Elite Learning

Podcast Transcript

No Longer Greek to You: Understanding COVID-19 Variants Episode 1 – With COVID-19, Change Is Constant

The following transcript has been lightly edited for clarity.

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Transcript

(SOUNDBITE OF MUSIC)

DR. DEBORAH MARTIN, HOST: Welcome, I'm Dr. Deborah Martin with Elite Learning.

With SARS-CoV-2 variants, it seems we've been through an alphabet soup — well, a Greek alphabet, anyway. Much has been learned about the virus and its variants since the original strain was detected in Wuhan, China; and much remains to be seen concerning future variants.

To make sense of all things COVID-19 variant-related, we were joined by Dr. Daniel Griffin, a physician-scientist specializing in internal medicine and infectious disease. Dr. Griffin's expertise extends to global health, tropical medicine, parasitology, and virology, including COVID-19. To learn more about Dr. Griffin's extensive background, please see the show notes that accompany this podcast.

Here's Dr. Griffin.

(SOUNDBITE OF MUSIC)

DR. DANIEL GRIFFIN, GUEST: OK, this is great because I'm hoping everyone enjoys this. But I'm also hoping that people are going to walk away with lessons learned. I have certain objectives, teaching objectives, that I'm hoping people will walk away from this with. And so let me go through these.

We're going to be talking about COVID-19 variants. One is, I want people at the end of this to be able to list the major-- not all of the COVID variants, but just the major COVID variants. I also want people to understand that there's nothing surprising here. There's nothing shocking here. I want people to understand that a virus constantly evolves and changes. That's actually part of the Darwinian pressure, the selection pressure, the survival of the fittest.

But I do want people to then take away, in this context, how do we understand our vaccines? And what are the challenges that vaccines are going to potentially face with the fact that viruses are constantly evolving?

Now one of the things I also want to discuss, not only the – we'll say, the act of vaccination – and the challenges that we have when it comes to the variants. But we're also going to talk about the impact of the variants on monoclonal antibodies. I want people to have an understanding there because I do think that that's really important.

And then the last, sort of to wrap it up, really, what are the differences between the ancestral Wuhan variant? And we're going to bring it all the way to the Omicron variants. We're going to talk about all the variants, but we're going to focus a lot on the Omicron variant. I want people to understand what those big differences are. How does that sound, Dr. Martin?

MARTIN: That sounds great. But all of those names brings up a question for me. Who actually names these variants?

GRIFFIN: OK. So you know, most of this – and this is this difference between, as we talk about variants and strains. You'll hear me make that important distinction between variants and strains. Strains actually takes a whole international committee getting together. The variants we're going to talk about – variants of interest, variants of concern – and how the WHO is taking the lead on identifying and spreading the word about these.

MARTIN: Great. I'm glad to know that I'll get my answer because it's kind of like some of those other names that are out there: You feel like there's a whole creative team behind a naming convention, whether it's hurricanes or storms or variants of viruses. So I look forward to hearing about that. Thank you.

GRIFFIN: Excellent. All right. Well, let's start off, as I like to do, with a case study. Let's make this about real people, not just abstracts.

So we're going to start off, and this is a real story. A 40-year-old schoolteacher without any prior medical problems is seeing me for a telehealth visit. She has acute COVID, and she's a bit confused, a bit concerned. She has lots of questions.

She explains that she received two doses of the Moderna vaccine. She just got her booster dose back in November. I'm seeing this woman in the end of December. And she reports that she tested positive right at the end of December, New Year's Day, but has no symptoms. She doesn't quite understand what happened.

So we're going to talk a little bit about what happened. We're going to talk about variants, whether or not we think that played a role in what happened here.

So the first we're going to start off with – and, as promised, understanding the language. So before we get into variants of interest and variants of concern, what are these numbers and letters? And what are people talking about? And what makes something a variant of interest, a variant of concern?

And so we're going to talk a little bit about the spike protein. Because it's really the spike protein, that hopefully everyone has become familiar with, which drives a lot of what we talk about. And what is this spike protein?

