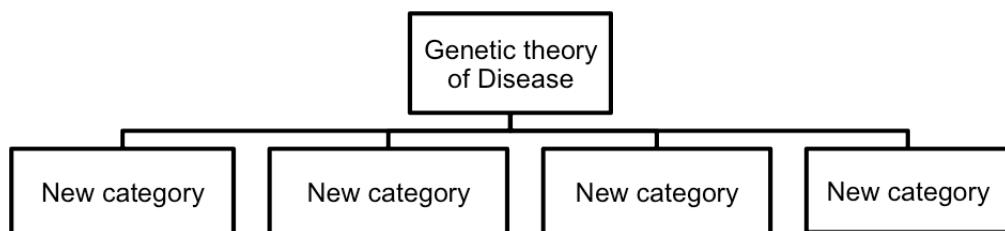
between the ancient theories, which are general theories of Disease in this respect, and our modern medical theory, which is a collection of distinct theories for different classes of diseases. The distinction between “diseases” and “Disease” does not bear any ontological commitment. It only aims to distinguish between two different kinds of disease explanations: explaining diseases as distinct, individual and separate entities or trying to find common biological features to the concept of disease, as opposed to the concept of health.

### **Representing a genetic theory of *diseases* and a genetic theory of *Disease***

By applying the distinction between a general theory of Disease and theories of diseases made by Paul Thagard to our search for a genetic theory, we end up with two different possibilities – a genetic theory of *diseases* and a genetic of *Disease* that we represent in Figs. 2 and 3.



**Fig. 2: Typical representation of a genetic theory of *diseases*.** The genetic theory of *diseases* is a set of regional genetic theories. For each category of diseases, there is a specific genetic theory with specific mechanisms. Genetic mechanisms may differ for each class of diseases. This kind of theory does not change the way we classify diseases.



**Fig. 3: Typical representation of a genetic theory of *Disease*.** In a genetic theory of Disease, we may expect a genetic definition of Disease in general. Depending on this definition, some classificatory principles would appear and these principles would likely renew the way we classify diseases.

The first diagram (Fig. 2) is a representation of what we may call a genetic theory of *diseases*: it is a set of regional genetic theories, an extension of the example of the genetic theory of infectious diseases. Each regional theory would be defined either by distinct and specific genetic mechanisms (each regional theory would have its own genetic mechanisms), or by applying the same kinds of genetic mechanisms for each regional theory. These mechanisms could use similar concepts to what we saw in the example of the genetic theory of infectious diseases, providing that these concepts (“Mendelian inheritance”, “monogenic disease”) have been clarified in the meantime. In this approach, each category of diseases as we know it (autoimmune diseases, infectious diseases, cardiovascular diseases...) would stay the same, except for the elucidation of the genetic part of their physiopathology.

The second diagram (Fig. 3) represents what would be a genetic theory of *Disease* in general. In such an approach, it is the very definition of Disease that is likely to change and to receive a genetic interpretation. If there were a genetic definition of disease, we may expect some radical changes in the way we classify diseases. For example, we may expect the reclassification of the disease categories, as we know them, in new subclasses of diseases that are yet to be defined. The idea of a genetic definition of Disease is still theoretical, but there are some hints to it, as in network medicine [29] for example.

### **Network medicine: a genetic theory of Disease?**

Network medicine was born of the synthesis between network theory – a set of solid mathematical and computational methods developed to decipher the underlying architecture behind apparently anarchic networks such as the World Wide Web, social networks and biological networks – genomic medicine and systems biology. Combined, these three disciplines naturally led to network medicine, which aims to develop network-based approaches to disease by analyzing the interactions between different kinds of genomic networks in a given disease and between apparently distinct pathophenotypes.

The core of network medicine relies mainly on two biological properties of the cell: interconnectivity and functional redundancy [30]. The interconnectivity of the cell components implies that disease can never be understood as the

result of a single mutation in a single gene. On the contrary, disease is defined as a perturbation in a functional module, that is, in a complex network of intra- and extra-cellular components (genes, transcription factors, proteins, etc.) that interact to achieve a specific function. But a single perturbation in a functional module does not necessarily imply the occurrence of the disease. Indeed, the disorganization of a functional module does not necessarily lead to its inactivation: it can also lead to a rerouting of the function, or to a less efficient achievement of the function. Moreover, most cellular functions do not depend on a single, but rather on several, functional modules – a property called “functional redundancy,” which contributes to the robustness of the function. If a single mutation or a single environmental perturbation could breakdown a functional module, humans would be permanently ill. But there is some robustness in the way our bodies are able to adjust to a certain level of stress and genetic or lifestyle-induced perturbations. Based on this functional redundancy, disease can be defined in a more specific way: a disease is a dynamic and complex phenomenon that occurs with the progressive inactivation of several functional modules initially used to achieve the function.

In what sense can network medicine be considered a theory of Disease? First, this definition of disease is supposed to apply to most (if not all<sup>1</sup>) diseases: there is a common definitional framework for every disease, which is the first requirement of a theory of Disease, as opposed to a theory of diseases, which is merely a collection of disease classes whose mechanisms or explanatory frameworks may differ from one class to another.

