

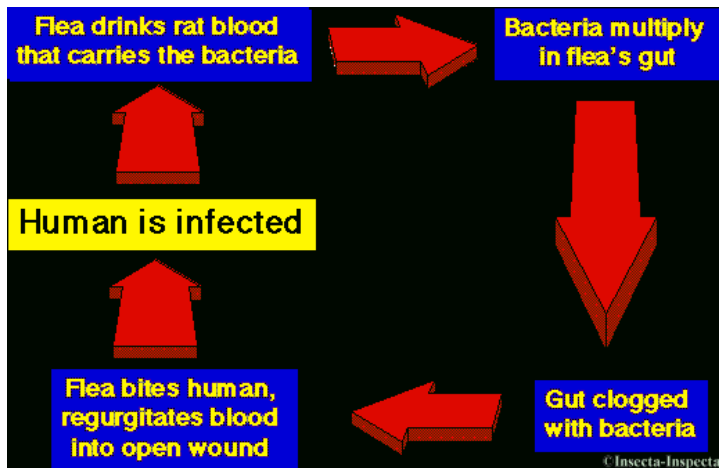
# The Black Plague, its Ramifications, and the CCR5-Delta 32 Deletion Mutation

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## Introduction

The plague is an infectious disease of animals and humans caused by a bacterium called *Yersinia pestis*. The plague usually results from being bitten by a flea from a rodent or by handling an infected animal. Millions of people in Europe died from plague in the Middle Ages, when flea-infested rats inhabited human homes and places of work. The chart in Figure 1 shows the process of how humans became infected with the plague by fleas via rats (Cartwright, 1991).



**Figure 1: The process of the transmission of the plague.**

Modern antibiotics are effective against the plague, but if infection is not treated quickly, the plague is likely to cause severe illness or death. Once people are infected with the plague, it spreads very fast. The disease causes fever and a painful swelling of the lymph glands called buboes, which is where bubonic plague gets its name. The plague also causes spots on the skin that turn from red to black. The purpose of this paper is to explore the causes of the plague and the effects it had on European society. The paper will also look into medieval medicine and how it was powerless to stop this deadly disease, along with how the survivors overcame the plague. Finally, this paper will discuss different theories on the CCR5-Delta 32 deletion mutation and its originations.

## **The Beginnings**

In the early 1330s, an outbreak of deadly bubonic plague occurred in China. Since China was one of the world's largest trading nations, it was only a matter of time before the outbreak of the plague in China spread to western Asia and Europe. In October of 1347, several Italian merchant ships returned from a trip to China and when they docked in Sicily, many of those on board were already dying of plague. Within days the disease had spread to the city and the surrounding countryside. An eyewitness recounts what happened:

“Realizing what a deadly disaster had come to them, the people quickly drove the Italians from their city. But the disease remained, and soon death was everywhere. Fathers abandoned their sick sons. Lawyers refused to come and make out wills for the dying. Friars and nuns were left to care for the sick, and monasteries and convents were soon deserted, as they were stricken, too. Bodies were left in empty houses, and there was no one to give them a Christian burial” (Naphy & Spicer, 2004: 26).

The disease struck and killed people with terrible speed. By the following August, the plague had spread as far north as England, where it was called “The Black Death” because of the black spots it produced on the skin. A terrible killer was unleashed across Europe and medieval medicine could not stop it.

## **Speed of the Plague**

The plague, after arriving on the shores of Italy and southeastern France in December 1347, traveled north to Paris and south to Spain by the summer of 1348, reached the southern coasts of England and Wales in the winter of that year, then east to Germany and north to the Midlands of England by June 1349, and finally encompassed Ireland, Scotland, and Scandinavia by late 1349 and 1350 (Aberth, 2001). Its speed was phenomenal because of the extensive trade routes in Europe at the time. Because of these trade networks, the plague was not only traveling

inland, but also seaward. As seen in Figure 2, the plague rapidly spread all over Europe from December 1347 to December 1350 (Naphy & Spicer, 2004).



**Figure 2: The spread of the plague along European trade routes, December 1347-December 1350.**

### **Causes**

People of the time were well aware that the plague traveled from person to person and was highly infectious. Medieval hygiene was a major factor in the spread of the disease. Hardly anyone took baths in the Middle Ages, and for many baptism was their first and last full immersion. Public baths were equated with houses of prostitution, and bathing in general was looked upon with suspicion as leading to immoral acts (Aberth, 2001). Clothes were rarely changed, except for church. They were also slept in for the sake of warmth and protection against the irritation of straw mattresses. Human waste could not be flushed out of sight, as urine, excrement, and blood of slaughtered animals all mingled together in the streets.

