Huntington's Disease Therapeutics Conference 2025 - Day 2

HDBuzz reported live updates on Bluesky from the 2025 HD Therapeutics Conference. Read on for coverage of Day 2. #CHDI2025

 

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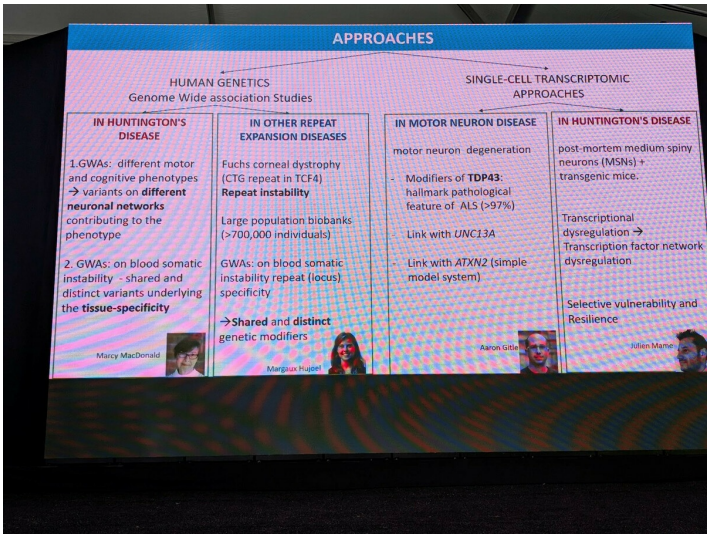
We're back for day 2 of the CHDI Huntington's DiseaseTherapeutics Conference! We're kicking things off with some exciting talks on genetic modifiers and learning how we can advance them toward therapeutics for HD.

Advancing Genetic Modifiers Toward Medicines

Today's session is all about genetic modifiers - genes that contribute to the age of disease onset - which were discovered through massive genetic studies that looked at levels of every gene in someone with the gene for HD. This let researchers identify genes that correlated with earlier or later HD onset. Genes related to somatic instability were identified as modifiers in large genetic studies, called GWAS, or genome wide association studies. Researchers are advancing GWAS data towards therapeutics. This wouldn't be possible without the collaboration between scientists and the HD community. Super exciting!



Day 2 of the conference was all about advancing genetic modifiers of disease toward therapeutics. The introduction provided a nice snapshot of some of the talks.

Seung Kwak: It's Not All About Somatic Instability

Our first speaker in this session is Seung Kwak from CHDI, who is talking about genetic modifiers that aren't related to somatic instability. These modifiers can change disease onset by 7-10 years (that's a lot!), but they don't seem to affect somatic instability.

Seung and others are building a pipeline to help them identify more non-somatic instability-related modifiers and figure out how they alter when symptoms begin. This will help identify new pathways in HD, diversifying the possible molecules researchers could target with new therapeutics.

Once they identify these genes, they'll try to figure out which characteristics of HD those genes control, like rate of disease progression or motor symptom onset. Seung thinks different modifiers might work throughout the course of HD as it progresses, contributing to various aspects of disease onset. By scrutinising which genes might contribute to which timepoints in HD progression, we'll have a better idea of when we could or should intervene with therapeutics that target each step.

Seung states that, "we're not alone", highlighting that other diseases are similar to HD, like SCA1, another neurological disease also caused by expanding CAGs. He stresses the importance of learning from these diseases, which can help advance what we know about HD.

> **"Interestingly, the non-mismatch repair modifiers seem to influence disease earlier. This means if we could perhaps find a way to target these "other" modifiers, we could find ways to intervene very early in disease. "**

