Ask A Biologist Vol 088 (Guest Melissa Wilson Sayres)

Monster DNA

In the tiny world of DNA, we might call genomes monsters. These huge sets of information include all the codes for all the genes present in an organism. From genomes, we can learn about the traits, diseases, and evolution of a species, and that's just a start. What might such a monster set of data do for us if it was about our very own North American monster – the Gila monster? Computational biologist Melissa Wilson Sayres tells Dr. Biology about the Gila monster, the life-saving venom in its saliva, and what we might learn from the monster genome.

Transcript

Dr. Biology: This is "Ask a Biologist," a program about the living world and I'm Dr. Biology. In case you don't have it marked on your calendar, each year, April 25th is designated as International DNA Day. You might be asking "Why do we pick the 25th of April?" Well, it was on that date in 1953 that the structure of DNA was first published in the journal nature.

By the way DNA stands for Deoxyribonucleic Acid. And I know that seems like a mouthful, but it seems only fitting because after all we're talking about something. It's the blueprint and instruction set for all living things. While the discovery of the structure of DNA was a milestone, learning how it works packages information has been keeping scientists busy ever since.

My guest today is Melissa Wilson Sayres, a computational biologist who holds positions in the School of Life Sciences and the Center for Evolution & Medicine, in The Biodesign Institute at Arizona State University.

Her work revolves around population genetics, biology of sex, and about a half dozen other research interests. For this show, we get to learn about a new project, you could call it a monster of a DNA project. Welcome to the show, Melissa, and thank you for taking time to talk about some of your work.

Melissa Wilson Sayres: Thank you so much for having me. I can't talk about it enough.

[laughter]

Dr. Biology: At the beginning of the show, I talked briefly about DNA, which is Deoxyribonucleic Acid, but I didn't use the word genome. Can you give a 60 second introduction -- and I'll give you a few more seconds if you need it -- about the genome.

Dr. Melissa: The genome is what we consider all of the pieces of DNA in our cells. Typically, that's all the DNA that's passed on from genetic parent to genetic offspring. You might wonder why I used the word genetic, and I try to use that to clarify that we can have lots of family relationships.

When we're studying DNA, we're really interested in the person, or the people whose DNA helped make us, but that doesn't invalidate any of the other family relationships that we have.

The genome itself can consist of the genes that we typically hear about, so you might hear about a variant of a gene involved in breast cancer risk, or a variant of a gene involved in, typically it's in cancer risk or in other disease risk.

There's lots of pieces of our DNA in between those genes that are involved in regulating when and where those genes are turned on. For example, every cell in our body starts out having the same DNA, but my eyes don't look the same as my toes.

The reason for that is that there's the timing and the amount of genes is different in my eyes and in my toes. In addition to those pieces of DNA that regulate when and where genes are turned on, there's a lot of stuff in between that's, kind of, space filler.

Some of it is parasitic elements that are taking up parts of our DNA. Some of it are genes that were around but died. Some of them are regions that we're still trying to understand what they do. That's kind of the most interesting thing to me is that we have this whole space within a very tiny cell and we're trying to understand what everything in that space does.

Dr. Biology: When you're talking about the human genome this is something that was actually one of the first genomes sequenced, and that's basically figuring all the pieces that are in there. And that was clear back in 2003 and we're still figuring out what we have unraveled. I think the message, when I think about it, is "Wow. There's so much more to learn just in the human genome."

We're going to shift gears just a bit. At the beginning of the show I was talking about a monster DNA project, and that was a little bit of a teaser...

Dr. Melissa: [laughs]

Dr. Biology: ...for the audience. Let's talk about your monster DNA or your monster genome project.

Dr. Melissa: To preface this, I've been studying human DNA and mammal DNA for about 11 years. Although sometimes we might refer to a person as a monster, I've never had the opportunity to study monster DNA and now, being at ASU, I've developed a collaboration with Dr. Dale DeNardo who, for much of his career, has been studying the Gila monster. The Gila monster, I have to say, I've completely fallen for this species. It is incredible.

Typically when I talk to people and I mention the Gila monster I get two responses, either "What is that?" and what it is, is this beautiful black and orange patterned reptile that's not terribly large. Bigger than an anole lizard but smaller than a cat, I would say, and there's a lot of interesting features about it.

The other response I get is "I'm so scared of them. I hope I don't get attacked by a Gila monster." To that I also have to respond that they are not aggressive. Typically, it's said that you have to help yourself get bit by a Gila monster.

