



***Lecture Exercise: Cystic Fibrosis: Exploration of evolutionary explanations for the high frequency of a common genetic disorder***

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***Synopsis:***

We present a guided classroom exercise in which students derive and evaluate hypotheses to explain the relatively high incidence of cystic fibrosis (and the alleles responsible) in European and European-derived human populations. Through this exercise students develop their abilities to apply evolutionary concepts, and generate and evaluate evolutionary hypotheses. Students also develop understanding of human genetic variation and the population genetics of genetic disorders.

***This document includes:***

- 1- Instructor's review on cystic fibrosis. This provides a brief review of the molecular biology, population genetics, and medical aspects of cystic fibrosis to prepare the instructor prior to class. It also includes a discussion of evolutionary hypotheses that have been advanced to explain the high incidence of cystic fibrosis in European human populations.
- 2- Instructor classroom flow and discussion prompt. This provides advice to instructors and a sample script for the use of these questions to stimulate classroom discussion and consideration of relevant evolutionary hypotheses.

In addition, this exercise uses an in-class question powerpoint. The questions on these slides comprise the heart of the exercise. Students address the questions in class, typically in discussion with small groups of fellow students.

***Cystic Fibrosis: Instructor's Review****Clinical Overview*

Cystic Fibrosis (CF) is an autosomal recessive genetic disorder of epithelial ion transport that affects a variety of organs and systems in the body (Nussbaum et al, 2007). It has until the second half of the twentieth century been highly lethal, with most afflicted dying in early childhood (Quinton, 1999). Recent medical advances have significantly increased the lifespan; people with CF born in the 1990's are expected to have a median lifespan greater than 40 years (Kreindler, 2010).

The gene affected in CF was identified in the late 1980s as coding for the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR), a transmembrane Cl<sup>-</sup> channel protein that also functions in regulation of other ion channel proteins (Kreindler, 2010). Over 1,400 variants of this gene have been identified that can lead to Cystic Fibrosis in the homozygous or compound heterozygous state (a compound heterozygote in this instance would be an individual bearing two different, but defective alleles for CF, who is functionally a recessive homozygote due to a lack of any fully-functional CFTR gene product). By far the most common of the CF alleles is the  $\Delta F508$  deletion; this is a deletion of a phenylalanine (F) codon at the 508<sup>th</sup> position on the gene that comprises approximately 70% of all defective CFTR alleles worldwide (Kreindler, 2010, Nussbaum et al., 2007).

CFTR function is important in regulation of the hydration of mucus secretions, and many of the symptoms of CF are associated with especially viscid mucous (Kreindler, 2010). In the lungs, this mucous impairs lung clearance, impedes air flow, and encourages an environment highly suitable for pathogenic microbes. Chronic lung infection is associated with recurrent lung inflammation and damage, and can eventually lead to respiratory failure (Cohen-Cymerknoh et al., 2011). In the pancreas, duct function is impaired, and the consequent retention of digestive enzymes in the pancreas is associated both with poor digestion and with pancreatic damage, including both CF-related diabetes, and the pancreatic fibrosis from which the disorder derives its name (Quinton, 1999).

Treatment of CF has traditionally been symptomatic, and includes a variety of modalities, including antibiotic therapy against lung pathogens, treatment of lung inflammation, a variety of techniques to encourage regular clearance of the lungs, pancreatic enzyme replacement, and nutritional management (Cohen-Cymerknoh et al., 2011). More recently, various approaches have been tried to enhance CFTR function in CF patients. One set of approaches has utilized gene therapy to attempt to incorporate functional CFTR in lung epithelial cells. Other approaches have used pharmacologic compounds to enhance the ability of mutant CFTR protein to incorporate into membranes and function effectively as an ion channel (Kreindler 2010).

***Epidemiology:***

Cystic Fibrosis is the most common lethal genetic disease in European populations (Cohen-Cymberknoh et al., 2011) with a frequency of CF alleles of approximately 2%, which results in a phenotypic expression of 1 in 2,500 Caucasian births (Cohen-Cymberknoh et al., 2011). The incidence is particularly high in some European-derived subpopulations, with an incidence at birth of 1 in 313 in southern Alberta members of the Hutterite religious group (Nussbaum et al., 2007). Reported incidences are far lower in non-European populations; for example 1 in 90,000 births for Hawaiians of Asian ancestry (Wright and Morton, 1968) or 1 in 350,000 births in Japan (Yamashiro et al., 1997).

