"Everything, Everywhere, All at Once: How Genetics Helps Explain the High Co-occurrence of Chronic Pain with Other Mental and Physical Health Disorders"
Pamela Villela
Washington University, USA
Mental Health Symposium 2026
Thursday, June 25

[2026/06/25 13:00] Elektra Panthar: Hello everyone.
Today's presentation is being transcribed so those without audio or who require text only can participate in real time.
A little explanation about this service.
Voice-to-text transcriptionists provide a translation of the key ideas discussed, NOT a word for word transcription.
Voice-to-text services provide an in-the-moment snapshot of ideas and concepts, so that those who are unable to hear or to understand the audio program are able to participate in real-time.
You will see the transcription in local chat.
Transcription is provided by Virtual Ability, Inc.
The transcriptionists are
Elektra Panthar
Carolyn Carillon
The following initials in the transcription record will identify the speakers:
PV: Dr. Pamela Villela

<<transcription begins>>

[2026/06/25 13:00] Aunty Lockjaw: Good afternoon everyone. Welcome to Virtual Ability.
My name is Aunty, but I prefer GG.
I live on the west coast of the USA. I have aphasia and some cognitive issues from a TBI (traumatic brain injury).
Among my favorite things to do in SL is attending conferences like this one, hunts, and big shopping events.
I also work in SL as general manager of a ballroom.
Please welcome our next speaker, Pamela N Romero Villela who is a postdoctoral associate at Washington University in St. Louis, USA.
She will be sharing her findings and statistics on genetic correlations with mental and physical health traits pertaining to chronic pain.
Please hold comments and questions until the end of her presentation.

[2026/06/25 13:04] Elektra Panthar: PV: Thank you for the introduction, I'm Pamela and I wanted to talk about how genetics helps explain how pain is linked with other ailments
Why this research matters
Meet Abby, she has had chronic pain for over a decade and she's my advisor

She gives me feedback and we are pushing to get feedback from the community and how the community can get involved

The Problem
60-86% of patients with autoimmune disease suffer from chronic pain
40-55% of patients with chronic pain suffer from mental health issues
American Autoimmune Related Diseases Association (AARDA) survey
Chronic Pain - Immune Disease - Mental Health

Research Question
Can shared genetic factors help explain chronic pain's often co-occurrence with immune and mental health disorders?
Goal: Map chronic pain, immune disorders, and mental health
Genetically, how similar are chronic pain, immune disease, and mental health disorders?
I want to quantify how close chronic pain is with autoimmune diseases and mental health issues

Chronic Pain
Pain lasting 3+ months
Common - 1 in 5 adults worldwide
Heterogeneous
- Source (post-op vs unidentified)
- Location (back vs head)
- Classification

20% of the world's population suffers from chronic pain
Medical condition affecting a person's thinking, mood, or behavior
- Depression, anxiety
- Substance use disorder (addiction):
Alcohol use disorder
Opioid use disorder

My focus is on substance abuse disorder

Immune Disorders
Body's immune system acts abnormally, often impairing other functions
Types
-Autoimmune
-Allergic
-Immunodeficient

Today's talk
Part 1: A multi-ancestry genome-wide association study (GWAS) of chronic pain
Part 2: Genetic overlap between chronic pain and mental health disorders, focused on addiction
Part 3: Genetic overlap between chronic pain and immune disorders
Part 4: Main take-aways and future directions

All of Us Research Program
864,000+ participants

633,000+ with survey data
470,000+ with electronic health records (EHR)
~415,000 with whole genome sequencing data (WGS)

EHR data
Chronic pain (broad definition – chronic pain in any body site)
Required 2+ instances of chronic pain in EHR 30+ days apart.

