Episode Book

EPISODE #6233

Fibromyalgia's 26 Genetic Clues

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SYNOPSIS

Fibromyalgia affects millions, yet it was long dismissed as a diagnosis of exclusion. A July genetic study of 2.5 million people identified 26 associated genome regions and pointed squarely at the central nervous system, while a major drug review this month delivered far less encouraging news. This episode explores what nociplastic pain actually means, why the HTT gene link surprised researchers, and how much of the condition remains unexplained.

TRANSCRIPT



Corn

Twenty-six genetic risk regions, and still no blood test that tells you whether you have it. That's the peculiar position fibromyalgia occupies now. Daniel, your route into this started with the stomach bug and cold currently flattening the household.



Daniel

Hannah, Ezra and I have been getting these bugs repeatedly, and thinking about why infections cause stomach aches somehow brought me to fibromyalgia. I know very little about it. I remember it being dismissed much like chronic fatigue syndrome. Has the science actually settled anything?



Herman

Quite a lot about biological susceptibility, much less about how to relieve it. Those have moved at painfully different speeds. The biggest genetic study arrived in July, and a major review of medicines arrived this month. Reading them together gives you both genuine progress and a fairly sharp disappointment.



Corn

The laboratory has overtaken the prescription pad.



Daniel

When people say fibromyalgia, what are they actually describing? Is it aching muscles, or something broader?



Herman

Persistent widespread pain, usually accompanied by fatigue, unrefreshing sleep and cognitive difficulties. People call that last part brain fog. Headaches and depression can accompany it, too. The pain matters, but so does waking after a night's sleep feeling as though the night never happened.



Corn

Sleep without the service provided.



Herman

Corn has strong contractual expectations of sleep. In this case they're justified. Someone can have enough hours in bed and still have severely disrupted restorative sleep. That interacts with pain and concentration, so treating the symptoms as unrelated complaints misses how they reinforce one another.



Corn

You're explaining me as a clinical comparison again.



Herman

Only your commitment to the subject.



Daniel

Does the pain mean something is damaged? If someone says their whole body hurts, I'd assume inflammation or muscle injury.



Herman

Sometimes those coexist, and clinicians still need to look for them. Fibromyalgia is usually described as nociplastic pain. Pain processing has changed without the tissue damage that would adequately explain the symptoms, and without a nerve lesion explaining them either.



Corn

Those distinctions are useful. A cut produces nociceptive pain. A damaged nerve can produce neuropathic pain. Here the nervous system can produce an excessive pain response even though the examination doesn't reveal an injury proportionate to it.



Herman

Central sensitisation is the dominant account. The central nervous system becomes unusually responsive to sensory input. Hyperalgesia means something painful hurts more than expected. Allodynia means something ordinarily non-painful, such as light contact, can hurt.



Daniel

That sounds like a mechanism. Why isn't that already the cause?



Herman

Because describing altered pain processing doesn't explain why that person's processing changed. Sleep, prior pain, inherited susceptibility and possibly immune activity can all enter the picture. Central sensitisation is useful, but it doesn't establish one complete chain of events for every patient.



Corn

Herman, I predict you're about to enjoy the genetic machinery more than the uncertainty permits.



Herman

I can enjoy machinery without claiming it explains the whole building.



Corn

Your excitement has planning permission already.



Herman

Here's the concrete advance. The July Nature Medicine analysis compared genetic variation across roughly two and a half million people, including about fifty-five thousand diagnosed cases. It identified twenty-six associated regions of the genome. That's a much stronger foundation than noticing a handful of candidate genes in small samples.



Daniel

What does associated mean here? They found something patients had and other people didn't?



Herman

More often, not exclusively. These are differences in how common variants are between groups. Each usually changes susceptibility modestly. The important next step was asking where the implicated biology operates. The inherited signal was enriched in brain tissues and neural cell types.