***Evolutionary hypotheses:***

The strikingly high prevalence of CF in European populations has led researchers to propose a wide diversity of evolutionary explanations. Valles (2010) pointed out that there are a number of separate, but distinct, phenomena associated with a high prevalence of a genetic disorder such as CF that a hypothesis might seek to explain. For purposes of these classroom exercises, we focus on two closely-related questions:

- 1) How can the incidence of CF alleles be so high in some populations, in light of the very strong natural selection against what has been historically a genetic lethal allele?
- 2) Why is the incidence of CF so much higher in European populations than elsewhere?

Hypotheses to address these questions necessarily involve some combination of the major evolutionary processes: mutation, genetic drift, and natural selection. We will consider each of these in turn.

***Mutation:***

One possible explanation for a high frequency of deleterious alleles at a particular locus is that the gene in question has a particularly high mutation rate (Valles, 2010). However, Cremonesi et al. (1996) observed that de novo mutations in CFTR have been found only rarely, and Bertanpetit and Caladell (1996) argued that the known pattern of allelic variation across the gene was not suggestive of a particularly high mutation rate. Additionally, if the mutation rate of the CFTR gene were extraordinarily high, it would be difficult to explain why the frequency of CF is high only in Europe (Jorde and Lathrop, 1988).

***Genetic Drift:***

Wright and Morton (1968) argued that while it was very unlikely for a recessive lethal allele to drift to as high frequency as observed in Caucasian populations, there are thousands of potential lethal mutations across the genome. CF might simply be the rare case in which drift had been so extreme. Another way in which genetic drift might be involved is with a founder

effect or bottleneck, in which European populations would have arisen from a small population that happened, by chance, to have a high incidence of the  $\Delta F508$  allele.

Most researchers have rejected the possibility of genetic drift as responsible for the observed incidence of CF in Europe. Betranpetit and Caladell (1996) and Valles (2010) argued that the European population has been too large for too long for drift to be a plausible explanation. Poolman and Galvani (2007) cited evidence from several population analyses of molecular markers linked to CFTR that suggested that natural selection had been acting on the CFTR locus.

***Natural selection:***

Natural selection has historically acted very strongly against CF mutations in homozygotes. Any role of selection in developing and maintaining the high frequency of CF alleles must therefore be through some advantage to heterozygotes with one CF allele and one fully-functional CFTR allele. Early analyses suggested that CF heterozygotes were more fertile than homozygotes for some unknown reason. However more recent analyses have suggested that these earlier studies were methodologically flawed, and that the fertility of heterozygotes is no higher than for homozygotes (Gallego Romero and Ober, 2008; Jorde and Lathrop, 1988).

Most recent hypotheses for the high incidence of CF in European populations have focused on heterozygote advantage in resistance to some infectious agent. Infectious diseases that have been suggested to select for CF heterozygotes have included typhoid fever, secretory diarrhea (including cholera), and tuberculosis (Valles, 2010; Poolman and Galvani, 2007). Poolman and Galvani (2007) suggested that a strong case could be made for a particular infectious disease as the selective agent for heterozygote advantage for the CFTR gene if three criteria were met:

- 1) Physiological studies should suggest a plausible basis by which the CFTR gene could be involved in resistance to that infectious disease
- 2) Clinical studies should show that heterozygotes do indeed have better outcomes when exposed to the infectious agent than homozygotes
- 3) There should be a good geographic match between areas with high historical incidence of the infectious disease, and those with a high incidence of CF alleles

Poolman and Galvani (2007) suggested that tuberculosis was the infectious disease that best met these three criteria, particularly the match between CF frequency and the geographic and historical incidence of the putative selective agent. Modiano et al. (2007) also stressed the importance of finding a selective agent historically tied to Europe, but instead identified diarrhea specifically tied to consumption of dairy products as the likely selective agent. Lubinsky (2012) proposed that the geographic pattern of CF incidence was best explained by a complex interplay of tradeoffs in resistance to tuberculosis, high blood pressure and Vitamin D deficiency. What these contemporary hypotheses for the evolution of CF have in common is the conclusion that heterozygote advantage of one form or another remains the most plausible explanation for the high incidence of CF in European populations (Betranpetit and Caladell, 1996; Modiano et al., 2007; Poolman and Galvani, 2007).