Now the spike protein is a protein on the outside of the virus. And this spike protein is 1,273 amino acids in length. So amino acids are the building blocks of our proteins. Those amino acids are coded by the genetic material of the virus. In us, its DNA. In the virus, its RNA. And that RNA is going to go ahead and code for this.

Now for each one of those amino acids, there's going to be three little base pairs, three little RNA bases, that are actually going to be coding for this. And when that code changes, we can end up with different amino acids in the protein at these different 1,273 sites. So how are we going to understand?

MARTIN: That's a lot of sites.

GRIFFIN: That is a lot of sites.

MARTIN: 1,273.

GRIFFIN: And can you think of the incredible amount of combinations? And so it gets worse – if it didn't already seem daunting. So you can have any of a number of amino acids at each one of these different locations in the 1,273. But you can also have deletions, and you can have insertions. You can take a little bit out. You can add a little bit in.

So the deletions, I almost think, are the simplest. They can say, oh, we have a 69-70 deletion. OK, amino acid 69 and 70 have been deleted. We can also have an insertion. Again, it'll be numbered. Where is this being inserted into this 1,273 amino acids?

MARTIN: Do deletions always have an insert to replace them?

GRIFFIN: No. Often what ends up happening is you have a shorter protein. So let's say you have a deletion at 242-244. You will actually have three less amino acids in our protein. So it can actually end up being either a little bit longer with an insertion, or a little bit shorter with a deletion.

We also can substitute. So let's take the receptor binding domain – and this is this area in the spike protein – goes from 331 to 528. And this is the section of the protein that binds to the cellular receptor, the ACE2 receptor.

And let's say somewhere in there, let's say, 417 –that's one that people are quite excited about – or 484. You can change the amino acid from an E – it's a special code, which amino acid is E – to a K. So if it's an E484K – if everyone hears about that – it's called the E484K, right there in the receptor binding domain, where we like to target the virus with antibodies.

And by we, I mean we with the monoclonal antibodies, and we with our immune system, that can actually make it difficult for those antibodies to bind there. Can also potentially change things. And we're going to talk a little as we get finally to Omicron, which we will get to, about what are those different amino acids that have changed and what are we worried that might result in?

So it's a little challenging understanding the language. But ultimately, those are the basics. We're going to have this little bit over 1,000-amino-acid-long protein, and the amino acids can change. And that can affect our body's ability to recognize that, our body's ability to target it, our ability maybe to do some testing to pick this up. And some of the immunology and pathology of the virus.

MARTIN: And I will say for those that are visual learners, as some of us are, we do have some interesting graphics in the notes that you may want to go take a look at and download. And we have kind of a graph that has those 1,273 amino acids kind of labeled.

GRIFFIN: So we certainly do. And the nice thing for the visual learners is, I've laid it out horizontally. And you can even compare to the ancestral Wuhan sequence. We actually have the amino acid sequence for the South African isolate, the original UK isolate. And you can see, where are there deletions? Where are there insertions? Where are there changes? So hopefully that helps our visual learners.

But maybe to make it a little bit simpler. When they first started to name the variants, they used what we refer to as the Pango lineage. And this was the B.1.1.7 or the P.1. I have to say, people started to quickly realize it was going to be very difficult for a lot of us who are not viral taxonomists to handle this new variant terminology.

There also was concern that people were going to start referring to the variants where they were earliest documented. And I think we saw an issue with that recently with Omicron, where it was reported in South Africa. They did a great job of extensive sequencing. And unfortunately, what can often happen is then you get your name attached to something you really don't want to be named after, a variant of a virus that is killing people, putting them in the hospital.

So early on, when people realized that this was happening, the WHO came up with a WHO variant of concern, and a WHO variant of interest terminology system, based upon the Greek alphabet. I knew being in a fraternity was going to be helpful.

(LAUGHTER)

MARTIN: And it's proven to be helpful. You know the Greek alphabet.

GRIFFIN: I feel like I wish I knew it better. I'm not sure in that fraternity we spent enough time in the Greek alphabet. I feel like we were doing some other things.

But, as you can imagine, what is the first letter of the Greek alphabet?