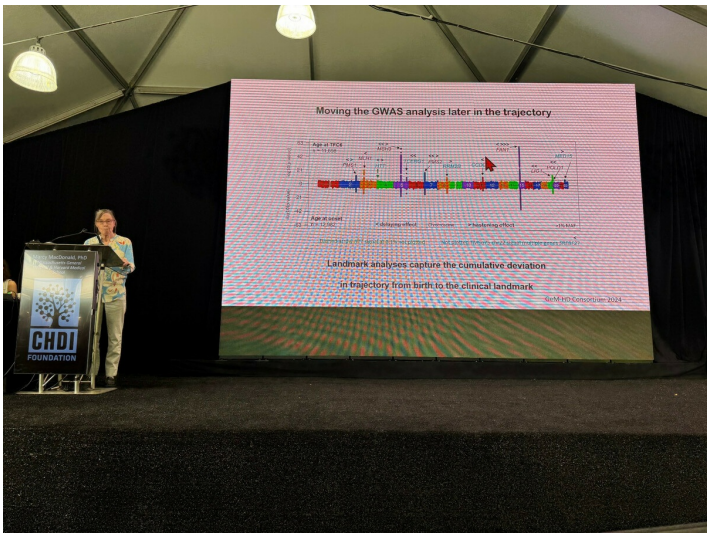
By leveraging what we know about HD to identify modifiers, e.g., striatalneurons are the most affected cells in HD, we can diversify how we identify modifiers and diversify what we learn and the types of therapeutics we could make. This could help determine if a combinatorial approach will be best.

Marcy MacDonald: Effects of The "Other" Modifiers

Up next is Marcy MacDonald, who was a key member of the team that identified the genetic mutation that causes HD in 1993. She's dedicated her career to further understanding HD to help get us closer to a treatment. She'll be sharing her team's work on genetic modifiers of HD. She starts by highlighting GeM-HD, a massive genetic study that first defined some of the genetic modifiers of HD. Marcy shared that the GeM-HD study wouldn't have been possible without the amazing collaboration we have between HD researchers and the HD community.

She reminds us that HD symptoms are the result of complex events at the molecular level. We have only just begun finding out what influences symptom onset, and some genes are already being targeted! But there are still discoveries to make as we get more and more data.

Many of the modifiers we have already heard about at this conference are involved in mismatch repair - an important process in looking after our DNA. These are the same genes that participate in somatic instability. However, there is almost an equal number of modifiers that have entirely different biology and which really warrant further study to figure out how they influence when HD symptoms begin.



Marcy MacDonald shared an amazing talk discussing genetic modifiers we don't hear as much about. There is almost an equal number of modifiers that don't influence mismatch repair, shown in blue on this slide. These really warrant further study to figure out how they influence when HD symptoms begin.

Marcy is sharing data that pulls out modifiers at different disease stages. Interestingly, the non-mismatch repair modifiers seem to influence disease earlier. This means if we could perhaps find a way to target these "other" modifiers, we could find ways to intervene very early in disease.

She also compared genetic modifiers across datasets. While there is some overlap, there are some modifiers unique to each dataset. However, multiple datasets do show DNA repair genes as common hits. She highlights that these differences are important to understand. Some modifiers influence movement symptoms of HD, whereas others seem to impact thinking symptoms of HD. Maybe this means modifiers underlie different aspects of HD biology.

Targeting those aspect-specific modifiers could help scientists develop future treatments tailored to treat different types of HD symptoms at different timepoints in the disease. This could give HD clinicians the option for precision medicine approaches to treat folks in the future. Marcy suggests that there could be modifiers specific for various biological processes, e.g., initiation of expansion, rate of expansion, cell-specific effects, cell toxicity, and response to neuronal loss. It would be fantastic to have targets against each one of these unique aspects of HD!

Further, she also urges the community to not think solely about exactly which cells are lost over time in HD, but also about what circuits to which these correspond. The loss of specific circuits is what underlies different HD symptoms in her opinion.

Now she's diving into specific non-DNA repair modifiers, starting with one called Lig1. Mice that model the genetic changes in Lig1 from GWAS have been made so researchers can deeply study how this gene influences HD.

> **"Some modifiers influence movement symptoms of HD, whereas others seem to impact thinking symptoms of HD. Maybe this means modifiers underlie different aspects of HD biology. "**

Another modifier she mentioned is RRM2B, which is more involved in motor symptoms and less involved in cognitive symptoms. RRM2B helps keep mitochondria (the cell's powerhouse) healthy under stress conditions. Marcy is sharing lots of details about the exact genetic changes that were found in these GWAS. She highlights that 12,000 people were needed to see these changes related to RRM2B. Highlighting how important it is to have HD families contribute to research!

The next modifier on Marcy's list is the CAA sequence that sometimes interrupts the CAG repeat stretch within the huntingtin gene. Research tells us that *this* is the strongest modifier of age of symptom onset, which can delay the onset of HD symptoms by up to 10 years. She highlights that the CAA interruption doesn't seem to influence CAG instability, but does influence HD symptoms.