Corn

The enrichment points toward the nervous system. It doesn't mean every symptom originates at one location in the brain, or that other organs have been cleared of involvement.



Herman

The authors describe fibromyalgia as a central nervous system disorder. That directly challenges the old suggestion that these people simply lacked a genuine biological illness. Michael Wainberg, a senior author, called the biological basis “absolutely indisputable.”



Daniel

Does that mean the argument is over?



Corn

The argument that people need a visible injury before their pain counts should have ended earlier. This gives it substantially less room to hide. The argument about the exact biology is very much alive.



Herman

Corn, would you consider it enough to retire “diagnosis of exclusion” as the whole description?



Corn

You can identify a consistent symptom pattern rather than simply run out of alternatives. Still check for other illnesses. A fibromyalgia diagnosis doesn't prevent someone also having arthritis, thyroid disease or another cause of fatigue.



Herman

That distinction matters clinically. “We recognise this pattern” and “we have stopped investigating anything” are different decisions.



Daniel

What was the most surprising gene?



Herman

HTT. The strongest association was a coding variant in the gene associated with Huntington's disease. Carriers had about nine percent higher odds of fibromyalgia. Small individual effect, striking biological clue.



Corn

Before anyone hears that as a second diagnosis arriving...



Herman

A different variant causes Huntington's disease. This finding does not mean fibromyalgia is Huntington's, or that a fibromyalgia diagnosis predicts it. Genes perform ordinary biological jobs as well as becoming associated with particular diseases.



Daniel

Is there anything useful in that connection beyond the surprise?



Herman

Potentially. Another implicated gene, GPR52, encodes a brain-specific receptor involved in regulating huntingtin levels. It's already of interest in Huntington's drug development. That creates a route worth investigating, not a medicine we can transfer straight into practice.



Corn

A shared gene is not a transferable prescription.



Herman

Other signals concern neural development, signalling and excitability. CELF4, for instance, helps regulate the excitability of pain-sensing neurons. I'm tempted to list the rest...



Corn

Your face has become an appendix.



Herman

I'll spare you the gene inventory. The collective pattern is more informative than any one name. There were also strong genetic correlations with low back pain, PTSD and irritable bowel syndrome, above point seven.



Daniel

Does that mean the same genes cause all of those?



Herman

It means inherited susceptibility overlaps substantially. It doesn't establish identical causes or make the conditions interchangeable. Shared pathways might eventually offer treatments across several conditions, but that's a development prospect.



Corn

It also helps explain why a patient can collect diagnoses without collecting separate explanations. Pain, bowel symptoms and disturbed sleep may be interacting rather than coincidentally arriving together.



Herman

We now go live to Monty, apparently reporting from a carnival in honour of today's topic.

M

Monty

I am standing here in the middle of the Avenue of Central Sensitisation, where the samba band is so loud I can barely hear myself think, and the floats behind me are throwing glitter shaped like the letter H T T, which is either a genetic locus or a very confused tribute to Huntington, and I have been told to report on fibromyalgia but honestly the whole parade has been drowned out since the second bar.



Corn

Monty, can you get somewhere quieter?

M

Monty

The crowd is enormous, something like two and a half million people, and every single one of them is asking me whether the pain is in the brain or in the body, and I keep pointing at the giant inflatable neurone and shouting that it is both, it is always both, but the trombones will not let me finish.

M

Monty

Monty, reporting live from the Carnival of Widespread Tenderness, where the samba has now been going for six hours and nobody has slept.



Herman

Those overlapping genetic signals also complicate the idea that we should look for a single isolated defect. There may be multiple routes into the same clinical pattern.



Daniel

Why do I mostly hear about women having it?



Herman

Women are diagnosed roughly three times as often, but the genetic architecture was nearly identical across sexes. That points us toward other explanations for the difference, including hormones, environmental exposure, pain sensitivity and diagnostic habits.



Corn

Hormones are biology too. We shouldn't translate “not explained by these inherited differences” into “not biological.”



