An Introduction to Evolutionary Biology

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Features of Mutations: Part 1

So, having looked at the various ways in which mutations can occur, We are now going to look at some of the features of mutations that make them interesting from an evolutionary biology perspective. So, just to clarify here, I am primarily going to talk about mutations occurring at the ATGC sequence level. I am not talking about chromosomal mutations, whole genome duplications, polyploidy, and so on and so forth. So, the first feature of mutations is that many mutations are pleiotropic. Which means that they end up affecting not one but multiple traits. So, just to give you one example, most of you probably know this person: this is Peter Dinklage, reasonably famous American actor who was, you know, Tyrion Lannister in Game of Thrones. So, this person, as you know, suffers from a certain physiological condition known as achondroplasia. So, in achondroplasia, what happens is that there is a gene called the FGFR3 gene. There are a few people who have this condition; they have a mutation in that gene and this mutation ends up interfering with the conversion of cartilage to bones. So, obviously, if anything affects your bone development, that is going to affect your stature. I mean, which is what we see in the case of Dinklage. But what it also does is end up affecting a huge number of other physiological functions. So, for example, people who have this condition often have what is known as sleep apnea.

So, you know some people, when they are sleeping, suddenly feel short of breath. And

they wake up like this; that is sleep apnea. Many of these people also have recurrent ear infections. So, the reason I am highlighting this point is that very often when one talks about mutations, they talk about mutation as You know this mutation leads to that one effect; this mutation makes the plants taller. or they make the plant shorter, or they make the plant go from yellow to green.

Now, that is because we typically end up focusing on one thing. But that does not necessarily mean that it is the only thing that the mutation is doing. Many a time, many mutations end up affecting multiple characters, and that is why. The effect of a particular organ from a particular mutation is important when considering its evolutionary effect. As opposed to its simple physiological effect, you have to think in terms of all the traits.

It is very, you know, evolutionarily, it is not useful to think about it as doing just one thing. Because most mutations actually do not do just one thing, they do many things. The second interesting thing about mutation is that many times there is a trade-off in the effects of a mutation. In other words, if it ends up benefiting you in one way, There are many cases where the mutations end up having harmful effects in other ways. So, just to give you one example, this is a particular frog that ends up eating poisonous toads, right? So this is the genus called Leptodactylus, and because these guys eat poisonous toads, So obviously, they need some way by which they can resist that poison.

So, it turns out this is a very interesting study by Mohammadi et al. I have given you the entire reference. So it turns out that these frogs have developed not one but 12 different amino acid changes. and mutations in a gene called ATP1A1. So the ATP1A1R gene is a very important gene for these organisms because they end up maintaining the ionic balance across the membranes. Now what these people did, Mohammadi et al. did, is they figured out that there are 12 amino acid changes. And then they ended up engineering the proteins with those amino acid changes and tried to figure it out. What functions those proteins are playing, and therefore, what is the role of each one of those amino acid changes? So, what they figured out was awesome.

So, they saw that initially, you know, let us say in terms of resistance to toxins, the organism was here, you know, and then. When the first mutation happened, it increased the resistance to the toxin quite a bit, but it also ended up reducing the enzyme activity. Remember, I told you this is a very important enzyme for the frog. So, that enzyme's activity was substantially reduced. Then there was a second change that further increased the resistance to toxins.

However, that again reduced the enzyme activity significantly. So, two amino acid changes are reducing the enzyme activity, and then there were subsequently 10 other changes. Because of this, the resistance level slightly increased, but the enzyme activity level increased quite a bit. So, this is how this organism was able to become more or less similar: the enzyme activity level remains similar. Although the resistance level went up quite a bit.

So, this is another example to show you that if you are thinking about what a mutation does to an organism, You also cannot just focus on one thing, say the increase in resistance to toxins. or an increase in the resistance to enzyme activity, an increase in enzyme activity, and so on. You always need to integrate over all the effects that a mutation has. So, this third one is actually almost personal. So, in evolutionary biology, most of the time we say that mutations are deleterious.

