

Crohn's Disease: An Evolutionary History

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Introduction

Crohn's disease is classified as an Inflammatory Bowel Disease. The disease is capable of causing severe inflammation in any portion of an individual's gastrointestinal tract and is often chronic in nature. The symptoms of Crohn's disease arise due to complex interactions between genes, the environment, and the patient's immune system. An initial trigger in the patient's gastrointestinal mucosa begins the complex process of inflammation involved in Crohn's disease.

Once the activation of immunity has begun, the body fails in its attempts to control the immune response and excessive inflammation occurs. This exacerbated inflammation is due to excess Th1 cytokine production and often inadequate Th2 cytokine creation. Th1 and Th2 cells are two types of lymphocyte subpopulations that secrete proteins (*e.g.* cytokines) that help regulate immune responses.

Having disproportionate levels of Th1 and Th2 cytokines is especially debilitating because Th1 cytokines are the driving force in fighting infections in the mucosa membrane. Without enough Th2 cytokines (the inhibitory cytokines) to inform the Th1 cytokines to cease attacking, excess inflammation and severe damage occur.¹ This imbalance of Th1 and Th2 cytokine production has led many to believe that Crohn's disease is an autoimmune disease. An autoimmune disease is characterized by the targeted destruction of self-tissue by the immune system.²

The complexities of Crohn's disease lie within the affected individual's genes. Multiple gene mutations (potentially more than 8) cause the many mechanisms present in Crohn's disease.³ Abnormalities arising on the NOD2, Vitamin D receptor, and Th-2 cytokine production genes may hold the key to unraveling the complexities of this disorder.⁴ These complex mutations could potentially interact with environmental factors to create toleration or possibly even selection for the genes that cause vulnerability to Crohn's disease.

Environmental Influence

The evolutionary history of Crohn's disease begins in Africa with a few chance gene mutations. The first important mutations arise on the NOD2 (CARD 15) gene and genes involving Th1 and Th2 cytokine creation.³ The NOD2 gene is similar to a gene that creates bacteria resistant proteins in plants.⁴ With the development of the NOD2 mutation, those carrying the alteration now have an increased vulnerability to contracting a bacterial infection in their gastrointestinal mucosa. However, the excess inflammation that is characteristic of Crohn's disease may not arise in individuals that carry the genetic material alterations because of factors present in the African environment. Helminthic worms and parasites are rampant in the environment and individuals are prone to contracting them.⁵ In individuals that have the NOD2 mutation, the contraction of the Helminthic worms may have beneficial aspects.

Studies have shown that infection with Helminthic worms may lead to elevation of the Th2 cytokine levels in patients.⁵ An elevation of Th2 cytokines would potentially offset the harmful qualities of having excess Th1 cytokines that continually attack an area of the gastrointestinal tract. An individual could potentially carry some of the genetic mutations that lead to Crohn's disease but not show the damaging excess inflammation of the disease because the Helminthic worms that lie within the patient's body balance out the individual's immune response. This is a beautiful example of pathogens interacting with the body's own

defenses. Parasites may modify the bodily defense system of individuals afflicted with Crohn's disease and thus cause the genetic mutations that lead to Crohn's disease to be tolerated in an early evolutionary environment with a plentiful supply of Helminthic worms. This hypothesis may prove to be falsified with further research into the potential benefits of Helminthic worms and other parasites but the potential of having no selection for or against the mutations because no Crohn's phenotype is manifested in this early environment is fascinating.

Early human evolutionary history took place in surroundings similar to the tropics of today. A great deal of sunlight (and thus Vitamin D) is present in both the tropics of today and the early evolutionary environment of humans. Interestingly, Crohn's disease is very uncommon in the tropics today.⁶ Vitamin D may hold the key to the toleration of gene mutations found in individuals with Crohn's disease in the tropics of today and in mankind's early African setting. A large amount of research has been conducted on the effects of the Vitamin D hormone, 1,25-dihydroxy vitamin D₃, and its possible benefits on autoimmune diseases. Through this, it has been found that the Vitamin D hormone decreases the Th1-driven immune response in autoimmune diseases.² This decrease of Th1 cytokines ceases inflammation in those afflicted with Crohn's disease. It would therefore be logical to believe that an environment with a large amount of sunlight and Vitamin D could potentially be beneficial to an individual with the gene mutations characteristic of those with Crohn's disease.

Genetic Mutation

An interesting gene mutation carried by those suffering from Crohn's disease is an alteration involving a Vitamin D receptor.⁴ This may make an individual carrying the mutations require greater amounts of Vitamin D for optimal health.² Imagine an individual in our evolutionary past with the Vitamin D receptor gene alterations. The only possible way for the harmful inflammatory effects of Crohn's disease not to be seen in this individual would be if he or she were relegated to an environment with a large amount of Vitamin D.

This is what could have potentially occurred in Africa. The individual acquired the plentiful mutations of Crohn's disease but the harmful inflammatory effects of the disease were not present because the individual obtained a large amount of Vitamin D that suppressed overactive Th1 cytokine production. The potentially harmful genes found in those with Crohn's disease may have been tolerated in this Vitamin D abundant environment.