### **Cystic Fibrosis in European populations. Instructor's classroom class flow and discussion prompt**

This document provides a guide for the flow of the class while performing the exercise. We advise faculty members using this exercise to carefully review the entire document prior to class, and then to bring a printed copy to refer to during class.

In this document, plain black text is used for a "script" of what the instructor will say to the class. The intention is to give a guide to the flow of the class, much as with lecture notes. Questions that are asked for students to answer are indicated with underlined black type. **Bold black text** is used to indicate a slide in the powerpoint to show to the class at this point in the exercise. Plain red text is used for comments and suggestions from the authors of this exercise to faculty members using it.

This exercise should, of course, be varied as the instructor sees fit, and presented in his/her own words; the text here is intended as an example. Indeed, it would be impossible for an instructor to present this exercise the same way twice, given that the points raised by students will vary. While we cannot cover every contingency, we use this "script" to explain important concepts and information that should help move the conversation forward.

Good morning. Today we are going to continue our exploration of evolutionary processes by considering the case of cystic fibrosis, a very serious genetic disorder, indeed one that was almost invariably fatal in early childhood prior to the development of effective medical interventions, and one that is still associated with very high morbidity and mortality. In many human populations this is one of the most frequent of such disorders, and we will explore the question of how it could have come to such a high frequency.

First, let's consider some of the basics of cystic fibrosis.

{The following provides an introduction to CF. This information could instead be presented to students ahead of class as a short reading, or by providing the appropriate slides on a course management website.}

#### **SLIDE: Introduction to CF**

Cystic Fibrosis (CF) is a genetic disorder of epithelial ion transport  
The gene affected in CF was identified in the late 1980s as coding for the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR), a transmembrane Cl<sup>-</sup> channel protein that also functions in regulation of other ion channel proteins.

#### **Slide: CFTR Gene**

The CFTR gene is found on human chromosome 7.

Over 1400 different molecular variants of this gene have been identified in humans that cause diminished function of the CFTR protein.

By far the most common of the CF alleles (that is those associated with the CF disorder) is the  $\Delta F508$  deletion; this is a deletion of a phenylalanine (F) codon at the 508<sup>th</sup> position on the gene. This allele comprises approximately 70% of all defective CFTR alleles worldwide.

**SLIDE: Question on Mendelian nature of CF**

The medical condition of cystic fibrosis results when an individual lacks CFTR proteins that function in a normal fashion. Would the  $\Delta F508$  then be considered a dominant or a recessive allele?

{This question reviews for students that loss-of-function alleles are typically recessive. It could be presented as a clicker question for each student to answer.}

Solicit answers from class.

Yes, the allele would be recessive- with two copies needed to manifest the disorder.

**SLIDE: Question on phenotype of compound heterozygotes**

{This question introduces the concept of a compound heterozygote, which may be unfamiliar to many students, and stimulates them to think about the functional implications of this genetic state}

An individual may be heterozygous for two different alleles that each, due to different alterations of the DNA sequence, lead to a lack of functional product.

**Slide: Question on compound heterozygosity**

What would be the phenotype of such an individual? Would they be expected to have cystic fibrosis, or not? Discuss with your partners for a minute and then we will all discuss this together.

{Throughout this exercise, students discuss questions with partners. These may be groupings that persist throughout the semester, or temporary, and they can be self-determined, or assigned by the instructor, as seems appropriate. It is often desirable to have groups of three students, as this usually keeps all the students actively participating.}

Solicit answers from class.

Assuming each allele results in a lack of protein function, such an individual should have the disorder. Functionally, from the point of view of having this recessive disorder, they would appear to be homozygotes, although molecularly they are heterozygous. A situation such as this, when an individual has two different “mutant” or non-functional alleles is known as compound heterozygosity.

