Updates from the EHDN Plenary Meeting 2020

Read our summary of the latest updates from the EHDN Plenary Meeting 2020

By Dr Rachel Harding | January 08, 2021 | Edited by Professor Ed Wild
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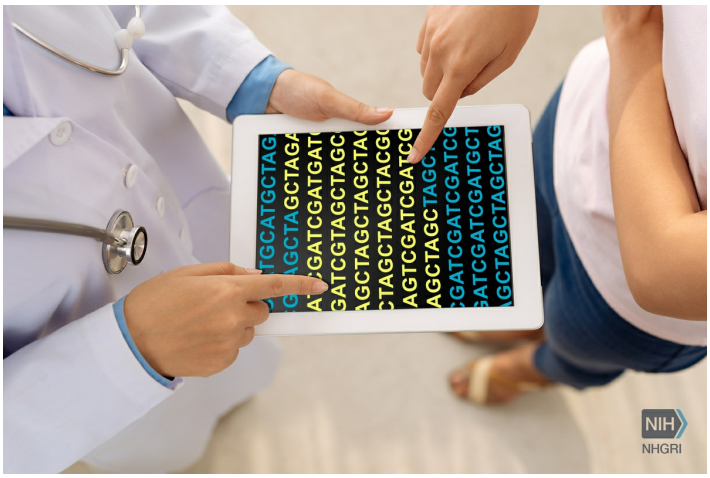
In September, the European Huntington's Disease Network (EHDN) hosted a virtual webinar event which comprised presentations on some of the latest scientific research as well as clinical studies of Huntington's disease (HD). Researchers, doctors, patients and other interested folks, tuned in for an afternoon of talks as well as question and answer sessions to learn and discuss some of the recent developments in Huntington's disease research.

The Science Sessions

Lesley Jones (University of Cardiff, UK) chaired the first session which covered some of the latest research from labs around the world working on Huntington's disease.



Researchers presenting in the science session covered some of the latest research on what we know about the huntingtin protein, the mutation which causes HD and new discoveries about the mechanism of HD, which might one day be used to help design new medicines.

Image credit: Darryl Leja, NHGRI

Frederic Saudou (INSERM, France) kicked things off with a talk about the function of the huntingtin protein. This is the protein encoded by the huntingtin gene which is mutated in patients with HD. This protein is one of the largest made in our bodies and it sticks to lots of other different proteins in the cell which makes it tricky for scientists to study. The Saudou

lab is interested in the role of the huntingtin protein in moving capsules called vesicles in nerve cells, a process which is critical for brain function. Using “brain on a chip” technology, they can look at how vesicle movement changes in patients with HD as well how brain cells connect and work together in their HD models.

Next, Darren Monckton (University of Glasgow, UK) presented an update on his group’s research on somatic expansion. As HDBuzz recently wrote, somatic expansion is associated with the severity of HD and the increase of the CAG repeat length in the huntingtin gene in certain cells and tissue types can lead to earlier onset of symptoms. Recently, scientists have found that certain small changes in the code of DNA repair genes can affect the amount of somatic expansion that occurs. This makes sense of the genome-wide association study data which shows that these small variations in sequence of DNA repair genes can cause symptom onset to start earlier or later for patients. Understanding the precise mechanism and which genes are involved could open up lots of opportunities to develop new therapies for HD.

Hilal Lashuel (EPFL, Switzerland) next presented his lab’s recent findings which implicate a gene called TBK1 in HD. TBK1 is able to mark the huntingtin protein with a special label called phosphorylation. When the huntingtin protein is marked by TBK1, nerve cells survive much better in laboratory models of HD and this effect is reversed if the activity of TBK1 is blocked. If we could activate TBK1 in HD patients, this could be a new way to treat HD.

The final talk of the science session was from George McAllister (CHDI Foundation, USA) who spoke about promising new oral therapies for huntingtin lowering. Although not yet in the clinic, there are a number of companies, including Novartis and PTC, who are developing huntingtin lowering drugs which could be taken as a pill. This would mean avoiding the intrathecal (spinal tap) or intracranial (injection into the brain) methods of delivering the medicine which is what many of the huntingtin lowering therapies currently in clinical trials use. Researchers hope that this would make it easier for patients to take the medicine. Having an oral therapy would also mean that the whole body could be treated, not just the brain, which would have the bonus effect of making it easier to measure how well the drug is working by measuring in blood for example. The effects of the medicine would also be reversible if treatment was halted. However, there are lots of potential issues which scientists need to carefully consider such as whether targeting the whole body is appropriate or is there would be off target effects. Preclinical and clinical studies will hopefully provide answers and we look forward to reporting on these exciting new therapeutics in the coming year or so.

Clinical Study and Trial Updates

The next session of the day was chaired by Jean-Marc Burgunder (University of Bern, Switzerland) and focussed more of the clinical studies currently underway to find new treatments for HD.

