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S1E2: Mutation, Selection, & Coronavirus

It would be extremely difficult to find anything good to say about the COVID-19 pandemic. But one of the few things even resembling a silver lining that I can find is I get to spend more time with my dog. That's him now, letting you know it's time for a walk.

[SFX: barking, walking, more barking]

I would guess this is probably the case with a lot of pet owners. Nothing against my colleagues and coworkers, but I really like being with my dog. When we go out for walks now, we see a lot of other people out with their dogs too, even more than we used to. And that's not the only place I see more dogs. Many of my web meetings have had all kinds of dogs making guest appearances. And do you know what I've been struck by? There are a LOT of different kinds of dogs. It's not that I just discovered this, I have known there are different breeds for a long time, but it has been awesome to see all the different sizes, and shapes, colors, and faces of the different dogs and pups. The same is true for the different cats, birds, fish, snakes and lizards that have popped into the meetings too.

When you see all of these different animals you can appreciate the beauty of diversity. You see clear evidence that there is a lot of variation between species and even among members of the same species. It is amazing to me how all this variation among individuals in all of these species is the product of the same processes acting on all living and close-to-living things. A lot of the variation in not only these pets, but also the plants in your garden, bacteria, viruses, and even you and me are the results of mutation, inheritance, and evolution. That's right, even the virus that's causing the COVID-19 pandemic, SARS-CoV-2, is doing what it's doing because of basic biology.

[Intro Theme]

I'm Phil Gibson, and welcome to BioTA. In this episode, we will explore mutation, compare two types of selection, and figure out what we mean when we talk about evolution and herd immunity. By exploring these topics, we can not only understand the source of the different traits we see in species, lineages, and populations, but also how different organisms ranging from dogs to viruses change in response to their environment. How they adapt. How they evolve.

Before we get started, I want to remind you that information about where to find a transcript, the resources I used, and other items for further exploration can be found at the end of this

episode. I also give suggestions for some books and websites you can check out if you want to dig deeper into the evolution topics I get into here.

OK, let me begin by laying out the path we're going to follow. What I am going to do, is start small by thinking about mutation as the raw material of evolution in everything from viruses to you and me. Next we will think at a little bit bigger scale and consider to how selection acts on the consequences of mutations to drive evolutionary change in a population. And then finally, we will use what we know about evolution to think about a question that has come up a lot in talking about the COVID-19 pandemic, and that question is do populations evolve herd immunity?
[Theme OUT]

There are two important concepts that we need to know about for all of this to make sense. The concepts are phenotype and genotype. Any and all of the different features and traits of an organism from the cellular level on up are what scientists call its phenotype. Height, color, smell, metabolic rate, number of ACE-2 proteins receptors on the surface of cells in your nose, and hundreds of other traits are part of an organism's phenotype. Many of these traits are controlled to a greater or lesser extent by the combination of genetic instructions contained in their DNA, what scientists call the genotype of the organisms. Perhaps you have heard about genotypes and phenotypes when learning about Mendelian genetics or inheritance. Let me give a quick example of genotype and phenotype with dogs to make sure we're all together.

Think about a phenotypic trait like spots on a dog. There are multiple, different genes on the chromosomes that control hair color and whether the fur has spots or not. For each of these genes, an animal gets one copy of the gene from the mother in the egg and one from the father in the sperm. These copies of a gene are called alleles and they can be the same or different from one another. If the alleles are the same (say both mother and father both only have the alleles for spots on their fur, so their gametes contain only those alleles), the puppies will have spots, too. But if the alleles are different within or between the mother and father (say the mother has spots and the father doesn't) each puppy may have spots or not, but the litter might have only one type or a mixture. The unique genetic combination of alleles for every gene in that organism is what makes up its genotype, and reproduction mixes half of each parents' genotytpe to make unique offspring. Unless you are an identical twin, your genotype is unique from every other individual in the universe.

The way the genotype is expressed too make the phenotype, is through one gene acting alone or multiple genes acting together with one another. The environment can play a role too, but let's save that for another time. For now, just think about the genotype alone affecting the phenotype. This will apply to a lot of traits, but you can use spots on dog fur as a simple example to keep in mind as we go through this.

Let's next ask ourselves, where do all of these different phenotypes and the genotypes that produced them come from?