MARTIN: Alpha.

GRIFFIN: Alpha. And what was the first variant of concern? Alpha. Now this was the earliest documented sample, was in the UK. I think we can say that. I think that's OK at this point. But we don't want to refer to it as the UK variant. We want to refer to it as the WHO variant of concern, Alpha.

Now what I will say, because you're going to say, OK, this is easy. So we've got variant of concern Alpha. And then comes Beta. And then they're going to jump to Gamma. What happened?

There are variants of interest as well. And we're going to talk a little bit about what gets something from a variant of interest up to a variant of concern. But let's go through the major WHO variants of concern, and then we're going to add Omicron to this list.

So we have Alpha. We have Beta. We have Gamma. We then had Delta. And now we have Omicron that's sweeping through. So think of those as the progression.

And they're not necessarily in that sequential order, right? Because sometimes these have been circulating for a while before they've been identified. So the Alpha earliest documented samples were from the UK. Beta, earliest documented sample was from South Africa. Gamma, earliest documented samples down in Brazil – not something that really became a large global concern, interesting enough. Showing that certain variants of concern have the ability to do really well in one place but not necessarily outcompete other variants of concern in other places.

Delta, initially described in India. And that actually, I think we're all quite familiar with the success that Delta has had throughout much of the world. But the other lists – and these, I don't want people to feel like they need to remember these. I do think people can remember Alpha, Beta, Gamma, Delta, and Omicron. But there were certain WHO variants of interest which never actually rose to the status of concern.

There was an Epsilon, which we were quite excited about, the Epsilon and the Iota here in New York City. Concerns for a while that that might actually have a great fitness advantage. Zeta, Eta, Theta, Kappa. So there's

a number of different variants of interest that are always being monitored before something potentially rises to this high level.

So let's talk a little bit. What is a variant of interest, and what is a variant of concern?

MARTIN: If I could ask a question before we dig into that. I'm really interested in knowing who is sitting behind that microscope, looking for the variants? And how many samples do they look at?

GRIFFIN: Now I think this is great. And this is, unfortunately, one of the challenges. So how are we finding that there are amino acid changes, right?

MARTIN: Exactly. Yes.

Yeah, so we don't have the ability, or we often don't use the ability, to take a protein, isolate the protein, and then break it down into the amino acid sequence. So what we do is, we look at the blueprints. We look at the plans. We look at the RNA that's coating.

So a lot of people hear about sequencing. They hear about PCR. So what we're actually doing in the lab – some places better than others – is a certain sample, let's say, maybe 10% or 20% – that seems like a reasonable amount of the samples collected – we are actually looking at the RNA sequence that is coding for the spike protein.

MARTIN OK.

GRIFFIN: And we analyze that looking for particular changes that might be concerning.

And so originally there was a reference Wuhan RNA sequence. Then we started to notice some changes that identified with the Alpha sequence. And then, when we notice the RNA sequence of the spike protein that matched what was being seen in South Africa, there were a couple.

We get back to our language. The 484 site was changed from one amino acid to another. The 417 site was also changed. So we're starting to see these telltale changes. And the changes, that mutations are in the RNA. The amino acid changes are in the proteins.

And that's what was happening. We're tracking. We're doing all the sequencing. But it's a sampling of the sequence. And then we go ahead, and we report if we start to see one of these sequences starting to dominate, starting to increase in frequency.

MARTIN: OK. Thank you.

GRIFFIN: No, excellent question.

So what is a variant of interest? And we're back to the WHO. So the WHO has defined this. And I think this is important, so they can explain, what are we talking about? What do you mean, WHO, when you say it's a variant of interest? Why are we interested?

So a variant of interest, SARS-CoV-2 variant, has two qualities. It has genetic changes that are either predicted or known to affect the virus characteristics, such as – this is a tricky word, transmissibility – disease severity, immune escape, diagnostic or therapeutic escape. So maybe our tests or our therapies are not going to work.

The next is you actually have to see significant community transmission, or multiple COVID-19 clusters. So you don't just find an isolated sequence. You have to actually start seeing numbers in multiple countries with increasing relative prevalence alongside increasing number of cases over time, or other epidemiological impacts to suggest an emerging risk to global health.