Selection

An alternative hypothesis to explain the success of the Crohn's disease phenotype is that it was selected for because it conferred greater reproductive success. As stated above, research has shown that a Vitamin D hormone may decrease the levels of Th1 cytokines in the body.² Since Th1 cytokines are vitally important for fighting infection, a substantial decrease in the number of Th1 cytokines, due to the Vitamin D hormone, could possibly have negative effects on any individuals exposed to large amounts of Vitamin D.⁷

It is therefore plausible to believe that Crohn's disease and its elevated Th1 levels may have been selected for to increase the ability of individuals in high Vitamin D concentrated areas to fight infection. An optimal Th1 cytokine level may have been reached in this highly concentrated Vitamin D environment with the acquisition of Crohn's disease. Crohn's disease mainly affects individuals during the prime years of reproductive success.⁸ This fact makes the idea of Crohn's disease selection for fighting off infection and in return increasing reproductive success somewhat logical. Selection would not occur on the Crohn's disease phenotype if it did not benefit or hinder the reproductive success of the individual during these prime reproductive years. Selection occurs for reproductive success and Crohn's disease may have been selected for to increase an individual's ability to fight infection and thus be more efficient at passing on his or her genes.

An individual may face an interesting tradeoff during the selection of Crohn's disease. The symptoms of Crohn's disease are usually less than beneficial, but in the right environment (one filled with large amounts of Vitamin D and Helminthic worms) the symptoms may not be as severe and Crohn's disease may be a tradeoff selected to fight

infection. The odds of dying from a mild form of Crohn's disease could potentially be far less than the odds of dying from contracting a deadly infection. This could be regarded as a tradeoff for reproductive success. The idea of Crohn's disease protecting against infection and increasing reproductive success could potentially mean that many more individuals contain the genetic mutations of Crohn's disease than were once thought. If sufficient numbers of the mutations found in Crohn's disease are not found in many diverse human populations, my hypothesis may be incorrect. New research into the potential benefits of Crohn's and the prevalence of gene mutations in the population must be performed.

The genetic mutations of Crohn's disease may have been prevalent in our early evolutionary surroundings (Africa) and eventually through migration moved to an entirely new environment (Europe). Europe is an environment without the abundant Vitamin D or Helminthic worms of Africa. This new novel environment of Europe has the potential to negatively affect those that carry the Crohn's disease genes.

Changing Environment

The new environment of Europe offers far less sunlight than the African environment. This characteristic property of Europe is most likely beneficial to many with genes lacking the mutation because they are exposed to far less sun and thus less deadly melanoma but individuals carrying the Crohn's disease mutations are negatively affected by the decrease in sunlight exposure. Crohn's disease patients are already at a selective disadvantage because their bodies make an excess amount of Th1 cytokines, which can destroy their own tissues, but now their potentially negative genotype is exacerbated in these new surroundings by a lack of Vitamin D, which could decrease their Th1 levels.² Crohn's genes were interacting with a novel environment and this contact potentially killed many individuals who held the mutated genes.

Centuries ago, through the implication of improved living conditions, hygiene began to improve in the European continent. This fact appears to have been positive for the general population but not for the percentage of the population that harbored the Crohn's disease gene mutations. This increased cleanliness further reduced the number of Helminthic worms and other parasites that Crohn's patients were exposed to. Without the large amounts of Helminthic worms in their environment, individuals with Crohn's disease no longer received the benefits of an elevated Th2 cytokine count.⁵ Their additional Th1 cytokines were then free to destroy their gastrointestinal tract through excess inflammation.

Socioeconomic levels for individuals also seemed to play a role in the rise of Crohn's disease in Europe and eventually America. The richer an individual becomes and the more hygienic his or her living conditions become, the greater the opportunity to contract Crohn's disease.⁶ A clear social stratification has begun to emerge within Europe and the United States. The poor are now far less likely to contract Crohn's disease, and the rich are becoming ill with excess inflammation.⁶

The new European and American environment once again began to shape the phenotype of Crohn's individuals when, about 6000 years ago, dairying was initiated. Lactase persistence began to be selected for with the expansion of pastoralist activities. Lactose digestion capacity (LDC) was beginning to become prevalent in northern Europe and North America. In current times, LDC is very uncommon in Africa and Asia.⁹ This pattern of LDC positively correlates to the pattern of prevalence of Crohn's disease in these continents. Crohn's disease is very rare in Africa and Asia.⁶ This fact leads many to believe that the key antigen that may interact with the NOD2 mutation in Crohn's patients and trigger a negative inflammatory process by the immune system is located in milk.¹⁰