They do have a very painful bite and they're described as one of only two venomous lizards but they don't have venom glands in the same way that snakes do or even a venom gland like the platypus, which is wonderful. But their bite, when someone's been bit, it's sometimes described as flaming lava through your veins. [laughs]

So you don't want to get bit but you really have to try to get bit. I've now watched many, many videos on YouTube of people recording Gila monsters, or Gila monster interactions between their cat, or a Bobcat, or a squirrel. The only time I've seen someone get bit is when repeatedly poking at the Gila monster, and going around it.

People say, "Oh, the Gila Monster will bite you if provoked." Well, if you're poking me all the time I might bite you too. [laughs]

Dr. Biology: Right [laughs] . Let's get into our Gila monster genome. Let me mention, this is part of the animal super power challenge. I love that just in itself.

Typically when you do a research, in the past, you would go to NIH, or NSF, or some federal, or maybe large philanthropic granting agency to get funding. You're actually doing crowd funding to sequence the genome of the Gila monster. Let's talk about this.

Dr. Melissa: There's couple of reasons why. One is that it's actually becoming much more difficult to get funding from these large agencies to do a genome. Genomes aren't the difficult, extremely expensive, extremely time consuming thing that they once were. That doesn't mean that they're cheap, still.

To do a whole high quality Gila monster genome will cost about $30,000. It cost millions of dollars to put together the human genome. In perspective it's much less expensive. It can be difficult to find funding from the traditional agencies for that.

Moreover, one of the things that I've always been passionate about is working with the public, and trying to share the science that we're doing. This is a way that we can have direct buy-in from the public, on the science that we're doing.

I can answer questions. The way that the particular site we're using, experiment.com, is setup is that people can ask questions once they've backed the project. About the project, they can share stories that they've had. We can build the community of interest around the Gila monster, its biology, and what we're aiming for is sequencing its genome.

Dr. Biology: Why would we sequence the genome of the Gila monster? As a species, humans were very...well, what would I've to say?

Dr. Melissa: Narcissistic [laughs] .

Dr. Biology: Yes. It's a big word, meaning it's all about us, right? It's all about us. Why are we interested in the genome of a Gila monster?

Dr. Melissa: There are a few reasons we should be interested in the genome of the Gila monster. For a large portion of the population -- lizards are scary, and gross. For them, I hope that this project will convince them that, that's not true, of lizards, or snakes and lizards. Particularly not true of the Gila monster.

We're hoping to showcase in particular with the animal super power challenge is that the Gila monster we believe has a super power. That super power is that there's a peptide in its venom, or to be more specific in its saliva, because they don't have the venom glands, in its spit, right?

We're interested in Gila monster spit. There's a peptide there that has been studied for a couple of decades now, and is been used in treatments that are very successful for Type II diabetes. You might wonder Gila monster spit! Well, for some of those people who poked Gila monsters enough, and did happen to get bit, one of the things that was noticed is that their insulin levels would drop when they were bit by the Gila monster.

There was some work trying to figure out what part of that spit was leading to regulating insulin. The challenge is though that we don't know much about the DNA of the genes that are expressed in Gila monster spit.

You can think of spit, and what's composed the saliva in the Gila monster, like other organs. Just like it takes certain genes to get my finger nails different from my nose, it takes different genes to get Gila monster saliva the way it is, and to get that burning lava feel.

With a genome we can start to see how many genes are there. We can look at the sequences of them, maybe which genes are interacting with which. One important part that doesn't often get conveyed when we're studying DNA is that genes don't act by themselves, they act in pathways, they have partners that they co-regulate with.

Part of what we can do with the Gila monster genome is, is try to infer which genes are working in a group together, that's actually allowing this peptide to be useful in treating Type II diabetes.

There are other things, just in general that are interesting about the Gila monster that are unique to it. It lives in the desert so it's native to Arizona and so some of the things that it does, it stores fat in its tail. It also stores water in its bladder so it can drink a sufficient amount of water and then uptake it later from its bladder which is interesting and weird. But it has these weird, that's me being a mammal, right? Judging something else for doing something in a different way, but I think its physiology is really interesting.

Other reasons you should want to find the Gila monster is it's just this fantastic and unique creature that is specific to our desert environment. It does not live across the United States. One of the things that we're finding is that as people are building their homes, we are encroaching on Gila monster habitats.