So you're tracking, at one point. We'll go back in history. It's all the Wuhan ancestral strain. Things seem fine.

But then you start to notice Alpha sequences start creeping up. You start seeing clusters. You start seeing it increasing relative to Wuhan.

That's when you start to get interested. You're not concerned yet. You're just interested.

You're looking at some of those changes, as I mentioned, saying, ooh, some of these changes are right there in the receptor-binding domain. Maybe some of these changes are right next to that infamous furin cleavage site. You're starting to talk with the scientists about maybe these are changes that are going to impact the biology of the virus.

MARTIN: I think about them, when I hear you talking, like those of our podcast listeners that also like true crime podcast. You know, you have your suspect or your person of interest, and then you have your suspect that is under arrest. So you have better evidence that the person of interest – we're keeping an eye on you. But the other has more information that leads to an arrest, and is more dangerous to society, if you will.

GRIFFIN: Now I think that's a great analogy. I don't know if our listeners have ever watched what I think is a classic movie, The Usual Suspects.

(LAUGHTER)

GRIFFIN: My wife is not a fan. Two hours of her life she'll never get back. But there are times that your suspicion is raised a little, and then you look a little bit deeper.

You want to get a little more information. Should I actually be concerned? You know, does the alibi hold? Is this a variant that may have some other issues? So let's go into that.

When do we rise to the level of concern? When does the WHO elevate a variant to a variant of concern, a VOC? So the SARS-CoV-2 variant of concern is going to meet that definition, as we talked about, the variant of interest. We're going to bring it in for questioning, so to speak. But then we start to look through. And we see one of the following three issues.

We actually see that there's some sort of fitness advantage. We're actually seeing that this variant is out competing some of the others. So we're seeing an increase in prevalence. We're seeing some data that there may be some increase in transmissibility, some sort of change in the COVID-19 epidemiology.

Or we're starting to see some change in the clinical disease presentation. Are symptoms different? Does it look like there's a change in the amount of hospitalizations or deaths?

And then number three – and this is sometimes hard to sort out, but critical – is there some impact on our public health and social measures, our available diagnostic vaccines, therapeutics? Are we having issues with our masking, with our distancing, with our exposure rules?

Are we having issues with our tests? Are some of the tests starting to have, we'll say, S-gene drop-out? Get into, what is that? Are some of our vaccines starting to have different effects? Is this impacting our therapeutics?

So I think that's really raising it to a new level. We're not just suspicious. We're not just interested. We're now concerned. We now have some evidence that this is rising to the level of being a problem.

MARTIN: And to this point, we've not needed to change the vaccine. Is that correct? Or is that something that's on the horizon? Just like the flu vaccine changes every year.

GRIFFIN: So I think that that's a great question, and probably great to bring in this point, because we're going to be talking, we're almost ready to start talking about Omicron. So let's talk a little bit about number three here.

So what are these changes over time? And I mentioned something called an S-gene dropout. So the way we're detecting that someone has COVID, someone has infection with SARS-CoV-2, is we might do that PCR test, which boy, a lot of people are familiar with. Someone sticking a Q-tip somewhere. Maybe sticking it farther in than you want them to be doing that. And what are they doing with that information?

Well, early on, what we were doing, putting that Q-tip pretty far in, so the midturbinate. So three-plus inches, way too deep. Feeling like you were getting a brain biopsy.

Putting that in a tube. Running that in a machine. We are actually trying to amplify up that genetic material, the virus, that RNA.

And there's a couple targets. There's a couple bits of RNA in that viral sample that you've got from that deep swap. I will say, you can now, we've realized you can probably get a pretty good sample from the front of the nose as well.

But what we were doing is we were amplifying the RNA that codes, the blueprint for the spike protein. But also, we were using it to amplify different other RNA sections. And it turns out it was actually quite good that we did that because the Alpha variant, for instance, changed enough that when we would try to amplify the RNA coding for the spike protein, sometimes it would not amplify up. We saw that with Alpha. We're actually seeing that again with Omicron.