Now, here at IISER Pune, I have many colleagues, and one of them is Professor M. S. Madhusudan. He is a physicist and also a bioinformatician. So, I was having a discussion with Madhu. And he, you know, said, "Yeah, most mutations are neutral; they do not affect the organism in any way." So, this happened a few times, and you know we realized that something was going wrong because I was referring to most mutations as bad, and he was referring to most mutations as having no effect. So, then we puzzled over how both could be true, and we chatted a lot; it actually took us quite a bit of discussion. To figure out that we are actually defining mutations in a very different way. So, for a structural biologist like Madhu, a mutation is essentially a change in the ATGC sequence.

Now, if there is a change in the ATGC sequence, then actually most mutations do not really have much of an effect on the organism. Why is that so? That is because, as I told you, many mutations do not even change the amino acid. Many mutations might change the amino acid, but they might change, let us say, a basic amino acid to another basic amino acid. So, it is like the same kind of amino acid that is being formed again; many of those changes actually have little effect. And thirdly, for many proteins, particularly the enzymes, you know that.

There is something called an active site, and around that active site, there is a lot of the protein backbone. So, any change that is happening in the active site might obviously end up. Having a change in terms of what it does to the organism. But if you are thinking about changes in the protein backbone, even if the amino acids are being formed. are of a different type even if they end up changing the conformation of the protein slightly.

That will probably not have much of an effect in terms of how the protein behaves. That is why a large fraction of the mutations that occur involve changes in the ATGC sequence. In terms of what they are doing to the function of the protein, they do not end up doing much. Which is why structural and molecular biologists define most mutations as neutral. However, evolutionary biologists like me most of us think in terms of mutations.

In terms of what effect they are having on the organism. So, if there is no effect at the organismal level, we do not even call it a mutation; we do not even think a mutation has happened. Now, why is it that evolutionary biologists think this way? Remember, evolutionary biologists, you know we are studying mutations long before molecular biology came about. So, for example, for people like Hugo De Vries, you know, who were studying mutations even before they knew. Do you know about DNA, DNA structure, or anything? Those people were studying the actual effect that was happening on the organism, right? And therefore, their conceptualization of mutation itself is a change in terms of the organisms you know whether it is being benefited or harmed. And that is something that evolutionary biologists have continued to study, and if you look at

it from that lens, Then, most mutations that actually cause a change are harmful. In that context, we say that most mutations are deleterious. So, is there a way to somehow bring both of these definitions under one umbrella that can be done? So, the simple way to think about mutations is that most mutations will not affect the organisms. But the ones that will affect the organisms most will be deleterious; most of them are going to cause harm.

So, let us give you an example of what I mean by this: this is a study that was done on yeast. So, what they did was take a certain protein known as HSP90. Most of you might have heard about this protein; it is a heat shock protein, and it ends up playing a role in terms of Allowing the organism to survive, as the name suggests, are temperature changes and high heats. However, heat shock proteins also have many other functions. And, therefore, if you end up somehow perturbing a heat shock protein, you see all kinds of effects on the organism.

So, what these people did was take 560 different mutations and ask what effect this is having on the organism. In other words, is it benefiting the organism, or is it harming the organism? And so this is a slightly busy graph; I need to walk you through this. So they had three different kinds of mutations, mutations that are leading to stop codons, these ones, the black ones, Mutations that are synonymous mutations, these white ones, and non-synonymous mutations, Mutations that are actually leading to amino acid changes are these blue ones. So what they did was scale it in such a way that the one which did not have any mutation is called 0. And then all the ones that have mutations leading to bad effects, the deleterious ones.

They are on the left side, and all the ones that are leading to a positive effect. In terms of survivorship, reproduction, or whatever, all those are on the right side of this line. So the first thing that you see is that an overwhelming majority are actually on this side, the left side. There are very few that are on the right side. And though on this side, the further you go from this 0 line, the more harmful the mutation is.

