LSUHS Podcast: Suicide Risk Genes

Audio	Video
Mark Klein: Today on the LSU Health Shreveport Podcast, we're looking at innovative research conducted here on our campus and how it helps shed light on an important topic that, frankly, can be difficult to discuss. In fact, topics like this are one of the reasons we launched this podcast. Some conversations require nuance, context, and the time to discuss them appropriately. A brief trigger warning: today's conversation addresses suicide and suicide risk genes. For additional resources and information, please refer to the episode description. Nearly everyone has been impacted at some point by the loss of someone to suicide. According to the World Health Organization, nearly 800,000 people die by suicide each year, and millions more experience suicidal thoughts or behaviors. Scientists have long known that suicide risk can run in families and that certain genetic factors are associated with suicidal behavior. What remains less clear is how these genes function and influence behavior. Today on the LSU Health Shreveport Podcast, we'll introduce you to one of the scientists helping answer that question. Our guest has spent more than 32 years in academic research. He was recently published in *Translational Psychiatry* after producing the largest behavioral study of its kind. He serves as a Professor of Psychiatry and Behavioral Medicine. Making his LSU Health Shreveport Podcast debut, Dr. Donard Dwyer. We're glad to have you here with us today. **Dr. Donard Dwyer:** Thanks for having me today, Mark.	Mark and Donard Dwyer, PhD, Interview in a Television Studio

Mark Klein:
Exciting things to talk about. I want to jump right into this study. What exactly were you looking for? As I understand it, this discovery actually goes back quite a ways and was somewhat unexpected.

Dr. Donard Dwyer:
Yeah, it was.
I was telling you earlier that this isn't something you would sit down and intentionally plan from the start.
In my research, we use a model organism called *Caenorhabditis elegans*, or *C. elegans*, a microscopic soil nematode. It's widely used because it's an excellent genetic model, but it also displays behaviors that may help us understand what's happening in humans.
The suicide-related research came about somewhat accidentally.
We were actually studying a completely different behavior, looking at how animals search for food and the genetic control of foraging behavior.
We noticed that one particular strain, which had a mutation in the equivalent of the human insulin receptor gene, behaved differently. Instead of becoming more active when removed from food and searching for it, these worms would simply sit still.
At first, I thought something was wrong with them, so I gently touched them. They were capable of moving, but they chose not to. They would remain there until they died.
Because I also work in pharmacology and psychiatry, we wondered whether different medications might restore their normal behavior. We tested antidepressants and antipsychotic medications.
When we exposed them to antidepressants, the worms began moving normally again.
That led to two questions. First, was this behavior relevant in any way to suicide? That was a significant leap of faith. Second, around the same time, several genetic studies had identified suicide risk genes. We wondered whether mutations in those genes would produce the same behavior.
We viewed the behavior as diminished motivation. The worms should have been searching for food but were not motivated to do so. One of the risk factors for suicide in humans is hopelessness, a diminished motivation to engage with life.
So we began testing those suicide risk genes.
We were able to obtain about 17 strains carrying mutations equivalent to known human suicide risk genes. Of those 17 strains, 10 displayed the same behavior.
We then tested various medications to see whether they could reverse the effect. Antidepressants were highly effective. Clozapine, which has also been shown to reduce suicidality, restored normal behavior as well. Lithium also worked in some strains, although not all.

That was the foundation for the publication.

Mark Klein:

Let's talk about the next phase. What happened after that?

Dr. Donard Dwyer:

The original behavior involved diminished motivation, but there was a second behavior we were interested in studying.

It's unfortunately named "social feeding." Normally, worms feed individually. Some strains, however, gather together along the edge of bacterial food sources and form clusters.

Researchers originally called this social feeding because the worms appear to be interacting socially. In reality, they're avoiding oxygen.

The edge of the bacterial lawn has lower oxygen levels, and these particular worms prefer that environment due to mutations in a gene associated with neuropeptide Y signaling.

Neuropeptide Y reduces anxiety. When it's absent, worms become more anxious and display exaggerated threat responses.

That interested us because exaggerated threat perception is another factor associated with suicide risk.

Broadly speaking, researchers often discuss four major categories associated with elevated suicide risk:

1. Hopelessness or diminished motivation
2. Exaggerated threat perception
3. Perceived burdensomeness
4. Impulsivity

The first phenotype aligned with hopelessness. The second aligned more closely with exaggerated threat perception.

Again, we tested medications and found a pattern similar to what we had seen before. Antidepressants and clozapine were especially effective.

We then looked more closely at what these genes actually do.

Many of them were involved with neuropeptides. Others affected neurotransmitters such as serotonin and glutamate, both of which have long been associated with suicidal behavior. Others encoded kinases, proteins that regulate many cellular pathways.

The final part of the study examined where these genes are expressed in the brain.

If these genes were working together, we suspected they might be active in similar brain regions. That's exactly what we found.

Many of these genes were expressed in areas associated with reward, motivation, fear, and threat processing, including regions such as the amygdala and hippocampus.

At that point, the story began to fit together remarkably well.

None of this had to happen. The worms didn't have to show similar behaviors. The behaviors didn't have to respond to medications. The genes didn't have to be expressed in related brain regions.

But they did.