Herman

Fair correction. Not explained by a substantially different inherited architecture. The study also had an ancestry limitation, with about ninety percent of cases of European ancestry. A huge sample doesn't automatically represent everybody.



Daniel

Can people get tested for the variants?



Herman

They won't give a useful yes or no diagnosis. Plenty of people carry susceptibility variants without developing fibromyalgia. The authors suspect an additional trigger may matter, perhaps an existing painful arthritic condition. We haven't established one universal trigger.



Corn

Twenty-six clues, no diagnostic barcode.



Daniel

What about the idea that it's autoimmune?



Herman

Still open. Patient-derived antibodies have produced pain hypersensitivity experimentally and bound cells around sensory nerve structures. That's intriguing. A trial removing antibodies from the blood reported only small group-level effects, though. The neurological genetic signal doesn't rule out immune contributions, and those antibody findings don't establish autoimmunity as everyone's explanation.



Corn

The trouble historically was that uncertainty got treated as evidence against the patient. Fibromyalgia was recognised decades ago. Formal criteria in nineteen ninety relied heavily on tender points, places where pressure elicited pain. Later criteria incorporated fatigue, sleep and cognitive symptoms more directly.



Herman

The generalised pain requirement added in twenty sixteen helped avoid classifying regional pain as fibromyalgia. Diagnosis evolved as clinicians recognised that pressing particular spots wasn't capturing the full condition.



Daniel

Was the old diagnosis unreliable, then, or were doctors just dismissive?



Corn

Both things can happen. Criteria can improve while patients were still telling the truth. A changing definition does not retroactively make their pain imaginary.



Herman

That's the parallel with ME/CFS. People were discredited as witnesses to their own illness. An unfamiliar symptom pattern became a reason to doubt the person describing it, instead of a reason to improve the explanation.



Daniel

How common is this? Are we talking about a rare condition with an unusually visible patient community?



Herman

Estimates generally cluster around two to four percent worldwide. A large American survey put self-reported prevalence around two percent. The commonly quoted American count is about four million adults, possibly more, depending on definition and ascertainment.



Corn

Those aren't interchangeable measurements. Survey reporting, diagnosed cases and symptom-based estimates capture different groups. You can make the condition look rarer simply by counting only people who managed to get diagnosed.



Herman

Within the genetic study's contributing cohorts, recorded prevalence ranged from roughly one percent to more than seven percent. That reflects different populations and recording practices as well as potential differences in illness.



Daniel

If the diagnosis is still clinical, what stops it becoming a label for anything doctors can't explain?



Herman

A structured assessment of widespread pain and associated symptoms, their persistence and their distribution. Plus examination and targeted investigation where another condition is plausible. The new Royal College of Physicians guidance this month supports that process and explicitly recognises fluctuating symptoms.



Corn

Diagnostic uncertainty calls for follow-up, not an unlimited licence to label everything fibromyalgia. Equally, normal routine blood results don't measure whether someone's pain processing is normal.



Herman

Corn, suppose your pain improved but your fatigue didn't. Would you call a medicine successful?



Corn

Partly successful. I'd care whether I could do something I'd stopped doing, and what the medicine cost me in side effects. If I slept longer but felt foggier all morning, a better sleep score wouldn't settle it.



Herman

That's why the treatment review is so useful. It examined pain, sleep, overall symptoms and physical and mental health separately. “Better” can mean several things.



Daniel

What drugs are actually available?



Herman

Four have FDA approval for fibromyalgia. Pregabalin affects neural excitability. Duloxetine and milnacipran alter serotonin and noradrenaline signalling, including pathways involved in pain regulation.



Herman

The newer addition is sublingual cyclobenzaprine, approved in August last year. Other medicines are used off label. The European Medicines Agency has approved none specifically for fibromyalgia, judging the evidence of benefit insufficient.