There are two challenges. One is that the Gila monsters are going along their typical route trying to find food, trying to survive, and people, who do to misinformation, are afraid of them and are hurting and killing them. Not everyone does, some people will call the Game and Fish Services, and they'll come and take the Gila monsters. But for some reason and we don't understand why, the Gila monsters cannot be re-homed.

They don't survive if we try to give them a new burrow. I moved from California to here. I grew up in Nebraska. I moved to Pennsylvania. I seem to be doing OK. I can find food, I find shelter. The Gila monsters don't seem to do too well with that. We don't have genetic resources for determining how much genetic diversity there is in Gila monsters. How much is human encroachment of their habitats affecting them.

Not only can we understand a bit more about their role in treating diabetes, we can also generate resources that can be used for conservation of Gila monsters.

Dr. Biology: I didn't know that you couldn't relocate a Gila monster.

Dr. Melissa: This is typically what my collaborator, Dale DeNardo, has experienced. He's been able to track Gila monsters, how large their range is, and watching them, and he works closely with Game and Fish and he has several Gila monsters in his lab for that reason. They're fairly sedentary so you can watch them, they kind of, not waddle. I'm not sure the best word to describe how they walk, but waddle is maybe the closest to it.

Dr. Biology: Especially a full one.

Dr. Melissa: Yes, a full one. Oh, I didn't mention that another fascinating thing about them is that they can eat a fifth to a third of their body weight in one sitting and they just hork it down. [laughs] It's just like, "Gulp, gulp, gulp." And they typically eat eggs or juvenile mammals, but if they can get one, they'll catch a squirrel or a rabbit and just swallow the whole thing down. Thinking about a third of your body weight, that would be a 150 pound person eating 50 pounds of food.

Dr. Biology: Wow.

[laughter]

Dr. Biology: Let's get back to our genome. The human genome project took 13 years. As you mentioned, millions of millions of dollars and lots of scientists around the world. You said that it's going to be around $30,000 to sequence the genome of the Gila monster. How long is it going to take?

Dr. Melissa: We anticipate it to take less than a year. That $30,000 does not include the cost of people to analyze it. We have that part covered. This is just to extract the DNA and to chop it up into little pieces and then to sequence it. And then we'll get that information back and we'll assemble it.

That's part of why we're really able to do this with crowdfunding. We're going to get the first third of it done in the crowdfunding. So there's several steps to doing a whole high quality genome, and the first part is scaffolding the genome. One part is we're going to get DNA from three males and three females so we can get a sense of some of the genetic diversity across Gila monsters but also, and I hadn't mentioned this yet, one of the really fascinating things about Gila monsters to me.

This is when I first got interested in them is that in humans, we have chromosomal sex determination and that is individuals with two X chromosomes typically have ovaries and make eggs and individuals with an X and a Y chromosome typically have testes and make sperm. The X and the Y are very different sizes. The Y chromosome is very small and has lost a lot of genes on it.

We know from doing some painting of the chromosomes, you can take a cell and paint the chromosomes. Gila monsters are just the opposite. Females have a large chromosome and a small degraded chromosome. Males have the two large sex chromosomes. So they have chromosomal sex determination like we do but just opposite.

Part of what's a basic science interest to me is trying to figure out what are the genes and the Gila monster's sex chromosome. Do they have a single regulatory switch like humans do? Or does sex determination occur differently in them? For me, when I said that I studied humans and mammals, a lot of what I study is evolution of sex chromosomes and sex differences. Here, it's also a chance to look at sex differences in a monster.

Dr. Biology: [laughs] We really do have to say that's one of those names that I know, Dale and most of the people that work with the Gila monsters, wished they didn't have the monster tagged to them because it really is unfair. I've spent a fair amount of time with him just because I've had Dale on the show as well.

I think they're, in many ways, cute. They're very interesting because they're different.

Dr. Melissa: They squat and they have little chubby tails, and they could be a dragon, they could be a teddy bear monster, right?

Dr. Biology: A good dragon. [laughs] What do you do with the information that you get from sequencing a genome? Where does it go, the information? What do scientists do with it?

Dr. Melissa: One of the things that we want to be absolutely clear about is that when we get the genome sequence, this will be publicly available. Anyone, anywhere will be able to download and look at the Gila monster genome. One of the first things that we do is we compare it to the genomes of different species that we have.

For example, to illustrate why we do this is if I said, "I want you to tell me about humans." Then I just gave you one human and I said, "Tell me, tell me about humans." Well, it's not very useful unless you have something to compare it against.