So how does it do that? We don't know for sure. Marcy thinks it may act indirectly to affect instability or act directly on certain types of brain cells, influencing their vulnerability.

In this tour de force talk, Marcy wraps up by summarizing that different symptoms happen at different times in HD. Genetic modifiers identified in GWAS can help us better understand why this is and develop interventions to help alter clinical signs and symptoms of HD.

Margaux Hujoel: Somatic Instability Lessons From 700,000 People

On day 2 of the conference, attendees shared their work in over 120 posters, presenting their most recent data about Huntington's disease, spurring new ideas and establishing collaborations.

Image credit: Jerry Turner, CHDI

Our next speaker is Margaux Hujoel from Harvard University. Her talk will go through what she's learned about the causes and consequences of somatic instability from genetic data from 700,000 people who donated samples, like blood or spinal fluid, to research. To understand genetic variations in HD and other diseases, we need massive datasets from thousands of people to be sure of the findings. As genome sequencing technologies have advanced dramatically in the last few decades, we now have access to HUGE datasets - very exciting.

She starts by summarizing the concept that HD is driven by somatic instability, the perpetual expansion of the disease-causing CAG repeat. However, researchers don't yet understand the nitty gritty of why instability is so important in HD.

Margaux is stepping back from the huntingtin gene, and studying how somatic instability happens throughout the entire genetic code (genome) to see what lessons can be learned through a broader lens. Other diseases are caused by expanded repeats so we could learn more about HD by studying them.

Two such diseases are Myotonic Dystrophy and Fuch's Corneal Dystrophy, an eye disease. Research into these diseases show that new cases arise through repeat instability that pushes a repetitive DNA sequence to a length that causes disease, very similar to what happens in HD.

Around the globe, there are various biobanks - places that collect tissues and fluids donated by people living with diseases. Using samples from these biobanks, Margaux and her team are learning more about somatic instability that has relevance across diseases.

> **"There are 18 different places in the human genome that are sensitive to somatic CAG instability, 9 of which are known to cause disease. "**

There are some technical challenges with analyzing long repeats in the DNA, but Margaux's team has come up with a work-around and found that the vast majority of expansions happen in only a handful of genes, helping to narrow down what we should focus on.

There are 18 different places in the human genome that are sensitive to somatic CAG instability, 9 of which are known to cause disease. Samples in the biobank from related people lets Margaux and her team map genetic changes in the genome over multiple generations. She found CAG expansions tend to expand more often than they contract and expansions happen more frequently with longer CAG repeat lengths. This isn't new for HD researchers, but it's interesting for us to know that this phenomenon isn't unique to HD and happens across the genome.

They also looked at how expansions differed between different types of tissue, like blood vs brain tissue. This matters as we need to know which biofluids or tissues might be best to track expansion, and to measure changes to expansion in forthcoming clinical trials which aim to slow down expansion.

Margaux showed data for various diseases where the repeat expansions were more likely in the germ line (egg and sperm) than blood, and vice versa. This suggests that cell type specific differences in CAG repeat diseases may not be the same, BUT cell type specificity does seem to be a common feature.

Another common feature across these diseases is that similar genes contribute to repeat instability, like modifiers related to DNA repair, like MSH3, PMS2, and FAN1 - all genes that are being heavily scrutinised in HD for the role they play in somatic instability.

CHDI's 20th Annual Huntington's Disease Therapeutics Conference brought together over 400 of the world's brightest minds studying HD to share data, learn from each other, and move the field forward.

Image credit: Jerry Turner, CHDI

Margaux suggests that we can apply some of her research to HD, cautioning thatsomatic expansion in blood may not match what's going on in the brain, but it could still be an interesting biomarker for therapeutics aimed at controlling expansion. The field is working hard to find biomarkers to track somatic expansion as potential treatments work their way toward the clinic. However, we can't take brain samples throughout clinical trials, so blood could be a way to see if such treatments are having the effect we want.

If blood samples turn out not to be a good surrogate for suchtherapeutics, we may have to rethink our strategy. This challenges current approaches in HD research, but that's what conferences are all about! Challenging what we know, getting people to think about things in different ways, and advancing HD research with a broad perspective.

Aaron Gitler: Modifier Lessons From Other Diseases

Up next is Aaron Gitler, who works on ALS (Lou Gehrig's disease) and will share findings from his own work that he thinks could be relevant for HD. Specifically, this involves his work on genetic modifiers.