Similarly, the further you go on this side, on the right-hand side, the more beneficial the mutation is. So, the first thing that you see straight away is that the number of beneficial mutations, Sorry, the number of beneficial mutations on this side is way, way less compared to the number of harmful mutations. This is the main thing that I wanted to show you, and this distribution of the deleterious mutations is not uniform. Most of the mutations they are causing a little harm, some of, you know, Okay, actually, the majority of the mutations are causing no harm; that is why they are all at 0; the peak is at 0. So, the mutations that are actually causing some harm, most of them are causing a little harm; a few of them are causing A little more harm to these guys, and then as you increase the harm, the fraction that is causing that harm is actually going down.

So, in other words, you have a kind of exponential distribution on this side. So, the harmfulness of the mutation is actually falling off exponentially, right? So, the main point that I want to make here is that because beneficial mutations are present, A population might have to wait a very, very long time in order to get a beneficial mutation. On the other hand, harmful mutations will keep on coming. So, this particular point, particularly about, you know, most mutations being harmful, will become important. When we talk about a kind of selection known as stabilizing selection, its justification will primarily come from this diagram.

The other thing I want to tell you is that particular distribution of fitness effects. So, this diagram shows the fitness or harmfulness and beneficialness on the x-axis. And the relative frequencies on the y-axis, this is what is known as a distribution of fitness effects or a DFE. So, the DFE of many organisms is actually of this type. The overwhelming majority of things that have been studied suggest that the DFE is of this type.

Now, the fourth point, which is a very important point, is about what are known as somatic mutations. And what are known as germline mutations. So, you know that in many organisms we have germ-soma differentiation; what is that? See, all organisms start as a single cell, the zygote. However, during the process of development in many organisms early on in development. A group of cells becomes the reproductive cells.

These are the ones that are known as germline cells, and the rest of the cells form the entire body of the organism. So, for example, when it comes to humans, our entire body is essentially made up of somatic cells, whereas there are a few other cells. In the case of males, it is those cells that are leading to the sperm. In females, these are the cells that lead to the ova. These cells actually differentiate very, very early, you know, during our embryonic development.

Now think about what the fate of a mutation occurring in a somatic cell will be. So suppose you know there is a cell in my hand that has become mutated, what will happen? In terms of its effect on me, obviously it will have an effect, but in terms of its effect on my kids, It will actually not have any effect because only the mutations that are happening in my sperm cells. Or somebody else's ova cells; those are the ones that are going to be passed on to the next generation, which is why. Only germline mutations are evolutionarily relevant; all somatic mutations are evolutionarily non-relevant with a caveat.

Please appreciate that. This is what we are talking about in terms of what is being inherited. However, somatic mutations can, and of course they do, contribute to the survival of the person. So, I mean survival and reproduction. So, the germline often contains things, mutations, and genetic variations. Which can have an effect on the somatic mutation rate.

So, just to give you an example, we know that cancer is a disease of the soma, right? So, cancer obviously is bad for us, or for any organism for that matter. So, cancer ends up affecting your, you know, probability of survivorship and the probability of how many babies you are going to produce. And therefore, many organisms in their germ line have variations that control the mutation rate of cancer. So, just to give you one major example, we know that elephants are very large organisms with lots of cells. The more the number of cells, the more the chances of getting mutations and accumulating mutations.

So, the elephants actually have 20 copies of what is known as the tumor suppressor gene TP53. And these copies, the 20 copies, actually reduce the chances of the elephant having cancer. To 50 percent of us humans who only have two copies of that gene. So, even though we are talking about a problem that will happen in the soma, The germline cells can and do affect the mutation rates in the soma. I mean that it is important; without that, organisms will, you know, suffer what are known as fitness consequences they would not be able to survive and reproduce properly. So, the basic implication here is that not all mutations are evolutionarily relevant. So, with this, we are done with four of the six features that we wanted to do. The remaining two we are going to discuss in the next discussion. See you.