By the 1300s, many peasant houses in England and northern Europe were made of timber and sat on stone foundations. Their earthen floors and walls provided shelter for the black rat, which is thought to have introduced fleas bearing the plague bacteria into Europe. Long houses provided shelter for animals, such as cows, pigs, sheep, cats and dogs – all of which carried fleas – alone with their masters under one roof. Most people hosted large amounts of fleas and other organisms on their bodies as well as in their clothes and in their bedding.

### **Aftermath and Ramifications**

In the wake of the plague, it is estimated that a full thirty-one percent of European society was killed. To suffer a comparable loss, the present-day United States would have to lose around eighty-four million citizens in five years (Naphy & Spicer, 2004). Death on this scale is beyond comprehension – then or now. In London, for instance, estimates show that twenty-five to fifty percent of the population died from an estimate of around 50,000 citizens. These figures can be misleading, as they give little idea of the overwhelming scale of the mortality. In the two months from February 2<sup>nd</sup> to April 2<sup>nd</sup>, 1348, a total of 2,000 bodies were buried in just one cemetery. Between June and September in London, when the plague was at its worst, 290 people were dying each day. These dead had to be collected, their houses cleansed, the infected linens destroyed, and funerals performed.

Most cities lost around forty percent of their populations and although the actual numbers of dead in any city is on a more imaginable scale than the overall fatalities throughout all of Western Europe. The mass deaths resulted in more than just bodies, however. Many industries and services rely on a critical mass of workers and jobs could not be performed when thirty-five percent of the workforce died in a few months. The plague caused an immediate demand for medical personnel, but these were extremely skilled individuals who usually got infected by

working in close contact with individuals who had the plague. This resulted in doctors dying faster and in greater numbers than members of the general public. There was an immediate demand for plague workers, hospital workers, and watchers to identify those suspected of infection, and gravediggers. Consequently, poor workers were often drawn into contact with the dead and dying for pay, which caused a large decrease in their population.

As dramatic as the scale of death was in medieval Western society, there should have been ample time to recover, but the plague reemerged in 1361 and led to a population decline of up to twenty percent. This second outbreak was half as deadly as the first, but this attack was followed by another that lasted from 1369-71. This third outbreak killed ten to fifteen percent of the population. Until the late fifteenth century, the plague reoccurred every six to twelve years.

The second outbreak marked a change in that the plague was more defined to urban areas. The strange fact about the Black Death was how it swept through not only rural areas, but also towns and cities as well. Further outbreaks tended to be localized in heavy population centers. Nevertheless, the impact on rural areas was still great because towns and cities, in the immediate aftermath of an attack, tended to repopulate themselves with country folk (Naphy & Spicer, 2004).

The cumulative impact of plague, even just confined to cities, was dramatic. The landscape itself changed; villages were abandoned, farmsteads fell into ruin, fields were left fallow and became forested. The desertion of towns and cities, through death and flight threatened communities with chaos. With fewer mouths to feed, farmers began growing less grain and diversified into areas of forestry, cattle-rearing and wool production. Workers either died or fled their posts, or simply refused to perform, preferring instead to indulge their appetites while they still had the chance (Herlihy, 1997). The collapse of the labor market meant that

wages could rise, and tenant farmers were able to find good, well paying jobs in towns. This increased the cost of rural labor and forced innovation in methods as well as adoption of less labor-intensive forms of production.

By the end of the fourteenth century, it was obvious that the plague had become a regular and destructive aspect of life. The Black Death had not been just one shocking catastrophe, but rather a horrible introduction to a new and reoccurring menace. Death, in the form of this new pestilential disease, danced across Europe on a cyclical basis, leaving devastated communities in its wake (Naphy & Spicer, 2004). Although the plague seems to have left many rural areas untouched after the late 1300s, the epidemic returned to towns and cities almost every decade.