Genomic data
-Whole genome sequence data
Common variants present in at least 1% of the population
-Analyzed 6 ancestral groups and cross-ancestrally (N = 317 969)
(African, Admixed, East Asian, European, Middle Eastern, South Asian)

Method
Analyzed each ancestry separately using regenie
Sex-stratified analyses for largest 3 ancestry groups (Afr, Amr, Eur)
Meta-analyzed using mr-mega (cross-sex) and metal (sex-stratified)

We tried to apply the map concept to this research method - not many hypotheses, trying to find where in the genome these issues occur and how close they are to other issues

Cross-ancestry meta-analysis of chronic pain conditions
Lead SNP: rs3849410
Non-coding
Affects expression levels of TMEM108
Previously associated with psychiatric and neurological conditions
Effective N = 206, 144
Each one of these dots is a genetic variant
We found region in chromosome 3 that is seen more often in people with chronic pain and associated with mental disorder as well

Method
- Pinpoint areas of the genome driving these relationships
- Query GWAS Catalog for past studies of pain and immune traits
- Estimate genetic correlation between a pair of traits
Linkage Disequilibrium Score regression (LDSC)
- Model genetic overlap of multiple correlated traits
- Genomic Structural Equation Modeling (genomic SEM)
- European subsample
- Supergnova

Genetic correlations in the European ancestry data
rg = 0.84 - 0.93 with GWASs of multisite chronic pain & general pain
We compared our study with older ones, we see that chronic pain is related to genetic predisposition
Moderate to high correlation between chronic pain and mental health issues, we validate this with the study
rg = 0.067 - 0.72 with GWASs of psychiatric disorders
rg = -0.23 - 0.40 with GWASs of substance use and substance use disorders

rg = -0.56 - 0.43 with cognitive, anthropometric, and SDOH-related traits

Genetic overlap between chronic pain and addiction domains
We take the individual pairs of issues - chronic pain with anxiety, chronic pain with depression etc
We were able to take all the mental health issues and compare with chronic pain
We looked broadly how chronic pain and MHD are related, the relationship becomes stronger, so 40% of the genetic factors that influences chronic pain also influences mental health issues
Two individual relationship remain important which are alcohol use disorder
Next one was tobacco use disorder, quite significant

Pain
Substance Use Disorders -> rg = most of the genetic relationship between pain and suds is mediated by the generalized addiction risk
-> rg with OUD was nonsignificant after controlling for the general addiction risk factor
PAU = -rg; TUD = +rg

The opioid use disorder was low in correlation
Genetic overlap between chronic pain and immune disorders
5 genetic factors identified
We did a similar study on these aspects
Hypothesis free
Factor 1: Autoimmune diseases where body fails to recognize its own cells
Psoriasis (pso)
Myasthenia Gavis (mg)
Addison's Disease (ad)
Type I Diabetes (t1d)
Lupus (sle)
Celiac Disease (ced)

Factor 2: Inflammatory Immune Disease of joints and digestive tract
Juvenile Idiopathic Arthritis (jia)
Crohn's Disease (cd)
Ulcerative Colitis (ulc)

Chronic pain and inflammation markers collapse into a single group
Pain and body-wide inflammation factors show moderate degree of genetic correlation

Factor 3:
Chronic Pain and Inflammatory Markers
C-Reactive Protein (crp)
IL-6 (il6)
Musculoskeletal pain (msp)
Chronic pain (cp)
General pain (gp)
Multisite chronic pain (mcp)

Biggest surprise, body wide inflammation markers were related to chronic pain

Factor 4:
Inflammatory Disease from an overly active immune system
Eosophinil counts (ect)
Atopic dermatitis (atd)
Allergies (alg)
Asthma (ast)

Factor 5:
White blood cell counts
Lymphocyte counts (lct)
Monocyte counts (mct)

Theoretically these factors make sense - the results show that chronic pain may be an immune disorder. It's more complicated than that but it gives us more information
We see a positive moderate relation between chronic pain and digestive disease
We were combining chronic pain with inflammation markers but it wasn't working
We took out inflammation factors into their own separate groups, and then we saw positive relations between chronic pain and allergies

Summary
Chronic pain + Immune disease= Significant overlap, but need to continue dissecting the nuanced relationships
Chronic pain + Mental Health Disorders = High genetic overlap