The answer is mutation. Mutations are any change in the DNA. Mutations don't always have an effect on the organism, but sometimes they do. If the mutation has no effect on how a gene is expressed or if the mutation happens in a region of the DNA that doesn't code for anything, then we call it a neutral mutation because it has no effect—it doesn't help or hurt the organism. If the mutation occurs in a place that does affect how the gene is expressed and does influence the phenotype, it can have a negative effect. That is, it can harm or even kill the organism. For example, a mutation could change a gene so that the proteins it makes can't conduct metabolic reactions properly or maybe cells with the mutation behave erratically. That is clearly a bad thing and if the mutation is severe enough, the organism will not survive. If the organism dies before it is able to reproduce, it won't pass the mutation on to any offspring.

But mutations aren't always bad. A mutation could cause a change in the phenotype that benefits the individuals that have this new allele. In that case, the mutation is that raw material that evolution can work on to drive change and promote adaptation.

Let's go back to thinking about dog spots. Suppose all of the dogs in a population have the same fur with no spots. Now, imagine that a mutation occurs in the gametes, the sperm or eggs of one individual. Just a little change in the DNA, maybe changing a cytosine for a thymine at one location in the gene, and it causes the fur in the offspring from this mutant sperm or egg to have spots instead of a single color. What we have here is a case of a mutation, a genetic change in the DNA produced a unique phenotype in the offspring that inherited the mutation. If you were a dog breeder, you might selectively choose to breed the spotted puppy once it's grown so that you can have more puppies with this phenotype (that is, more spotted puppies). If you do that, the mutation (the new "spotted" allele, as opposed to the original "solid" allele) will have a selective benefit for that individual. After several generations of your careful and informed selective breeding with other owners, what biologists also call artificial selection because humans are making the choices, the spotted allele will be more common in the population. The population now has new genetic variation that can produce new genotypes and phenotypes. The population has genetically changed. It has evolved. That's all evolution is, a change in the genetic characteristics of a population.

Let's take those ideas we just talked about and apply them to the novel coronavirus. Just to keep things easier to describe, I am going to lump viruses in with living things for this episode. I know I have expressed the opposite opinion elsewhere, but because at least as far as how DNA works and the actions and consequences of selection and evolution, virus particles experience exactly the same kinds of things as living organisms.

Obviously, viruses don't inherit genetic material from their parents like dogs or people do. Instead, they infect cells, and then use those cells' molecular machinery to make more copies of the virus. Despite this violent and unorthodox beginning, a virus's genetic material works pretty much the same way as any other organism's. Genes in the viral DNA or RNA are

expressed just like the host's genes once they infect a host cell. That's what makes you sick and that's how more virus particles get made.

Sometimes, when the virus is replicating and making more copies of the virus inside of the host cells, mistakes occur. The mistake in replicating the viral DNA or RNA is a mutation like we talked about before. If a virus particle with that mutation infects a cell, and the cell makes copies of that mutation, then every descendant from that virus particle and their decedents will have that exact same mutation. You can think of it as a typo in a document. Every time you make a copy of that document, you make a copy of the typo, too. Where the mutation occurs, how it affects what the virus does, that is of critical importance.

Coronaviruses are known to cause diseases in humans and agricultural animals as well as a number of wild species, particularly bats. Studies have found over 200 different coronaviruses in bats (Banerjee et al. 2019; Wrobel et al. 2020; Dominguez et al. 2007). That's about 35% of all the viruses that are known to infect bats. Although coronaviruses can cause intestinal or respiratory illness in humans and others mammals, they don't seem to cause serious health problems for bats. Many researchers are actively investigating why that is with the hope that it can lead to new therapies for humans.

[SFX: Bat cave IN]

So, although we can't say with 100% certainty, bats are a highly probable starting point for studying the evolutionary history of the SARS-Cov-2 virus. Like other zoonotic diseases, the virus eventually made its way from a wild animal population where it originated, possibly through one or more intermediate hosts, until it finally infected a human and made them sick. But it is also possible the virus that jumped from a wild animal to a human may not have been lethal. The virus could have been residing in human populations before we were even aware it existed, causing little or no symptoms until one or more mutations changed everything. So, let's next compare SARS-CoV-2 to other viruses to see if we can figure out what those mutations were.