Mark Klein:
Let's jump from the lab to real life.
How do you hope work like this changes the way people think about suicide and suicide risk?
Dr. Donard Dwyer:
I'm glad you asked that because ultimately we want this work to go far beyond studying worms.
One of the most important takeaways is that many people may not appreciate how strongly biology and genetics contribute to suicidal behavior.
What these studies show is that certain genes can produce fundamental biological changes.
One of the themes that emerged is that many of these risk genes are normally involved in ancient survival systems. That suggests there is a deeply rooted biological basis for behaviors that can ultimately place someone at risk for suicide.
When we begin thinking about suicide as a biologically driven condition, similar in some ways to other diseases, it changes how we approach it.
I often use the example of a brain tumor.
Mark Klein:
I'd like to go deeper into that comparison because it's a really interesting way of reframing how we think about this issue.
Dr. Donard Dwyer:
That's exactly why I use it.
When someone dies from a brain tumor, our response is sadness and sympathy. We recognize that a disease process occurred.
When someone dies by suicide, however, people often immediately begin asking questions. Was there a failure of character? A failure by family? Friends? Physicians? Therapists?
The reactions are fundamentally different.
Yet there are striking similarities.
Both conditions involve biology and genetics.
Both involve environmental influences. In one case, it may be trauma or adversity. In the other, exposure to carcinogens.
Both involve reduced resilience in important systems. For example, resilience in coping mechanisms versus resilience in the immune system.
Eventually, both conditions can overwhelm the systems designed to manage them.
In one case, a tumor grows beyond the body's ability to control it. In the other, hopelessness and despair can overwhelm normal psychological defenses.
There is also an element of lost control. A tumor escapes the immune system. In suicidal behavior, impulsivity and emotional overwhelm can bypass logical thinking.

The parallels are remarkably strong.
Yet society often treats these situations very differently.

Mark Klein:
Where do you hope the public conversation around suicide goes from here?

Dr. Donard Dwyer:
My hope is that we eventually think about it much more like other serious medical conditions.
Some brain tumors respond to treatment. Some unfortunately do not.
Similarly, some people experiencing suicidal thoughts respond well to treatment, whether that's psychotherapy, medication, social support, or a combination of approaches.
Others may experience more treatment-resistant forms of illness.
That reality should not lead us to blame anyone.
Families should not feel that the outcome occurred because they didn't love someone enough or because they failed in some way.
Rather, we should understand that many biological, psychological, and environmental factors were interacting together.

Mark Klein:
Earlier you mentioned that suicide is often the result of a combination of factors.
Do we know how much is driven by genetics versus outside influences?

Dr. Donard Dwyer:
Not precisely.
There is clearly a significant genetic contribution. Suicide risk does run in families.
There are also biological factors involving neurotransmitters, hormones, and neuropeptides that may be influenced by genetics, environment, or both.
External factors matter too. Things like bullying, trauma, and adversity absolutely play a role.
But many people experience those same events without developing suicidal thoughts.
That's why it's difficult to separate the factors cleanly. They interact with one another in complex ways.
Trying to reduce it to a simple percentage may actually obscure how interconnected those influences really are.

Mark Klein:
Thinking back on this research, what surprised you the most?

Dr. Donard Dwyer:
The moment when the different behaviors started fitting together.
One behavior involved diminished motivation. Another involved exaggerated threat perception.
Eventually, it became clear that both behaviors related to survival.

Searching for food, avoiding danger, responding appropriately to threats, these are ancient survival mechanisms.
That realization helped us see the bigger picture.
These risk genes appear to support our drive to survive. When those protective influences are disrupted, individuals may become more vulnerable.
That was one of the most meaningful moments in putting this entire story together.

Mark Klein:
As we wrap up, what do you hope families ultimately take away from this research?

Dr. Donard Dwyer:
First, I hope it helps reduce guilt and blame.
I've seen those emotions devastate families, particularly when the loss involves an adolescent or young person.
Second, I want people to understand that although some cases may be very difficult to treat, we never stop trying.
People who struggle with suicidal thoughts are often engaged in an enormous and heroic effort simply to keep moving forward.
Anything we can do to support that effort matters.
Pay attention. Listen. Watch for signs that someone may be struggling. Remove obstacles where possible. Offer support.
At the same time, recognize there are biological and genetic forces involved as well.
My hope is that families can hold both ideas at once: understanding the biology while never giving up on helping someone.

Mark Klein:
I'd like to finish on a more practical note.
If someone notices a loved one struggling, what would you recommend as a first step?

Dr. Donard Dwyer:
While the clinical side isn't my area of expertise, I can offer some general thoughts.
One of the biggest warning signs is diminished engagement with life.
We often ask people whether they're still enjoying hobbies, activities, friendships, and the things that once brought them happiness.
Encouraging someone to reconnect with life can be important.
At the same time, many people need professional help to get back on course.
A good starting point is often a primary care physician. Be honest about what you're experiencing. Listen when loved ones express concern.
Unfortunately, stigma still exists around mental health treatment, and reducing that stigma would help many people seek care earlier.
Most importantly, remember that nobody should blame themselves.

Audio	Video
If you're experiencing these thoughts, there is help available and there are treatments available. But if you never speak up, you lose the opportunity to receive that help.	
Mark Klein: Thank you so much for your time today. I really appreciate you being here and talking with us about this important research. The full publication will be linked in the episode description below. For more information on the LSU Health Shreveport Podcast, you can find us on YouTube, Spotify, Apple Podcasts, and wherever you get your podcasts. If you're interested in appearing on the show, send us an email at **SHVCommunications@lsuhs.edu**.	LSUHS Podcast animation.