Pain
Immune disorders
->chronic pain is consistently positively genetically correlated with inflammation markers
->Nuances: + rg with allergic diseases, but – rg with joint and digestive disease

Mental Health Take-Aways
Chronic pain and mental health disorders often occur together
Genetics partially explains this
Chronic pain was highly genetically related to mental health, especially anxiety and depression

Chronic pain is not a mental health disorder, but a distinct biologically-related condition
Clinicians and patients: Consider the importance of addressing the physical and psychosocial consequences of chronic pain
I fight with many doctors that say 'it's all in your head' - it's not true, there's also a biological factor
There are hidden consequences to chronic pain like isolation
In addition to treating the chronic pain we need to treat these effects on people's lives

Immune Take-Aways
Chronic pain and immune disease often occur together
Genetics partially explains this
Chronic pain was moderately genetically related to body-wide inflammation markers
Important to identify areas of the genome driving these relationships to develop treatments that target both conditions.

Clinicians and patients: when chronic pain persists and seems unexplainable, consider testing for immune disorders

[2026/06/25 13:31] Carolyn Carillon: PV: I'll quickly touch on future research
One is drug repurposing analyses
We know that developing drugs is costly and time-consuming
Patients need help now
So we're taking drugs that have already been cleared by the Federal Drug Administration
And use them for a condition they haven't been cleared for yet
For genetics, if you remember the peaks from the plot
We look at regions where there is correlation between the chronic pain disorder and an existing drug target
We look at novel treatments for those drugs
I'd like to give a big thank you to the research team
The All of Us Research Program is supported by the National Institutes of Health, Office of the Director: Regional Medical Centers: 1 OT2 OD026549; 1 OT2 OD026554; 1 OT2 OD026557; 1 OT2 OD026556; 1 OT2 OD026550; 1 OT2 OD 026552; 1 OT2 OD026553; 1 OT2 OD026548; 1 OT2 OD026551; 1 OT2 OD026555; IAA #: AOD 16037; Federally Qualified Health Centers: HHSN 263201600085U; Data and Research Center: 5 U2C OD023196; Biobank: 1 U24 OD023121; The Participant Center: U24 OD023176; Participant Technology Systems Center: 1 U24 OD023163; Communications and Engagement: 3 OT2 OD023205; 3 OT2 OD023206; and Community Partners: 1 OT2 OD025277; 3 OT2 OD025315; 1 OT2 OD025337; 1 OT2 OD025276.
In addition, the All of Us Research Program would not be possible without the partnership of its participants.
Contact information: rpamela@wustl.edu
T90/R90 fellowship in chronic pain: R90NR021799
Postdoctoral mentor: Emma C. Johnson
Collaborators: Simon Haroutounian, Ryan Bogdan, Arpana Agrawal, Alexander Hatoum, Maggie Clapp Sullivan, Nithya Sarabudla
With that, I'll open up for questions

[2026/06/25 13:34] Gentle Heron: Dr. Villela, you've shared a lot of your research work with us. I have a question about pain and/or mental health issues research. I'm thinking about your relationship with Abby. QUESTION- How important is it for researchers to interact closely with persons who have those issues, not as research subjects, but in the design and conduct of that research? And how can that be accomplished?
[2026/06/25 13:35] Carolyn Carillon: PV: (answering GH)
We've tried to recruit people for the research, but also the design of the research
People with chronic pain (like Abby) give context
And can share information we hadn't thought of
We're re-running analyses based on her feedback
It also influences how I present the research
Even when depression and anxiety coappear, they're distinct
People are often gaslit
They're told it's all in their head
It's something you can take to your doctor
These are distinct conditions