Researchers sequenced the SARS-CoV-2 virus and found that, genetically speaking, it's very similar to a virus named RaTG13 that is common in bats (Boni et al. 2020). The RaTG13 virus can't infect humans. But when we compare gene sequences in the RaTG13 and SARS-CoV-2 RNA, we find two big differences—that's at least two mutations, changes in the genotype that give the SARS-CoV-2 a new, novel phenotype (Andersen et al. 2020). So, remember when we said that viruses infect cells, and then use those cells' molecular machinery to make more copies of the virus? Well, one of the mutations we're talking about with SARS-CoV-2 makes the lipids in the viral coat stickier so the virus attaches to cells better. If the virus can stick to cells better, it's more likely to be able to hang on long enough to infect a cell. That's a serious advantage. Another thing: the spikes that surround the outside of coronaviruses (you know, the things that give coronaviruses their name)? Well, this mutation also allows the spikes to attach to specific proteins called ACE-2 proteins. These ACE2 proteins are found on the surface of

cells in the human respiratory system and other locations like the intestines and blood vessels. That mutation makes it a whole lot easier for the coronavirus to infect humans (Chen et al. 2020). There's one other thing going on that gives this coronavirus an advantage in humans, and that is that human blood is full of a molecule called furin, which is thought to increase the virulence of some pathogens like viruses. RatG13 doesn't react to furin. SARS-CoV-2 does (Wrobel et al. 2020; Izaguirre 2019; Xia et al. 2020; Coutard et al. 2020). All of these changes give the SARS-CoV-2 virus an ability to infect humans that the RaTG13 virus doesn't have. The novel coronavirus got a new phenotype from the new mutant genotypes.
[SFX: Bat cavge OUT

[Ding ding]
Let's take a short but important conceptual side trip here. Mutations happen at random. That's an important thing to keep in mind. Mutations are a RANDOM process. No matter how much an organism might need a particular trait to do a little better and survive in their environment, they can't cause a particular mutation to occur because they need it. And the environment can't cause a particular beneficial mutation to occur on purpose. But if it does happen, and that random mutation. causes a beneficial phenotype in a particular environment relative to others that don't have the mutation and new phenotype, the mutation should become more common in the population over time. It's just like the dog fur example above. The random mutation caused a new phenotype. You represented the environment when you selected which dogs to breed. That's how the random process of mutation and the non-random process of selection in the environment drive evolution of adaptations through differences in survival and reproduction .

OK, back to thinking about the novel coronavirus.

The mutations we mentioned earlier gave the new coronavirus the new phenotype of being able to infect humans. But there are others. For example, this new virus has the unfortunate ability to hide in asymptomatic individuals, allowing these people to unknowingly spread the virus particles being manufactured inside them. The novel coronavirus tends to replicate more in the upper respiratory tract as opposed to deeper in the lungs. Data indicate it affects different races and age classes differently. What is important in all of this is that these phenotypic changes in the virus have given it a tremendous advantage in its new host (us), as we are all painfully aware.

You might think that would be the end of the story for coronavirus, but it's not. The virus continues to evolve and change based on the random process of mutation and the non-random nature of selection. Evolution never rests. As long as DNA replicates, there will be errors, which means there will be mutations. And as long as there is variation in the environment, which influences the success of the different phenotypes produced by those genotypes, there will be natural selection and adaptation. And we know the novel coronavirus is already doing just that.

You see, the SARS-Cov-2 virus isn't just one genotype. Comparisons of samples from many infected individuals have already found hundreds of different mutations. Most of them are neutral mutations. One of the mutations, however, has caught the attention of scientists (Kupferschmidt 2020) . The mutation is in a gene that encodes for a spike protein. The original form of the protein is called D614. The mutation is called G614 and has to do with the particular amino acid at position 614 on the spike protein that has changed. This mutation seems to happen independently in different populations. However, whenever the G614 variant arises in a population, it increases and spreads rapidly, becoming the most common variant (Zhang et al. 2020; Grubaugh, Hanage, and Rasmussen 2020; Korber et al. 2020). Does this mean that G614 has greater success in humans that D614? Is there something about us and the change in the spike protein which increases its ability to infect more individuals? It might be due to chance, but researches have noted that this single mutation makes the virus more infectious. The ability to infect cells and make more virus falls under what evolutionary biologists call fitness. So, based on what we know now, the G614 variant appears to have greater success, or higher fitness relative to the D614 variant. It doesn't necessarily make the virus more lethal, but it might be making it better at finding and infecting new hosts.