Antigen Studies

The most cited antigen in studies involving Crohn's patients is *Mycobacterium avium Paratuberculosis* (MAP). This bacterium causes a disease similar to Crohn's in sheep and has been found in a high percentage of individuals infected with Crohn's disease.¹¹ Through co-evolution, the pathogen appears to have evolved to survive the pas-

teurization of milk.¹⁰ An ability of the pathogen to evolve much faster than individuals with Crohn's disease, gives the pathogen a clear advantage. The ability to survive the high temperature of pasteurization potentially means the bacterium could now be transmitted in our novel environment through milk, cheese, or yogurt.¹²

In viewing the symptoms of Crohn's disease one observes that diarrhea is prevalent in the manifestations of the disease.¹ The existence of diarrhea as a Crohn's disease symptom could be viewed in two ways. Diarrhea could be an evolved defense to expel MAP from the body or it may be present due to manipulation of the host by the bacteria to form an efficient way of transportation for the pathogen. Interestingly, individuals infected with Crohn's disease also experience the symptom of deficiency of iron.¹ It may appear that the low iron count of Crohn's patients is harmful to the patient and is a negative effect of the disease manifestation but this may not be so. Insufficient iron may be present in Crohn's individuals because iron is needed by bacteria to grow and multiply.¹³ By the body decreasing the amount of available iron in its tissues, it may in fact be creating an environment less than suitable for a multiplying pathogen. Two perceived negative symptoms of Crohn's disease can now be explained as defense mechanisms in the presence of the MAP bacterium.

With the discovery of *Mycobacterium avium Paratuberculosis*, the evolutionary constraint of breastfeeding in mammals now presents a problem for individuals that carry the Crohn's disease genes. Research has shown that breast milk can transmit MAP.¹⁰ It has also been observed that breastfeeding is correlated with higher instances of Crohn's disease.¹⁴ This circumstance creates an interesting tradeoff and constraint for those who could potentially be vulnerable to contracting Crohn's disease. Breastfeeding has many positive benefits to the immune system and other functions of the body but if breastfeeding passes on a bacterium that may trigger a severe inflammatory response by the immune system, then the negative aspects of breastfeeding may outweigh its positive aspects.

The evidence that MAP causes the trigger that initiates the excess inflammatory response of Crohn's disease is controversial because recovering the bacterium from samples and individuals involves many complex chemical processes.¹² This fact makes the research of this pathogen's relevance in the pathogenesis of Crohn's disease arduous and inconclusive. Better techniques for the recovery of the bacteria are needed but the relation between *Mycobacterium avium Paratuberculosis*, the evolution of lactose digestion, the use of milk, and Crohn's disease is undoubtedly interesting.

Relationship with HIV

The fascinating aspects of the evolutionary history of Crohn's disease continue when one investigates the effect HIV has on individuals affected by Crohn's disease. When an individual contracts HIV, his or her Crohn's disease mysteriously goes into remission.¹⁵ This phenomenon is most likely due to that fact that HIV causes a decrease in the patient's immune system response. Without the excessive immune response and inflammatory processes, Crohn's disease is nothing more than unexpressed genetic mutations. The relationship of Crohn's disease to HIV offers an interesting but unlikely tradeoff. Although acquiring HIV stymies the symptoms of Crohn's disease, it is much more in the individual's benefit to show the effects of Crohn's disease rather than HIV. HIV is much more deadly than Crohn's disease and this fact makes this tradeoff improbable. The relationship between HIV and Crohn's disease is remarkable. It proves the complexities of the interactions between genetic mutations, environment, and the immune system in creating a very severe disease.

Conclusion

The hypotheses presented throughout this paper must be thoroughly tested. The research into Crohn's disease must now include the prevalence of the Crohn's genetic mutations in the general population. A better understanding of their prevalence would create improved insight into their potential toleration in an early evolutionary environment. More research must be performed on how Vitamin D and its specific hormone, 1,25-dihydroxy vitamin D3, affect the immune system in not only individuals suffering from Crohn's disease but in every individual. A clear understanding of the immunity of the body and its correlation to Crohn's disease is crucial since the Th1 and Th2

cytokine imbalance is imperative in the manifestation of the disease. Finally, studies into the effects of antibiotics and drugs specifically targeting *Mycobacterium avium Paratuberculosis* must be performed. The idea of bacterium or pathogens causing Crohn's disease is controversial and studies into antibiotics would be greatly advantageous. The evolutionary history of Crohn's disease is multifaceted and fascinating. It involves potential toleration of gene mutations due to an early environment that leveled out the Th1 and Th2 cytokines through Helminthic worms and sunlight.

The journey continues into a new environment, Europe, where the gene mutations were no longer tolerated and became hazardous. The negative aspects of the genes may have multiplied when they experienced gene flow into new cultures that exposed the genes to a new bacterium presented in milk. A new exposure to bacterium creates unforeseen defense mechanisms and co-evolution between host and pathogen. Now in a new novel environment the complex nature of Crohn's disease is shown through the constraint and tradeoffs of breastfeeding, the interesting effects of AIDS on Crohn's disease, and social stratification of the disorder. The journey of Crohn's disease through our history has been extraordinary and deadly. A better understanding of the past and present mechanisms of Crohn's disease may have the potential to save lives.

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