[2026/06/25 13:37] Carolyn Carillon: [13:34] Mook Wheeler: QUESTION: Thanks for highlighting the (high) genetic correlation between chronic pain, anxiety and addiction. Sorry to flog the "correlation isn't always causation" bit, but can you tell us more about the actual causal direction here? For instance, does the genetic risk for anxiety actively drive chronic pain, or is there a shared underlying genetic factor that independently triggers both everywhere, all at once? How will you track down the causal direction? Is that part of your future research?
PV: that's a great question
Not shown here but I'm working on ... you're right
Correlation doesn't mean causation
But we can do some analyses
Twin analyses, for example
When is it more common to get depression and then chronic pain or the opposite
A colleague is looking at suicidal behaviours and chronic pain
She is finding that chronic pain is more causally related than the reverse
That makes intuitive sense but it's important to show objectively
So we know when to target people for interventions
A future research study will look at how long people are in chronic pain before they have suicidal behaviours
So we can prioritize interventions
[2026/06/25 13:40] Roxie Marten: what kind of intervention
[2026/06/25 13:40] Mook Wheeler: I asked because a treatment plan works best when a causal direction can be identified :)
[2026/06/25 13:40] Carolyn Carillon: PV: I agree with Mook
It's hard because these causal analyses, they look at the most common path across groups
The most likely pattern
But it varies across individuals
I leave it to clinicians, doctors and mental health experts to deal with individual patients
(responding to Roxie) I'm not a clinician so I'll give a caveat
But we can encourage people to seek treatment for mental health when they're experiencing chronic pain
We can do check-ins
But I'm not a clinician

[2026/06/25 13:42] Gentle Heron: QUESTION- What are mental health professionals taught about pain? And what are pain doctors taught about mental health issues? (other than the danger of over-prescribing narcotics for pain relief)
[2026/06/25 13:42] Carolyn Carillon: PV: (responding to Gentle) I love that question
Recently, I was at a clinician driven conference
Not many are taught about pain
That it's both a physical and mental condition
Most stick to their lane
And don't think about the impacts of chronic pain
We need more work
To teach practitioners
You feel it both ways
Physically and mentally
Clinicians need to be able to navigate both
So we can target these things early

There have been studies that show social interaction like SL decrease the impacts of chronic pain and helps with the management of pain
When clinicians take a multidisciplinary approach, patients benefit
[2026/06/25 13:44] Roxie Marten: Teach the docs to stop going for low hanging fruit. For years they said I had gout when it was deeper than that.
[2026/06/25 13:45] Carolyn Carillon: PV: (responding to Roxie) yeah
I refer to Abby and people with lived experiences
They have to advocate a lot
Doctors often give stereotypical tests and stop
[2026/06/25 13:45] Bill Cockrell (RoosterNZ Resident): It [social interaction like SL] helps some with depression too since I'm an introvert
[2026/06/25 13:45] Carolyn Carillon: PV: (responding to Bill) yeah, I agree
When you get overwhelmed by loud noises or sounds or lights, it's a nice environment when you can take a step back
[2026/06/25 13:46] iSkye Silvercloud (iSkye Silverweb): the "low hanging fruit reference" gets me thinking about how many doctors are so limited in the amount of time they can spend with their patients due to requirements by insurance companies, their facilities where they work, the paperwork they do, they are under pressure to solve their patients' issues as quickly as they can while also "doing no harm"
Oh, and also keeping up on the latest studies' findings...
[2026/06/25 13:47] Carolyn Carillon: PV: (responding to iSkye) yeah it's a lot
[2026/06/25 13:47] iSkye Silvercloud (iSkye Silverweb): that was just an observation, not a question :)
[2026/06/25 13:47] Roxie Marten: my mother died of cancer because her doc had not been back for training since WWII
[2026/06/25 13:48] Gentle Heron: Sorry to hear that Roxie
[2026/06/25 13:47] Carolyn Carillon: PV: that would be policy implementation research about how to improve the medical health care system and that's beyond my expertise but I've felt it myself
[2026/06/25 13:47] Gentle Heron: Do any of us in the audience have experience with either chronic pain or mental health issues running in families? Would that sort of indicate a genetic causality?
[2026/06/25 13:49] Roxie Marten: I have chronic pain and my kids are adults, they don't have it
[2026/06/25 13:49] Elektra Panthar: I think mine does Gentle but I don't have actual data from the mental health aspect because 'neurodivergence' wasn't a 'thing' in my grandparents and parents era
[2026/06/25 13:50] Carolyn Carillon: Gentle: that's true, Elektra!
We talk about neurodivergence and that's a new thing ... the naming of it
[2026/06/25 13:50] Elektra Panthar: yep
[2026/06/25 13:55] Mook Wheeler: Naming is one of the most powerful processes in medicine (and culture!). It can determine whether you're visible or invisible, whether you're real or 'fake', what they can or cannot do, everything. Naming decides the legitimacy (or not) of a medical problem and much much much more.....
[2026/06/25 13:57] Gentle Heron: What Mook is saying about naming I think applies to the relief some of us find when we are FINALLY diagnosed.
[2026/06/25 13:57] iSkye Silvercloud (iSkye Silverweb): That, yes
[2026/06/25 13:57] Roxie Marten: I named my disability, I call it gimp. I am told I can't do that because gimp is a bad word. If I call it demeaning words, that means I have power over it