**Slide: Medical Overview of CF**

Many of the symptoms of CF are associated with especially viscid mucous secretions. In the lungs, this viscous mucous impairs lung clearance, impedes air flow, and encourages an

environment highly suitable for pathogenic microbes. Chronic lung infection is associated with recurrent lung inflammation and damage, and can eventually lead to respiratory failure.

In the pancreas, duct function is impaired, and the consequent retention of digestive enzymes in the pancreas is associated both with poor digestion and with pancreatic damage, including both CF-related diabetes, and the fibrosis (pathological formation of fibrous tissue within the organ) from which the disorder derives its name.

**SLIDE: Medical outcomes of CF**

Prior to the identification of CF as a distinct disorder in the 1930s and the development of effective therapies, most individuals with this condition died in early childhood, largely from poor nutrition.

Advances in treatment of the respiratory issues has led to a major increase in lifespan- people with CF born in the 1990's are expected to have a median lifespan greater than 40.

**SLIDE: Question on allele frequency**

CF is particularly common in Europe and in European-derived populations. For these populations an estimated 1 in 2500 births is of an individual with CF. What do we expect the frequency of loss-of-function CF alleles to be in Europe? Take a minute to calculate this.

{This question and the next review applications of Hardy-Weinberg proportions}

Solicit answers from class. This could be done as a clicker question for each student to answer.

Yes, the frequency of recessive alleles (all of them summed) should be the square root of the frequency of the recessive phenotypic condition- in this case 1/50 or 2%.

**SLIDE: Question on carrier frequency**

What proportion would we expect to be CF carriers? Take a minute to calculate this.

Solicit answers from class. This could be done as a clicker question for each student to answer.

By Hardy-Weinberg calculations, this should be  $2pq$ , or  $0.02 * 0.98 * 2 = 3.92\%$

This is one of the highest frequencies for truly lethal recessive alleles (as these alleles were historically) observed in a very large population. This brings up the question of how the frequency has come to be so high- because until quite recently, natural selection has clearly been acting to eliminate these alleles any time they have been found in an individual in a homozygous state.

This is an evolutionary question, and so we need to think about the evolutionary processes that might be involved.



**Slide: Question on major evolutionary processes**

To start let's think about what the various evolutionary processes are. With your partners take a minute to write down a list of the major evolutionary processes.

Solicit answers from students.

{This question assumes that the major evolutionary processes of natural selection, genetic drift, mutation and gene flow have been previously discussed in class. We suggest writing these on a blackboard, projector, etc. as they come up in the discussion. If more specific examples or concepts come up (e.g. founder effect, heterozygote advantage, indicate that these are subtypes or example of these four major processes. If the class has previously considered other evolutionary case studies, one could skip this question and proceed to the next).

Of these processes, gene flow would largely be unsatisfying as an explanation for the high frequency of this allele seen in European populations. It would suggest that the alleles had migrated in from some other population, which would simply defer the explanatory question- we'd still be left with the question of how the allele came to a high frequency in whatever population this first happened. It is also the case that the frequency of this allele is higher in European-derived populations than in any others- making it unlikely that the alleles entered Europe from elsewhere.

So let us leave aside gene flow as an explanation, and think about the other three evolutionary processes as potential factors in the evolution of CF, particularly the high frequency in Europe.

**SLIDE: Question on mutation, genetic drift and natural selection as explanations for the high frequency of CF in Europe**

So what I'd like you to do is to work in your groups, and spend several minutes considering whether you can come up with a way each of these three factors might have led to the observed high frequency of CF. That is, come up with a story of how the high frequency of CF arose, relying on mutation as the only factor. Then come up with one that relies only on drift, etc. Also discuss in your groups how plausible each of these would be, and why.

{This question begins the discussion of a number of questions that are the heart of this exercise. Students should take ample time in their groups to consider and discuss their answers.}

Let's take each evolutionary factor in turn and consider its possible involvement in determining the high frequency of CF in Europe.

Let's start with mutation- did any groups come up with an explanation of how mutation could have led to the observed incidence of CF, and how plausible does mutation seem as an explanation?