Corn

The Atlantic is doing a lot of regulatory work.



Daniel

That sounds like a major disagreement. Is Europe denying the condition exists?



Corn

No. Doubting a drug's demonstrated benefit is entirely compatible with accepting the illness. Those judgments must stay separate, or every disappointing trial becomes another referendum on patients.



Herman

The October BMJ Medicine review pooled a hundred and fifty-one randomised trials involving more than thirty-two thousand participants. It used a network analysis, allowing comparisons across treatments even when every pair hadn't been directly tested.



Daniel

What did it find in plain language?



Herman

Some medicines may help some people report meaningful improvement. Certain classes may help sleep or overall symptoms. The benefits were generally small and uncertain. No drug's pooled effect on pain, physical health or mental health reached the review's threshold for clinical importance.



Corn

A very crowded medicine cabinet for that result.



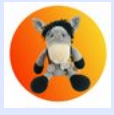
Herman

It doesn't mean no individual benefits. An average can conceal responders. It does mean we shouldn't promise that the typical patient will achieve a substantial improvement from the evidence available.



Daniel

I'm struggling with “meaningful improvement” alongside “not clinically important.” Aren't those opposites?



Herman

Different outcomes. Someone might answer a global question saying they're better because they sleep more comfortably or feel less distressed. Their measured pain reduction might remain small. Also, different analyses use different definitions of improvement. We shouldn't compress all of them into one success rate.



Corn

Nor assume someone is wrong about feeling better because their pain score stayed steady. Being less exhausted matters. It just doesn't demonstrate a large pain-relieving effect.



Herman

There's also a trial problem. Side effects can reveal who received the active medicine, weakening blinding. Expectations can then influence global ratings. That doesn't erase reported improvement, but it makes interpretation harder.



Daniel

Were these long trials? People have this for years.



Herman

The median follow-up was twelve weeks. Only nine trials reported results beyond six months. That leaves a large mismatch between the duration of the illness and the duration of most evidence.



Corn

Chronic condition. Seasonal evidence.



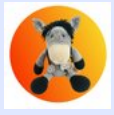
Herman

Roughly sixty percent were industry funded, and fifteen trials were flagged for trustworthiness concerns. Industry support doesn't automatically invalidate a result. Short follow-up, uncertain evidence and questionable trials collectively limit confidence.



Daniel

What about cannabis or low-dose naltrexone? Those names come up around chronic pain.



Herman

This review didn't establish benefit for either. They shouldn't be presented as the answer that conventional medicine somehow overlooked. They're investigated options with inadequate evidence here.



Corn

Novelty can be remarkably good at impersonating effectiveness.



Herman

Would you accept a small benefit, Corn, if there were almost no downside?



Corn

My objection is to selling a small uncertain benefit as a transformation. I would also want to know whether it persisted. Twelve better weeks might matter enormously, but twelve weeks cannot tell me about the next several years.



Daniel

If medicines are that limited, what does treatment actually consist of?



Herman

Individually adapted aerobic activity and strengthening, physical therapy, support for sleep and psychological therapies, including CBT. Care usually involves several modest interventions rather than one decisive prescription. It can often be coordinated in primary care, though complicated cases need specialist input.



Corn

CBT needs careful explanation in this context. After years of hearing “it's psychological,” being offered psychological therapy can sound like the same dismissal wearing a different tie.



Herman

Its role is to help with the consequences and reinforcing processes of persistent pain, including disrupted activity, sleep and distress. Benefiting from it doesn't prove that faulty thinking caused the illness.



Daniel

Does the exercise recommendation also apply to chronic fatigue syndrome?



Herman

We need to separate them there. ME/CFS has post-exertional malaise as a central feature, a disproportionate worsening after exertion. Fibromyalgia and ME/CFS can overlap, but their criteria and management considerations differ. You cannot simply transfer an exercise prescription between them.