### **Medieval Medicine and Theories**

Though plague is now easily cured by a dose of penicillin, the Middle Ages lacked an understanding of modern medical knowledge, as causes and cures of disease remained elusive. The medieval diagnosis for the Black Death fell into two categories. Many believed that the plague was God's scourge, his righteous retribution raining down like arrows from the sky upon man in terrible judgment of his abundant wickedness and sin (Aberth 2001). English bishops ordered processions and prayers to ward off the pestilence, as medical authorities admitted that they could do little or nothing if the plague sprang directly from the will of God. Another theory that gained wide circulation was an astrological explanation. In October, 1348, in response to a request from King Philip VI of France, medical faculty announced that the plague had been caused by a conjunction of the planets Saturn, Jupiter, and Mars at exactly 1:00 P.M. on March 20, 1345. The essence of this universal and distant cause is that when the three planets lined up in their respective orbits, Saturn and Mars, both malevolent planets breeding illnesses and wars, outweigh the benign influence of Jupiter. Citizens of Paris believed that the disease was caused

by vile things in the air, such as plague-producing vapors that came from earthquakes and exhalations from swamps and rotting corpses. This idea that the plague traveled in corrupted air shaped the preventive measures men took to ward off the disease. The most common antidote recommended against the poisoned atmosphere was aromatics, such as herbs, flowers, and perfumes that were to be sprinkled around the house. There was also a rival medical opinion that advised ingesting foul odors. Under no circumstances were baths taken, because it was thought that they opened up the pores of the body to the infected air. Violent exercise, especially of the sexual kind, was to be avoided because it would overheat the body and make one more susceptible to invasion.

Cures for the plague were hard to come by. The standard medieval medical response to serious illness was to open veins with a knife or use leeches to let out a certain amount of blood from the body. The purpose of this was to restore the balance of the body's four humors- blood, phlegm, cholera (yellow bile), and melancholy (black bile). In the case of the plague, doctors mapped out those veins that should be opened depending on where the buboes or swellings appeared.

There was little anyone could do to stop the onslaught of death; doctors refused to visit the sick and could not cure them if they did. When doctors admitted to the powerlessness of their own profession, it showed that the Black Death had conquered medieval medicine.

### **The CCR-5 Delta 32 Deletion Mutation**

How did Europeans survive the plague? A team of six scientists at the National Cancer Institute's Laboratory of Genetic Diversity discovered that a genetic mutant (called CCR5) gave human carriers immunity against HIV and therefore AIDS (Cantor, 2001). The mutant CCR5 could only be traced back to seven hundred years ago. During the time of the Black

Death, a pathogen that like HIV-1 utilizes CCR5 established an immunity in ancestral Caucasian populations. This shows a link between the Black Death and AIDS. Descendants from a Caucasian who contracted the plague in the mid-fourteenth century and survived, may have complete immunity to HIV/AIDS. It is believed that up to fifteen percent of the population falls into this category.

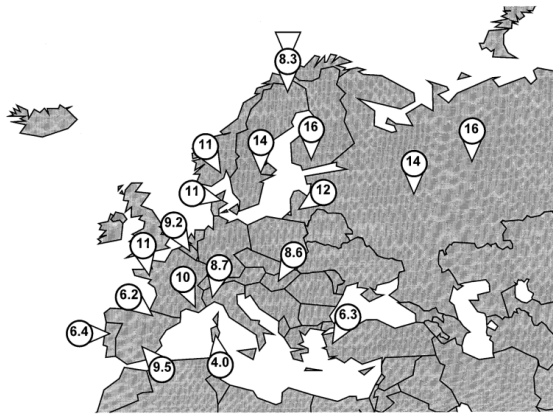
J. Claiborne Stephens, David Reich, and David Goldstein did analysis of the CCR5-Delta 32 allele to date its origin by the coalescence of haplotypes. They suggest that the most common ancestral CCR5-Delta 32-bearing haplotype arose by a deletion mutation of the CCR5 allele on the most common CCR5 haplotype. The age of this CCR5-Delta 32 bearing haplotype has been estimated at around 700 years old, or a range of 275-1,875 years. Stephens, Reich, and Goldstein (1998) did analysis on individuals homozygous for CCR5-Delta 32 and families carrying the CCR5-Delta 32 allele to determine chromosomal haplotype phase variants at CCR5 and seven microsatellite loci. Tests revealed that there was strong linkage disequilibrium between CCR5-Delta 32 and tandem-repeat polymorphic markers.