This discussion may go in a variety of directions. Some factors to note and bring up, if students do not:

- There are really two senses in which CF has a high frequency in Europe. One is that it has a higher frequency in Europe than do other recessive lethal disorders. The other is that it has a higher frequency in Europe than elsewhere. A hypothesis should try to explain each of these observations.
- The high frequency of this genetic disorder relative to other recessive lethal disorders could be due to the gene having an unusually large number of sites where mutation could disrupt function, and/or because there is a particularly high mutation rate in that portion of that chromosome.
- For mutation to be responsible for the higher incidence of CF in Europe than elsewhere, the mutation rate for this one particular gene would somehow have to be higher in European than non-European populations. This seems unlikely, and the possibility has largely been dismissed by researchers.
- Mutation alone therefore seems unlikely to explain the high incidence of CF, although mutation must be ultimately responsible for creating the variant CF alleles

Let us now consider drift- did any groups come up with an explanation of how this could have led to the observed incidence of CF, and how plausible do these explanations seem?

This discussion may go in a variety of directions. Some factors to note and bring up, if students do not:

- Drift can take various forms: founder effect, bottleneck effect, or simply slow random change from generation to generation
- Slow gradual drift across the entire European population-a large population distributed across a wide geographic area is unlikely- a founder event or bottleneck in the history of the current European population is more plausible

If you think about it, following a founder event or bottleneck, the frequency of a deleterious allele may be high, but it should decline generation after generation, due to selection.

{The next section deals in some detail with the decay of the frequency of a recessive lethal allele, to demonstrate that even following a founder event with a high proportion of CF alleles, by now we would expect a much lower frequency for CF in Europe than actually observed. If time is limited, one could skip this and simply state this as a fact and move on}

Let us think about this process quantitatively.

**Slide: Question on maximum frequency of recessive lethal**

What is the highest possible frequency for a recessive lethal allele such as those for CF in a founder population?

### Solicit answers

One might think it would be 100%- but that would mean that everybody was a homozygote, and since this is a recessive lethal, they would all die without having children, and the population would be extinct.

Really we don't have to think about the homozygotes, since they will not contribute to the next generation. So effectively, the highest possible proportion in the breeding pool will be 0.5, if every individual is a heterozygote.

This is of course very unlikely, even if one had a very tiny founding population, but let us take it as the most extreme case. Let us say that the founding population of all Europeans consisted entirely of CF heterozygotes, and the frequency of CF alleles was 0.5.

In a large, randomly-mating population, we can calculate the number of individuals who will manifest the CF phenotype each generation- it is  $q^2$ . We can then calculate what the allele frequency is in the breeding gene pool, with those alleles removed, and therefore see how the frequency changes from generation to generation.

So we can calculate how many generations it would take such a population to go from an initial allele frequency of 0.5, the maximum to 0.02, which is seen today in Europe. This would be exactly 48 generations.

Or, at 20 years per generation, less than 1000 years. So a founder effect or bottleneck could only explain the current European allele frequencies if it had happened in the last 1000 years, and then only if were an extreme bottleneck, down to a very few individuals who happened to all be heterozygotes for CF.

At no point in the last 1000 years has the population of Europe been below 30 million.

So like mutation, genetic drift does not seem like a plausible explanation for the high CF frequency.

This leaves only natural selection to consider.

Did any groups come up with an explanation of how natural selection could have led to the observed incidence of CF, and how plausible does selection seem as an explanation?

This discussion may go in a variety of directions. Some factors to note and bring up, if students do not:

- Given that the homozygous state has historically been lethal, selection to maintain CF alleles would have to be operating in heterozygotes, that is some sort of heterozygote advantage would be operating

Did any groups speculate, or does anyone want to speculate now, on what sort of way this advantage might operate? How might being a heterozygote actually help an individual?

There is a good chance that someone will bring up resistance to infectious disease, as this is the case with the most familiar example of heterozygote advantage, that of human variation in hemoglobin and resistance to malaria. If not, students can be reminded of this example.

Depending on the class, other speculations may be presented, possibly including that heterozygotes have greater fertility. If this is not mentioned, bring it up:

The infectious resistance hypothesis and some other hypotheses focus on heterozygote advantage helping reduce mortality associated with some potentially harmful factor. Thinking about natural selection, another possibility is that in some way heterozygotes attain greater fertility than homozygotes for the common fully-functional CFTR allele.