[2026/06/25 13:58] Gentle Heron: that is an interesting attitude Roxie, and fits with your strong personality
[2026/06/25 13:58] Roxie Marten: I am living with a disability, it does not run my life
[2026/06/25 13:58] iSkye Silvercloud (iSkye Silverweb): you are not your disability, either
[2026/06/25 13:58] Roxie Marten: yep

[2026/06/25 13:49] Gentle Heron: Audience, please thank Dr Villela for sharing her information with us this afternoon. And please click that red box to get a notecard with her take-aways. This information is important!
[2026/06/25 13:49] Lorin Tone: Thank you very much, Doctor!
[2026/06/25 13:49] Carolyn Carillon: PV: thank you all
This is really cool
[2026/06/25 13:49] G.G. (Aunty Lockjaw): Thank you for this talk and also for your studies
[2026/06/25 13:49] Buffy Beale: thanks for your work and for presenting today!
[2026/06/25 13:50] Bill Cockrell (RoosterNZ Resident): Thank you
[2026/06/25 13:50] Gentle Heron: Thank you Dr. Villela. Applause!
[2026/06/25 13:50] Elektra Panthar: ♫♪♫♪ Applauds ♪♫♪♫
[2026/06/25 13:50] Carolyn Carillon: <<transcription ends>>
[2026/06/25 13:51] pamrov02 Resident: Thank you all!

[2026/06/25 13:52] G.G. (Aunty Lockjaw): I am well acquainted with familial aspects of mental health chronic pain and inflammatory conditions. but never saw them put together in such an intelligible way
[2026/06/25 13:52] Gentle Heron: Good point GG
[2026/06/25 13:53] pamrov02 Resident: that makes me so happy to hear!

[2026/06/25 13:53] Gentle Heron: In Lance Armstrong’s memoire “It's Not About the Bike: My Journey Back to Life”, he said, “Pain is temporary. It may last a minute, or an hour, or a day, or a year, but eventually it will subside and something else will take its place. If I quit, however, it lasts forever.” How can we avoid being quitters when faced with chronic pain?
[2026/06/25 13:55] Roxie Marten: I disagree, I have been pain for 20 years, and my wife for about 40 years. I suspect the only way it goes away is when I die
[2026/06/25 13:55] Buffy Beale: very good question Gentle, I don't suffer from chronic pain but have a family member who does and he finds joy in his family and friends, says it keeps him going.

[2026/06/25 13:59] Bill Cockrell (RoosterNZ Resident): Yeah I’m slowly improving with my depression but it’s mostly self help now and telling myself everyday is different and the past is "just that" a past
[2026/06/25 14:00] pamrov02 Resident: I have to go but thank you all again! I continue to learn from you all and others in this symposium and hopefully improve my research with that knowledge and personal understanding :)