This session started with a talk from Sarah Tabrizi (UCL, UK) which presented insights from the open label extension of Tominersen, the huntingtin lowering therapy developed by Roche. This extension study looks at the long-term safety of the treatment in a small group of premanifest HD patients over the course of 15 months. One of the key findings of the study was that waiting longer periods of time between doses of Tominersen still lowered huntingtin sufficiently, and that the more spaced out treatment regimen also resulted in fewer negative side effects for the treated patients. This 8-week treatment regimen will now be used in the GENERATION HD1 trial which will evaluate whether Tominersen treatment improves outcomes for HD patients. We know that this drug lowers huntingtin levels when we measure a treated patient's spinal fluid, which clinicians use as a proxy for measuring huntingtin in the brain. Now the scientists need to work out if the huntingtin lowering is sufficient to improve patient symptoms. The trial is now fully enrolled and we are grateful to the 791 HD patients from around the world who signed up for this critical clinical trial. Despite the COVID-19 pandemic, Roche states that it is working hard to mitigate any effects to the ongoing trials whilst keeping patients, clinicians and HD families safe.

Next, Anna Heinzmann (ICM Institut du Cerveau, France) presented an update on the PRECISION-HD study, another huntingtin lowering therapy developed by Wave. Wave's therapy specifically targets the mutated form of the huntingtin gene which could be a preferred approach as it leaves the unmutated huntingtin levels intact. However, this treatment is only available to patients that have a specific barcode in their DNA as this is how the drug targets the mutated version of HTT so not every patient is eligible. So far, the scientists at Wave have shown that their therapy is safe in patients but will follow up with more findings in the first quarter of 2021 which we hope will indicate how well their drug is working to lower the mutated from of HTT.

Many exciting updates were presented on HTT lowering therapies as well as other types of medicines scientists have designed which they hope might slow or stop the progression of HD

The following presentation gave an overview of the SHIELD HD natural history study, which is being run by Triplet Therapeutics. Anne Rosser (University of Cardiff, UK) explained how this study will lay the groundwork for future clinical trials which aim to target DNA damage repair pathways. Triplet have shown in the HD mouse models that reducing the levels of certain DNA damage repair proteins can halt the process of somatic expansion. By targeting somatic expansion in this way, Triplet hopes to treat the underlying pathology of HD. They are running this natural history study in order to inform the design of a future clinical trial and to work out what measures they might need to take of patients to find out if their therapy is working. The HD patients enrolled in this study will be assessed by a variety of methods over the course of 2 years by clinicians and both the data and samples (such as blood) taken from the patients, will be critical for scientists to better design the future clinical trials.

Bernhard Landwehrmeyer (Ulm University, Germany) gave the next talk about PROOF-HD which will assess the potential for treating HD patients with the drug Pridopidine. Scientists have recently made headway in understand how Pridopidine might be working and think its acts through a type of nerve cell receptor called the sigma 1 receptor. Activating this receptor, as Pridopidine is believed to do, is thought to have a variety of downstream effects which are hoped to improve HD patient outcomes. Although earlier trials for Pridopidine had disappointing results, this new trial hopes that by looking at treating early manifest patients for much longer they may see better outcomes for patients.

Ralf Reilmann (George Huntington Instititut, Germany) presented an update on the Uniqure AAV gene therapy which also aims to lower huntingtin. Uniqure's AMT-130 therapy is delivered in a one-shot brain surgery and this virus-based approach irreversibly alters the patient's DNA resulting in reduced HTT levels. Scientists have been able to show that this treatment is both safe and effective at lowering HTT in both small and large animal models of HD such as rats, pigs and monkeys. The current AMT-130-01 study will look at how this translates into humans and whether the drug is still safe in the small number of patients who will receive it. 26 patients will receive the therapy by brain surgery and will be monitored at specialist HD clinics around the world. Enrollment is ongoing in the US for the study.

Anne-Catherine Bachoud-Levi (INSERM, France) gave a talk about the MIG-HD clinical trial. This trial investigated the use of stem cells in treating HD in a long clinical study spanning more than a decade. Although the treatment tested in this specific trial was not successful in treating HD, the scientists learnt a lot about best practises for this type of stem cell transplantation treatment. Since the trial, there have been huge breakthroughs in our understanding of stem cells. Bachoud-Levi and team are hopeful that new stem cell-based therapies may help HD patients in the future.

The final talk of the day was from Hugh Rickards (University of Birmingham, UK) who discussed the Huntington's equal access to effective drugs (HEATED) project. As there are an increasing number of very exciting drugs in clinical trials, many people in the HD

research community expect there to be a few which might be approved for use in HD patients. However, it is likely that these might be very expensive meaning that not all HD patients would be able to access them immediately. Rickards is working to understand the challenges of HD drug affordability and accessibility to ensure as many patients as possible are able to access therapies when they become available.

Rewatch online

You can watch all of the talks on the EHDN website. To find out more about the current HD clinical trials, visit HD Trial Finder.

Dr. Harding declares no conflicts of interest. Prof Wild is an investigator and advisory board member on the Roche and Triplet Therapeutics clinical trials programs. For more information about our disclosure policy see our FAQ...

GLOSSARY

huntingtin protein The protein produced by the HD gene.

clinical trial Very carefully planned experiments designed to answer specific questions about how a drug affects human beings

therapeutics treatments

open label A trial in which the patient and doctor know what drug is being used. Open label trials are susceptible to bias through placebo effects.

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

stem cells Cells that can divide into cells of different types

Receptor a molecule on the surface of a cell that signalling chemicals attach to

manifest after HD diagnosis, or when symptoms are already showing

vesicle a tiny 'bubble' produced by a cell that can deliver chemicals to other cells

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

HTT one abbreviation for the gene that causes Huntington's disease. The same gene is also called HD and IT-15

AAV a virus that can be used to deliver gene therapy drugs to cells. AAV stands for adeno-associated virus.