With the Gila monster, we're both going to compare against different Gila monster individuals, and we'll also compare against different species so we can see which parts of the Gila monster DNA are very conserved so may be very important. Which parts are changing very quickly in the Gila monster and so maybe part of what makes the Gila monsters so unique with its saliva, with its pattern, with its fat storage, with its bladder storing water.

By comparing against other species, we can see both what's unique and what's shared across those species.

Dr. Biology: So this leads me into who would use this information so I could see drug companies? Obviously, for medical purposes. As you mentioned, conservation could give us the key to why maybe they're not easy to relocate. The interesting thing to me about it is that when we talk about DNA as you mentioned, it's inside all these cells, and it's packaged in such a way that it's extremely efficient because it has a lot of information in it.

It takes a while to learn what that information is there. It's just like giving someone a huge library. Just because you have the library doesn't mean you understand it because you have to read it and into some cases you had to understand the language.

Dr. Melissa: Yes.

Dr. Biology: Who's involved with this? Who's going to be doing this work? It's you and Dale but I suspect there's more.

Dr. Melissa: For the first stage and you're absolutely right. What we're doing in effect if I can expand on your metaphor is we're building the library and then we're going to let that resource be shared with everyone. For the building that resource part, it's going to be individuals that are working with me in the lab.

We have postdoctoral researchers, the people who have a PhD and are gaining extra training. We have people who are in graduate school right now. There's both master students and incoming PhD student.

One of the things that I'm most excited about is that we have a lot of undergraduate students involved in this project. If you are interested you can go to my website and see that I've been really dedicated to training undergraduates both in biology and in computational biology. Gaining the skills that they'll need and that are translatable to any kind of biological research that they'd be interested in.

Part of this project will be training across those different levels in what do you do when you get a file back with 400 million tiny pieces of DNA in it. It's the most complicated puzzle you could think about and nobody's showing you the picture of what you should be putting together.

We're going to work together with them to learn about different pieces of how you put that puzzle together because you take a certain strategy. That's one of the other aspects of the crowdfunding is that it's really allowing us to focus on training students also.

Dr. Biology: I have to mention that that's one of the things, I think the School of Life Sciences does a really good job and by design. Undergraduates who come to ASU that want to get into the world of science, you don't just study it, you do it.

Dr. Melissa: Yes. That's one of the things I noticed in my lab and many other research labs here. Doing research as an undergraduate at ASU is not just washing glassware, it's not just by osmosis being around other people. You're involved in the projects and that is both incredible and sometime frustrating because science doesn't always give us exactly what we're looking for. We can run into walls and challenges.

To me that's the most important part of undergraduate training here is that we work together so they're not struggling by themselves. We're struggling as a group together to try to figure out what the challenges are, or how we can overcome them and really make them the students prepared and integrated.

I don't in my lab consider there to be a hierarchy. There are people who have training and expertise in certain skills and they help with training other people who need to learn those skills but the people with the expertise maybe a sophomore who's already been working in the lab for a year-and-a-half or they maybe the postop that's coming in. We work together really as a team.

Dr. Biology: I want to shift in to a part of the show that I do with all my scientists. I have three questions. We'll jump into them. When did you first know you wanted to be a scientist? Was there an, aha moment?

Dr. Melissa: No. There was no aha moment. I have always liked the natural world around me. Maybe the moment was realizing what it was that I wanted to do in science but I always thought that science was interesting. In particular I was actually interested in mathematics. I majored in mathematics as an undergraduate.

What got me to switch into my particular area was that I did a research experience for undergraduates at the University of Nebraska Lincoln in the math department there where we worked on mathematical biology. We used systems of differential equations to model tumor growth and how we might be able to treat it.

I suppose seeing how useful computation in mathematics was to biology and that we could make real meaningful differences in biology by using computation and mathematics. That really turned the tide for me about where I was thinking of going.

I applied to graduate school in the math department and in a biology department that had a bioinformatics program. I ended up obviously choosing the bioinformatics program. What was really interesting about that program is that it allowed me the opportunity to do rotations with different people.

As a math major I didn't do experimental biology research. I had taken genetics. I had taken a couple biology classes but I were one...I was amazed they let me in because it was a computational biology program and I had training in neither biology nor computation to the level that my peers did. I recognize now why because in science it's really useful to have a diversity of opinions.

Although I felt a little bit like I didn't belong, I do hope that I was able to contribute to things in a way that was meaningful. While I was there I first learned about yeast and it smelled wonderful in the lab like bread every day that we would go in and in growing the yeast and doing different experiments with them.