Indeed, this has been proposed for CF, and early studies suggested that CFTR heterozygotes had more children than ordinary homozygotes. However, more recent analyses suggest that this is not the case.

So we are left with heterozygote advantage leading to disease resistance as the most common mechanism discussed in recent literature on the evolutionary history of CF.

**Slide: Question on best possible evidence that a particular infectious disease acts as a selective agent for CFTR heterozygote advantage**

To start with, let me ask you- What type of study or experiment would you suggest if you were trying to determine if a particular infectious disease acts as a selective agent for CFTR heterozygote advantage?

Solicit answers

If no students suggest clinical evidence, bring this up:

So, the strongest evidence for heterozygote advantage would likely be clinical evidence that heterozygotes in fact have lower incidence or severity of a disease than ordinary CFTR homozygotes

Perhaps surprisingly, several different diseases have been hypothesized to be the one for which CF heterozygotes have some sort of resistance. The major hypotheses for the selective agent for heterozygote advantage include:

- 1) Diarrheal diseases, including cholera
- 2) Tuberculosis
- 3) Typhoid fever

For the most part, clinical evidence that CF heterozygotes have resistance to these diseases is hard to come by. That is at least partly because molecular tests to determine CFTR genotypes have only been available to researchers in recent decades, and cholera, tuberculosis and typhoid are not terribly common in contemporary Europe or European-derived populations.

So other types of evidence may be needed instead to examine the plausibility of these diseases as selective agents responsible for the high incidence of CF in Europe.

**Slide: Question on types of evidence that would support hypotheses**

So what I want you to do, is in your groups, discuss what other types of evidence might support one hypothesis or another? For example, what sorts of observations about cholera and CF and/or CFTR genotypes would support this as the selective agent? What sorts of evidence would weaken the hypothesis that cholera has been the selective agent responsible for the high frequency of CF in European populations?

Solicit answers from students and discuss

This discussion may go in a variety of directions. Some factors to note and bring up, if students do not:

- Physiological studies should suggest a plausible basis by which the CFTR gene could be involved in resistance to that infectious disease
- There should be a good geographic match between areas with high historical incidence of the infectious disease, and those with a high incidence of CF alleles

There have been plausible hypotheses of physiological interactions of diarrheal diseases, typhoid and tuberculosis with the CFTR protein function.

For example, there is evidence that some toxins produced by intestinal bacteria interact with the CFTR protein. This suggests a possible role for altered function of CFTR affecting interactions with these bacteria and the diarrheal conditions associated with them.

Similarly the bacterium in typhoid appears to interact with the CFTR protein, at least in mice.

Proposed mechanisms of interaction of tuberculosis with CFTR are more tangential and perhaps less well demonstrated. There is some evidence that CFTR function affects the pH of lysosomes. This may affect the functioning of lysosomal enzymes including arylsulfatase B. Diminished activity of this enzyme may create a lung environment with decreased sulfate availability, which may hinder the functioning of the tuberculosis bacterium.

While the physiological link between CFTR and tuberculosis may be weaker than for diarrheal disorders and typhoid, one recent study suggested that the historical and geographical incidence of tuberculosis is the best match for the observed incidence of CF. However, another recent paper suggested that diarrheal disorders tied to increased dietary use of dairy in

European populations provides the best geographic and historic fit to the incidence of CF. Another recent paper suggested that a complex set of tradeoffs among resistance to tuberculosis, vitamin D deficiency and high blood pressure best explains the geographic pattern of CF incidence.

**SLIDE: Question on take-home message**

There is more that could be said on this topic, but for our purposes, we have covered the topic sufficiently that we should be able to come to a provisional conclusion.

What I'd like you to do in your groups is to come up with today's take-home message. I'd like each group to write a very short, one or two sentence summary of what the evidence we have discussed suggests about the question of how CF has evolved to a high incidence in European populations.

Answers can be solicited verbally, with the act of producing a summary helping students to review the material discussed and providing a satisfying ending to the class. Alternately, this can be an opportunity to focus on writing. In this case, instruct students to submit written answers (one per group) and to make these as clear and elegant as possible. These can be emailed to the instructor, or collected on paper. These can then be shown to the class on a projection system, compared and discussed as to what makes for a good, succinct, clear and accurate summary.

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