ALS can be caused by changes to a gene called TDP-43. Like huntingtin, this can cause the build up of protein clumps associated with disease. Interestingly, this gene was also recently implicated in HD.

> **"This challenges current approaches in HD research, but that's what conferences are all about! Challenging what we know, getting people to think about things in different ways, and advancing HD research with a broad perspective. "**

Aaron found a gene, called ATXN2, that suppresses protein clumps of TDP-43. While ATXN2 seems to be a modifier of ALS, it also causes a disease, called spinocerebellar ataxia 2. He found that in some ALS cases, there is a genetic expansion of CAG repeats in the ATXN2 gene. Interestingly, he's found that different CAG repeat lengths in ATXN2 cause different disease features in different cells. Quite a complex system!

In mice that model ALS, when Aaron reduces levels of ATXN2, the mice live much longer lives and disease features in cells of the brain seem to disappear. This suggests that ATXN2 could be a good target for ALS therapeutics.

His work suggests that there are bits of genetic information contained in proteins when people have disease that aren't there in people who don't have these diseases. The inclusion or exclusion of these pieces of genetic information happens through a process called splicing.

Through this work, he may have identified a genetic cause of TDP-43 disease that could be targeted for therapeutic benefit. He suggests that similar biological mechanisms may be at play in HD, particularly given the newly published association between HD and TDP-43.

Julien Marnet: Hunting For The Master Switch In HD

Our last speaker of the day is Julien Mamet, who works at Core Biotherapeutics, a company focused on developing therapeutics that target genes called "transcription factors" - genes that act like master regulators to control the levels of lots of other genes.

Julien looks at large datasets, mapping how genes within certain cell types connect in a hierarchical way to regulate each other. Doing this in cells with and without HD allows him to identify differences and figure out how to target master regulators within these hierarchical networks. Julien reminds us that not all transcription factors are equal, so lots of effort is put into understanding which of these master regulators may be dominant. They call these the "core" components of the network. In disease, these "core" master regulator genes are thought to drive disease.

They're working to integrate lots of different datasets to build a library of networks and identify cores within those networks. This will help them identify targets that they can design therapeutics against that they think could improve disease signs and symptoms. For HD, they're starting to build these networks using datasets from various cell types in the brain. From these networks, they've identified core genes called "HOX". HOX genes are particularly strong in neurons that are vulnerable in HD.

In HD, these HOX genes seem to alter thousands of genes that are necessary for the proper function of brain cells. Julien finds that these HOX genes are core genes within the networks of early and late stages of HD. Julien suggests that because HOX genes are unchanged in brain cells not largely affected by HD, they should be safe to target with therapies. Interestingly, they see something similar for other diseases caused by CAG repeats, suggesting a possible therapy that targets HOX could be effective for more than HD.

That's it for us today! Stay tuned for updates from the last day of theTherapeutics Conference to learn more exciting updates on Huntington's disease research!

Sarah Hernandez is an employee of the Hereditary Disease Foundation, who has provided financial support to researchers who have work described in this article or are on the Scientific Advisory Board. Tam Maiuri works for the Huntington's Disease Society of America, which has relationships with many of the companies who attended this meeting or were mentioned in articles related to this conference. For more information about our disclosure policy see our FAQ...

GLOSSARY

spinocerebellar ataxia A family of diseases which result in characteristic movement disorders. Many types of spinocerebellar ataxia are caused by the same type of mutation as HD – a CAG expansion.

transcription the first step in making a protein from the recipe stored in a gene. Transcription means making a working copy of the gene from RNA, a chemical messenger similar to DNA.

therapeutics treatments

mitochondria tiny machines inside our cells that process fuel into energy, enabling cells to function

CAG repeat The stretch of DNA at the beginning of the HD gene, which contains the sequence CAG repeated many times, and is abnormally long in people who will develop HD

biomarker a test of any kind - including blood tests, thinking tests and brain scans - that

can measure or predict the progression of a disease like HD. Biomarkers may make clinical trials of new drugs quicker and more reliable.

dominant A genetic condition that only requires one copy of a mutation to occur

splicing the cutting up of RNA messages, to remove non-coding regions and join together coding regions.

neuron Brain cells that store and transmit information

somatic relating to the body

genome the name given to all the genes that contain the complete instructions for making a person or other organism

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