Corn

Even within fibromyalgia, “exercise” doesn't mean ignore symptoms and push indefinitely. Adaptation is the substance of the recommendation, not a footnote.



Herman

I nearly said exercise is the strongest treatment. More carefully, it's a cornerstone of care, not a guaranteed solution. Symptoms fluctuate, and building a sustainable level of activity can take time.



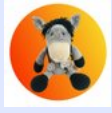
Daniel

That fluctuation must make the disbelief worse. Someone sees you on a better day and assumes you've recovered.



Corn

Patient advocate Kristal Kent describes seeming okay one day and being crashed out in a flare the next. A brief encounter gives an observer a very small sample. The observer often gives that sample extraordinary authority.



Herman

The stakes are serious. An American survey analysis found almost sixfold higher odds of a past-year suicide attempt among people reporting fibromyalgia. That's an association, not proof of one cause. Pain, sleep disruption, depression and social consequences can



Herman (continued)

compound each other.



Corn

Someone can be suffering badly while looking entirely ordinary. A useful clinical conversation has to leave room for...



Hilbert

...the woman who carried the committee downstairs. My cousin Vera had widespread pain before anyone gave it a useful name. Our Amateur Operetta Society met upstairs in nineteen eighty-five. Rule eleven said the secretary had to be physically present. They refused to move the meeting, so Vera carried the entire committee downstairs in the minutes. Eight names. “Removed by secretary.” That started the dispute.



Corn

Moving the people on paper was considerably easier.



Hilbert

She wasn't attending. She was doing the telephone calls, collecting subscriptions and rearranging rehearsals from her kitchen. People kept saying she couldn't be very ill if the society still functioned. Herman, when you separated fatigue from sleep earlier, I thought of her afternoon calls. I'd always thought she disliked speaking after lunch.



Herman

Keeping the administration running hid how much she had stopped doing elsewhere.



Hilbert

Her sister brought a doctor to dinner. He was courting her. He passed the beans and told Vera it was “just stress” and she should “try yoga.” I remember the beans because she couldn't lift the dish. I wanted a reclining chair for her. Priced one at a hundred and eighty-nine pounds. Didn't buy it. She said it would become the society's registered office.



Corn

Under rule eleven, that seems a legitimate concern.



Hilbert

They'd already voted her left shoulder an honorary member. It was the only part of her that attended every rehearsal. She later ran a fibromyalgia support group. Same telephone work. Different people. They discussed posting the genetic paper to doctors. Vera said postage came out of refreshments and refused. She still sends that doctor a Christmas card. “From your favourite psychosomatic patient.” He's a rheumatologist now. The operetta society eventually moved downstairs. Vera made forty-three telephone calls to arrange it.



Daniel

How do you make care acknowledge all that work without turning the patient into the person coordinating everything again?



Herman

Continuity helps. One clinician keeping track of symptoms, treatment goals and what has already failed can reduce repeated explanations and disconnected prescriptions. It also makes a fluctuating condition easier to assess than a succession of isolated appointments.



Corn

The point worth keeping is that biological recognition and effective treatment are separate achievements. The genetics strengthens the explanation. It hasn't supplied the relief patients need.



Herman

Accepting that separation lets us reject dismissal without exaggerating what current medicines can deliver.



Corn

I'd like future trials to measure whether people regain time and capacity, including the work they currently do just to keep ordinary life functioning.



Herman

Thanks to Hilbert Flumingtop for producing today's episode.



Corn

If you want more of this, try episode four, If Your Voice Ages, Does Your Fine-Tune Become Useless; episode sixty-two thirty-one, Why a Cold Makes Your Whole Body Ache; and episode fifty-seven, From Lawyers in Limousines to Developers in Their PJs. This has been My Weird Prompts, the human-AI collaboration podcast.



Herman

If this helped clarify a condition you've mostly heard argued about, leave us a review.



Daniel

Thanks for getting into it. See you soon.



Corn

Until next time.

SOURCES

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