OK, so we know the virus is evolving. But what about us? Are we evolving in response to the virus? Because it affects survival, can we say that the virus is exerting some sort of selective pressure on human populations?

Viruses and other diseases have definitely played a significant role in human evolution. and there is no doubt that introduction of severe viruses and other new diseases has exerted a strong negative force on populations that had encountered the pathogen for the first times. There are many unfortunate examples throughout history of this unintentionally and intentionally happening to populations of indigenous peoples and other groups where the survivors of these encounters had immune systems that could handle the disease. These are definitely instances of genetically distinct groups are varying in their ability to fight off disease, so there is no way except to view that novel disease as a selective force. But that is not what is going on with coronavirus, especially when we talk about a population showing herd immunity. We are not talking about letting the disease cull the weak. In this modern age, that is no way to combat disease.

There has been a fair amount of confusion about this point, in particular. Some people have suggested that we should just let the disease spread and wait for herd immunity to evolve. Unfortunately, it doesn't work that way and it's not that simple. Let's untangle some misconceptions here because herd immunity and a population evolving in response to selection from a disease are two different things.

Herd immunity is not selection. Selection occurs when a disease sweeps through a population and kills individuals whose genetically-based phenotype makes them susceptible to the disease more so than others. That seems to be what has happened in bats. Their high viral load

suggests that they have genetically-based features that have been favored by selection in the past and accumulated in their populations. This is what probably one part of what allows them to tolerate so many viruses as part of their normal existence.

Herd immunity is different. Herd immunity is not a change in the genetic characteristics, the allele, genotype, and phenotype frequencies that happen after selection. Herd immunity is a change in the immune system status of individuals in the population. It occurs when the vast majority of individuals in a population have already encountered a virus (either naturally or by vaccination) and their immune systems are turned-on so they can effectively mount a defense against reinfection and spreading a disease (Fine 1993; Krisch 2020; Randolph and Barreiro 2020)

Let me explain how this works. . .

Think about a population of humans who have never been exposed to a new disease. Suppose when an individual is infected, they experience the disease, and after recovering they are immune and can't catch the disease again. When the new disease is introduced into the population, people become sick and spread the disease to others. As more individuals go through this process, there are fewer and fewer individuals that the disease can potentially infect because they have all had their immune system stimulated to protect them against another infection.

This is also what happens with immunization. Because the vaccine stimulates the immune system of vaccinated individuals, introduction and spread of the disease is fundamentally blocked. It can't spread. Even individuals who can't be vaccinated get protection because the herd immunity of others in the population prevents the virus from spreading. It cuts back transmission That's how vaccines stop the spread of diseases from achieving pandemic proportions. That's how we have stopped so many diseases that have devastated lives. That's why we don't see victims of polio, smallpox and countless other merciless illnesses as much as we used to. That's why measles, an exceptionally problematic and potentially lethal disease in children, doesn't cause the large-scale outbreaks that used to be so common, we vaccinate. And because we vaccinate in large numbers, we can stimulate immune systems and achieve herd immunity.

So what about the novel coronavirus? Why not get on with life and wait for herd immunity? The simple answer for that is numbers. For herd immunity to be effective, you need 80% or more of a population to be immune to the disease. An additional problem is that in the process of all those individuals becoming immune, a lot of other individuals die along the way. As we have unfortunately seen, COVID-19 can be lethal. So one problem with waiting for herd immunity is that a lot of people would probably die needlessly because we decided to just let the virus spread. This disease spreads fast, and even with what appears to be a relatively low mortality rate, our healthcare infrastructure would be overwhelmed with the numbers of ill that will be experienced. We've already seen a glimpse of what that looks like. Someday, if an effective

vaccine can be developed, then an active immunization problem that includes a large majority of the population could help us get to herd immunity (Coburn, Wagner, and Blower 2009).