I did a rotation working with the Arabidopsis, this mustard weed. My third rotation was in genetics of sex chromosomes and I found myself staying up at night reading extra papers, trying to absorb everything that I could and realizing there were more questions than answers in my head. I still find myself feeling that way every day that there's more things that I want to know about that field.

Dr. Biology: Did you always like math?

Dr. Melissa: Yes I always loved math.

Dr. Biology: You're always good at it?

Dr. Melissa: I suppose I always did well. I get these questions sometimes and it's challenging to me because I'm not a math-wiz so chess I'm terrible at chess. I always tried to like chess because I felt like if you're good at math you should be good at chess. I don't know why I had that perception.

I never felt like a math-wiz but because I liked math and I had parents who encouraged me to do the thing that I liked, I stuck with it but I never felt I was really excellent at it. I have peers who I took classes with who I could see it clicked for them and everything was quick and easy all of the time.

It wasn't easy to me but it was fun and I suppose I feel very lucky that I had teachers and family who supported me in doing the things that I found was fun instead of what I...I get most frustrated with this one. I'm a parent now and I see other parents say "Oh math is hard, you don't worry about it. Math is hard for everybody. Just try to get through it" but being hard doesn't mean it still can't be fun.

I guess it's why I hesitate a little bit with that because I never felt like it came especially easy to me but it was like solving problems. It was like doing puzzles and I thought that was fun and so it wasn't easy but I wanted to do more of them.

Dr. Biology: Now I'm going to take it all away. We got down this path.

Dr. Melissa: [laughs]

Dr. Biology: I'm going to take all the things you've been doing. You can't be a scientist, I'm going to take...the mathematics is going to go away. I'm going to take away teaching because I know you'd love to teach. This is an exercise and stretching. What would you do and what would you be if you could do anything or be anything?

Dr. Melissa: If I can't do the things that I'm doing now, I would be an artist. I love sketching and drawing and painting and I appreciate how much work and passion goes into that as much as any field. I used to keep sketched books. I used to think about just doing art all of the time. Maybe that's not so strange. There's a lot of creativity in science as there is in art.

Some of the people I find that like doing science the most also they like thinking about different ways of doing it trying to see the question from a different angle. In similar ways artists often have their unique view of life and of reality. There's no one view of that that is exactly correct.

We get to interpret it in different ways. I'm always an off artist and really try to support them because what artists are doing is fundamentally creating new information in the same way that scientists are creating new information.

Dr. Biology: To add to that is we design experiments. We use the word design for a reason. Having the ability to approach a problem from different angles as you said is very important for the artist and the scientist.

Dr. Melissa: Maybe I skirted your...”you can't do the things you're already doing.” But, I still want to be a creator.

[laughter]

Dr. Biology: The last question, what advice would you have for a young scientist or perhaps someone who's been doing another career and realize that they really love mathematics or they love biology and they want to switch?

Dr. Melissa: You can do it. I say I'm a little caught off guard by that question. One of the challenges to getting in science is thinking that the people who are doing it already have everything mastered. We are not masters. There is this concept that the more you learn the less you know because you're recognizing how much out there there's still to discover.

For anyone who is trying to get into science, there will always be things you don't know because there's always things that none of us know. Every now and then there's going to be people that you come across that will judge you for your background or for what you know or don't know.

Maybe the best advice is to realize that getting into science, science is no different than any other field in that sense that there are people who will be supportive of you, there are people who have big egos, there are prejudices that exist in science that it's not sheltered. We are humans doing science and you are human who can do science also and you are welcome.

Dr. Biology: On that note, Melissa Wilson Sayres thank you for visiting with me today.

Dr. Melissa: Thank you so much for having me.

Dr. Biology: You've been listening to Ask a Biologist and my guest has been Melissa Wilson Sayres, a computational biologist who holds positions in the School of Life Sciences and the Center for Evolution & Medicine in The Biodesign Institute at Arizona State University.

To like to know more about the animal superpower challenge, you can point your browser to experiment.com/grants/animal-superpower. We also have a link on the companion website for the show along with the few other links to learn more about DNA.

The Ask a Biologist podcast is produced on the campus of Arizona State University and is recorded in the grassroots studio house in the School of Life Sciences, which is an academic unit of the College of Liberal Arts and Sciences.

Remember, even though our program is not broadcast live you can still send us your questions about biology using our companion website. The address is askabiologist.asu.edu or you can just Google the words "ask a biologist." I'm Dr. Biology.

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