DNA samples were taken from thirty-eight different ethnic groups from Europe, the Middle East, and North America. These were typed for CCR5 and the results ([Table 1](#)) show a north to south gene frequency gradient (Stephens, et. al. 1998). The highest of the frequencies was in northern Europe and the lowest was in Greece. These data confirm the high frequency of CCR5-Delta 32 among northern European Caucasians, a gene frequency cline across Europe and Asia reflecting recent population admixture, and virtual absence of CCR5-Delta 32 among native Africans, East Asians, and American Indians (Stephens, et. al. 1998). The composite three-locus haplotype of five CCR5-Delta 32 alleles and seven CCR5 containing haplotypes and their frequencies were typed in the sample (Stephens, et. al.1998). ([See Table 2](#))

Stephens, Reich, and Goldstein (1998) used the nonrandom association of tandem-repeat polymorphic markers and CCR5 alleles, phylogenetic histories, and present haplotype frequencies to calculate the time required for a new mutation of an ancestral haplotype to produce the modern distribution of haplotypes, on the basis of the coalescent theory.

Their findings indicate that there was a recent deletion mutation of the CCR5 locus that mediates host response to HIV. Stephens, Reich, and Goldstein also found that the CCR5-Delta 32 allele is found exclusively among Caucasians and is on a geographic cline of north to south, with a high of fourteen percent. The recent occurrence plus the key role CCR5 plays as a required coreceptor for HIV-1 infection and progression to AIDS, leads the researchers to believe it occurred because of a strong selective pressure, such as a widespread epidemic like the Black Plague.

Frederick Libert, Pascale Cochaux, and Gunhild Beckman have also done research in the area of the CCR5-Delta 32 mutation and where it originated. Their work involved taking DNA samples from eighteen different ethnic groups in Europe and doing a haplotype analysis. Figure 3 shows the CCR5-Delta 32 allele frequencies that were found for European populations (Libert, et. al.1997). As with Stephens, Reich, and Goldstein, the research of Libert, Cochaux, and Beckman came to the conclusions that the CCR5 mutation occurred during a single event with a strong selective pressure around 700 years ago.



**Figure 3: CCR5-Delta 32 frequencies in European populations.**

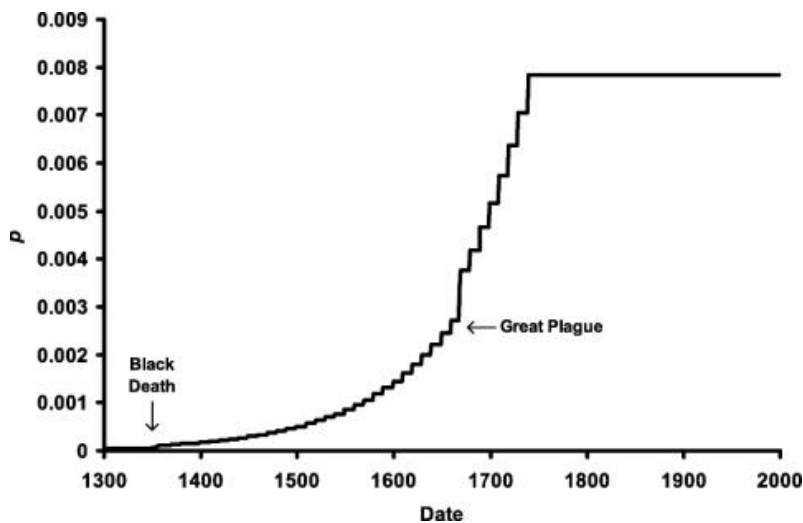
Alison Galvani and Montgomery Slatkin from the University of California at Berkeley refute the claim that the CCR5- Delta 32 deletion mutation arose from the plague. Instead, their research indicates it arose during smallpox epidemics in Europe. They point out that although the allele has resistance against HIV-1, HIV has not existed long enough in the human population to account for this selective pressure. Galvani and Slatkin find that by using a population genetic framework that takes into account the temporal pattern and age-dependent nature of certain disease, they found that smallpox is more consistent with this historical role.

The CCR5 chemokine receptor is fundamental to establishing HIV-1 infection. The receptor is exploited by HIV strains that predominate during the primary phase of infection to gain entry into immune system cells, including macrophages and CD4+T cells (Galvani & Slatkin, 2003). The CCR5- Delta 32 deletion produces resistance to HIV-1 by preventing the expression of its receptor on the cell surface. The CCR5- Delta 32 allele provides complete resistance to HIV-1 in the homozygous state and partial resistance in the heterozygous state.