Second, from such a perspective, the *explanandum* of disease explanation changes. Our current classification of disease delineates diseases based on similar phenotypes and symptoms, neglecting the different ways in which the same disease can occur. Network medicine, to the contrary, aims to identify disease in a more specific and sensitive way: for each disease a functional subnetwork (the entire set of redundant functional modules) is identified and based on this modular

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<sup>1</sup> The application of this framework is easy to imagine for most monogenic and complex diseases, including the infectious diseases that we previously discussed. It may prove difficult for some specific cases such as environmental poisoning or brutal accidents. On the other hand, defining these cases as diseases may itself be problematic.

identification, a disease can be defined in its preclinical state and in an unequivocal way. Moreover, the aim is not to explain separately the occurrence of every disease but to understand how diseases are functionally related to each other. Diseases themselves have intertwined relationships and are understood as functionally related entities, since different diseases may share some components in the composition of their module and that the failure of one functional module in a disease A can have an influence on the disorganization of one of the functional modules of disease B. It is based on these hypotheses that the proponents of network medicine hope to explain not only comorbidity (for example the relationship between obesity, metabolic syndrome and cardiovascular diseases) but also syndrome families or the extraordinary importance of some genes in common diseases [31]. Searching for a common origin to different individual diseases can thus be considered as a step towards a theory of Disease.

Third, network medicine may completely change the way we classify diseases [32]. What matters here is not the main organ disturbed by diseases as in most of the anatomo-clinical classifications nor it is the identification of a main cause (infectious, genetic, autoimmune); what matters is the identification of a given module composed of genetic and non-genetic components at the cellular level. It is still not clear on which classificatory principles network medicine would rely since a functional subnetwork is supposed to be specific for a given disease. Therefore, to some extent, classifying diseases into classes or categories does not make sense and each disease is a class of its own (identified by a unique functional subnetwork). Still, in this respect, network medicine seems closer to a theory of Disease that is supposed to renew our disease categories than to a theory of diseases that keeps our disease classification and our disease categories intact.

We have explained in what sense network medicine might be considered a theory of Disease and not a theory of diseases, but in what sense is this theory of Disease genetic? And in what sense is it a general framework or at least a first step toward a strong interactionism in disease explanation? Both genocentrism and weak interactionism approach the multicausal model of disease explanation as a binary choice between genes and environment, with these options being defined in a rather loose way. In network medicine, this multicausal model is refined and genes and environment are defined in a stricter way, thus offering a more fine-grained causal background for an interactionist disease-explanation. Human

disease genes are all those genes known to be involved in diseases, but not every gene is a human disease gene. For example, essential genes that are involved in key cellular functions or key developmental features cannot be human disease genes, since mutations in these essential genes are usually lethal *in utero*. There are other biological properties of human disease genes [33, 34] that we cannot review here in detail: we only want to draw the attention on the fact that network medicine takes into account the fact that not all genes have the same functional role in a cell [35]. Different types of environment are acknowledged as well. For example, some proponents of network medicine [30] distinguish between the environment E, which designates external environmental modifiers commonly shared between individuals close to each other (such as nutriments, bioclimatic conditions or pollutants) and the environment E' that designates a more internal environment, depending on the individual history, epigenetics, intrinsic stochasticity, and which is strictly independent of the genotype. This distinction between E and E' is necessary to understand how two monozygous twins raised in a similar environment may have a different set of functional modules at some point in their life. Not only does network medicine give us a framework to redefine the initial unsatisfying dichotomy between genes and environment in disease explanation, it also allows a redefinition of the distinction between Mendelian monogenic diseases and polygenic disorders. Indeed, the causal selection problem was deeply entangled with an unsatisfying account of Mendelian monogenic diseases as diseases where genes are necessary and sufficient for the occurrence of disease and of polygenic diseases as diseases where genes and environment interact in a more complex way. In network medicine, Mendelian monogenic diseases are understood as diseases with low redundancy and weak robustness and polygenic disorders as diseases with high redundancy and strong robustness. This explains why few genetic mutations can lead to the occurrence of Mendelian monogenic diseases while many mutations and environmental perturbations would be necessary for triggering the occurrence of polygenic disorders, without compelling us to consider monogenic diseases as “more genetic” than others.

While we cannot assume that network medicine, a field in its infancy, has all the characteristics of a genetic theory of Disease, it seems promising. One issue that remains to be addressed is assessing whether such a theory can be given a full

and explicit mechanistic account, given the dynamic and complex relationships existing between the different components of the functional modules and the interactions existing between these functional modules and the different types of environmental backgrounds.

## Conclusion

As long as it is embedded in a misdirected quest to deem genes the most important causal factor in disease causation, the current geneticization of diseases cannot be interpreted as anything other than as an unsatisfactory expression of genocentrism. We proposed an alternative interpretation of geneticization, wherein a strong interactionist model underlies a unified mechanistic explanation for the genetic side of diseases.

Despite being closer to a mechanism sketch than a full mechanistic model, the genetic theory of infectious diseases supports this reinterpretation: it unifies infectious diseases from a genetic point of view through the identification of common genetic mechanisms and achieves a better explanation of the pathogenesis of infectious diseases than the germ theory previously did, while acknowledging a multicausal model in disease explanation.

Eventually, this genetic theory of infectious diseases may be considered as a heuristic tool to imagine two different types of genetic theory. On the one hand, we would have a “genetic theory of diseases” as a set of regional genetic theories where each category of disease could exhibit some specific mechanisms or where the same genetic mechanisms could apply to every category of disease. In this case, we would keep the same subclasses of diseases that we already know (infectious diseases, autoimmune diseases, cardiovascular diseases, etc.). We would have a unified explanation for the genetics of each disease category but that would not change the way we conceptualize disease. On the other hand, we would have a “genetic theory of Disease” with a new genetic definition of disease and a reclassification of every disease in new disease categories. We suggested that network medicine might offer the conceptual framework to develop such a genetic theory of Disease.

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