So that certainly raises something to the level of variant of concern, when one of our tests is starting to have difficulty. So fortunately we're amplifying up the RNA that codes for nucleocapsids, some of the other, we say, open reading frames. Those are still amplifying. But that was sort of the down-and-dirty, quick signal that something was changed about the virus.

The sequence coding for the spike protein had changed enough that those primers, that made up that PCR, or that PCR amplification, the spike protein, was failing. And that signal was actually dropping out. That's when you ever hear people talk about the S-gene dropouts.

Now the next thing I'll talk about – so we're still in diagnostics. What about some of those antigen tests? Now the antigen tests, which people may be familiar with, we've now got them in homes. People are doing this themselves.

These are not looking for the genetic material. But they're actually looking for the protein that is part of the virus, usually the nucleocapsid, which is another really common protein, not the spike. But in something like Omicron, there are enough changes that some of those antigen tests stopped working and had to be revised, pulled off the market until they were fixed.

Some of the variants of concern are going to affect and impact – and we'll get back to this – our ability to test and to detect whether or not a person has this or not. We also started to have some issues with some of our social measures. What we've seen over time is, it seemed that maybe people in the same setting, their risk of getting infection was impacted by variants over time.

And then vaccines. We're going to spend a lot of time on vaccines as we go forward, because a lot of our vaccines are specifically teaching our immune system about the spike protein. And since, as you have already probably learned, variants of concern are very much focused on changes in the spike protein, you can imagine potential challenges for our vaccines.

MARTIN: I do have a question. And maybe you're going to get to this later when we talk about – get into more of the variant piece. But for the home test that you mentioned, those don't necessarily have to be reported anywhere, the positive test. And there's no lab looking at them. So what do the millions of home tests that are being done, how does that impact the science and understanding where the virus is headed, since it's an unknown to scientists?

GRIFFIN: Yeah. No, I think that that's a great question. When we see that new case numbers in the US have peaked, maybe in certain areas they're on the way down. Are they on their way down because people have stopped going to our testing centers, where we report it?

People are doing those tests at home. And then if they get a result they don't like, they're tossing that in the trash. So this actually requires us to be constantly validating those tests, so that we know if they work or not.

It is a challenge. Certain states have taken up the mantle, so to speak. New Jersey, for instance, when they're giving out their home tests, there is a bit of an honor code, but you can register, report those test results, particularly if, they're positive. And then get guidance from the state.

Some of the hope is, not only will you get guidance, you'll get maybe a little bit of a care package with that, an incentive to report that positive test. But no, I think that's one of the challenges. A lot of these tests, particularly the BinaxNOW, one of our favorites, people do that.

They get a test. They get a positive or a negative. And then they sort of decide on the honor system how they're going to respond to that information. We're not necessarily getting all that information reported on high.

MARTIN: Right. And then the scientists, it's not part of the 10% pool that they are looking at to do a deeper dive into those tests. Because they don't have access to them.

GRIFFIN: I think that's actually a great point that you make there. As mentioned, maybe if we're doing a good job, we're sampling 10% to 20%. But there's probably a different demographic in who does home test, who goes to get tested. So is that 10% to 20% sampling of our sequences, is that really going to tell us what's going on in the community, if so many of these tests are outside of that pool that might be sampled?

And we ran into some trouble here, actually, in December. Early December we got the report 75% of variants here in the entire US, it's all Omicron. Here in New York, it's over 95%. It's all Omicron. This actually impacted some of our decisions about therapeutics, the monoclonal antibodies in particular.

And then the next week we got a revision. Ooh, those numbers were a little bit off. They were based on a small sample. Now that we've run more sequences, OK, maybe not quite so high.

So this is not an exact science. We are not sequencing all of the variants. We're not sequencing the particular variant in an individual, for instance, at point of care, to help make a therapeutic decision.

MARTIN: Thank you.

Please join us for the second episode of this two-part podcast. Dr. Griffin offered additional insight into the highly contagious Omicron variant and revealed some potentially unexpected data on its impact.

This is Deborah Martin for Elite Learning.

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