Another limitation to herd immunity, however, is that we still don't know some basics about the disease. For example, herd immunity depends on individuals being able to maintain an immune response in their body. For example, current measles vaccines stimulate an immune response that is sustained by the body. One-time inoculation with the vaccine usually does the trick. Measles vaccines used in the 60's didn't necessarily stimulate the long-term immune response, but the form used now does. Influenza vaccines, in contrast, require an annual shot because the flu virus keeps evolving.

While there are many promising vaccines and therapies being researched at an astounding rate now, we don't know yet how soon a vaccine will be available or how son it can be deployed at a large enough scale to halt spread through herd immunity. Health experts estimate it will require 80-90% of the population to be immune to SARS-CoV-2 for herd immunity to work (Randolph and Barreiro 2020). that's 800,000 of every million people. Current world and US population estimates at this time in 2020 are 7.8 billion and 331,000,000 respectively. So, we are talking about getting vaccines to or the immune system stimulated in around 6,240,000,000 people globally and 265 million in the US. As you can see, getting the vaccine, even if one that can maintain an immune response is possible, it will just be the first part of yet another stage in this long journey.

We've covered a lot of topics, so let's summarize and bring this all together.

Number one: Mutations cause variation in genetic material. Sometimes mutations have no effect, sometimes they have a negative effect, and sometimes they have a beneficial effect. Number two: If that mutation has an effect on phenotype and is heritable, natural selection can act. If the mutation causes phenotypes that negatively affect survival and reproduction, the mutation should become less common in the population. In contrast, if the mutation causes beneficial variation in the phenotype, natural selection can cause the mutation and the new phenotype to be more common in the population over time. That's how mutation and adaptation are related, and we can see examples of both in the SARS-CoV-2 virus. Mutations in the novel coronavirus affected how contagious it is and how it infects human hosts. This increased success caused virus particles that contained these mutations to become more common because they were better at infecting, replicating and spreading. Data show the virus is still mutating, still evolving, still adapting.

And finally, Number three: Although it kind of sounds like it has some superficial similarities to natural selection, herd immunity as part of a larger a strategy for combating the COVID-19 pandemic or spread of any virus is not about letting the virus run rampant and selecting against certain individuals and causing a genetic change in the population. Instead it is a different phenomenon related to how many individuals have had their immune system stimulated to

combat the disease. That's a tool we use quite frequently and effectively to protect humans as well as our four-legged companions.

Herd immunity is not about culling the herd, letting selection eliminate the weak so that only the strong survive. That situation is selection and evolution. Those kinds of changes involve what we have talked about earlier; A population undergoing genetic changes. Herd immunity isn't about the population changing genetically, it's about the immunity status of individuals in the population changing.

One of the strongest pieces of evidence we can see for how evolution works is in dogs.

[SFX: Walking dog, sniffs panting and barks]

All of the different species represent products of selection for different traits and features. Random mutations occurred, the new phenotype they produced was noticed and those individuals were selected to make the next generation, which had more of that favorable trait. Over time, sets of traits accumulated and that's how we got different breeds. Border collies, corgies, pointers, Jack Russels, beagles, and all the others, each with their special traits. And the same thing is even true of viruses. All the different strategies they use to invade cells are collections of tactics that originated with mutations.

In much the same way we intentionally selected certain traits in dogs, our bodies have unintentionally provided the selective landscape that has favored certain traits in viruses, but at our expense. Instead of selecting for favorable traits that make us happy like with puppies and dogs, however, it is our vulnerabilities that unintentionally select which traits make a virus successful and allow them to do the things they do.

[SFX: OUT, Theme IN]
I'm Phil Gibson and this has been BioTA. Before I get to the credits, I want to make an important announcement. Please, visit your local animal shelters and other rescue groups to either adopt a pet who will give you unconditional love or donate funds if you can because they need our support now as always. And if you do decide to purchase an animal from a breeder, please do your homework and make sure they know what they are doing. And like Bob Barker told us, please spay or neuter your pets. They would do the same for you.

OK, Terri Gibson helped with editing and co-writing duties.

Opinions expressed here are those of the author alone.

Thanks for listening, have a great day, and take very good care of your genetic material.

BioTA is a production of Under the Juniper Studios.

You can find a transcript of this episode and other resources on my website jphilgibsonlab.oucreate.com

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