The CCR5- Delta 32 allele is currently under intense selection in populations with a high occurrence of HIV-1. HIV-1 has not been affecting humans long enough to account for the selective rise of this resistance allele. The frequency of the allele is estimated at an average of

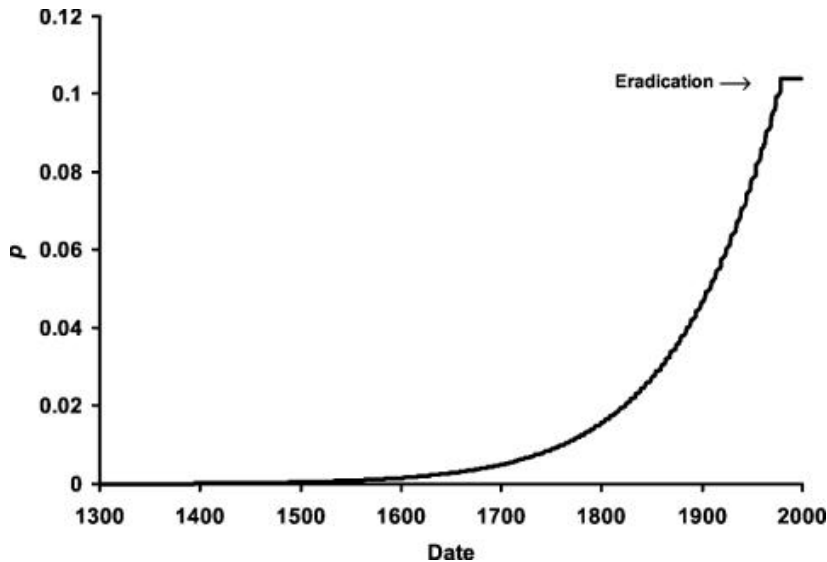
ten percent in European populations and it is almost completely absent in African, Asian, Middle Eastern, and American Indian populations. This suggests a recent origin, estimated at around 700 years based on the coalescent theory (Galvani & Slatkin, 2003). The theory that the high frequency of the CCR5 allele arose in Europe through strong selection from the bubonic plague has become known as the classic example of historical selection on an important locus. This hypothesis has gained widespread acceptance in the medical world, but Galvani and Slatkin believe that the high frequency of CCR5 arose because of smallpox.

The plague epidemic was caused by an indirect transmission from rodents through fleas. By comparison, smallpox was transmitted directly between humans, resulting in more continuous transmission. The researchers found that bubonic plague could not generate sufficient selective pressure to account for current CCR5-Delta 32 frequencies. The 400-year period of plague epidemics in Europe did not remove enough people of high reproductive potential to generate a sufficient selection coefficient (Galvani & Slatkin, 2003). As illustrated by Figure 4, Galvani and Slatkin's (2003) results suggest that the plague could not even have driven the resistance allele to one percent during the period it existed in Europe.



**Figure 4: Change in the frequency of a dominant resistance allele ( $p$ ), arising from plague deaths. The bubonic plague in Europe drives the frequency to 0.8%.**

Figure 5 shows that the continuous mortality from smallpox on European children could have provided the selective pressure necessary to generate the rise of CCR5- Delta 32 deletion to current frequencies of ten percent (Galvani & Slatkin, 2003).



**Figure 5: Change in the frequency of a dominant resistance allele ( $p$ ), generated by smallpox mortality. It takes a total of 680 years of smallpox for  $p$  to reach 10%.**

Galvani and Slatkin argue that plague could not have provided enough selective pressure to drive CCR5-Delta 32 to current frequencies because the epidemics only occurred in Europe during a limited time of around 400 years. Therefore, an earlier origin for CCR5-Delta 32 reduces the average selection coefficient caused by plague and does not increase the frequency of the allele (Galvani & Slatkin, 2003). Historical evidence suggests that smallpox occurred in Europe some 2,000 years ago, and an earlier origin for CCR5-Delta 32 would have given smallpox more generations in which to drive the allele to current frequencies.

## **Conclusion**

The Black Plague was a widespread epidemic that devastated Europe for nearly 400 years. It was caused in part by the uncleanness of the times coupled with overcrowding. There was nothing medieval medicine could have done because the disease was so advanced. Now, the plague is almost a forgotten memory, but many researchers believe that the one bright spot that came from it was the CCR5 deletion mutation that now protects some people from HIV. Much more research can be done on the CCR5 mutation and hopefully studies in the future will show how people without the CCR5 mutation can overcome HIV infection.

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