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[www.euro-hd.net](http://www.euro-hd.net)

## FEATURE ARTICLE

By Ed Wild (University College London, UK) and Jeff Carroll (Harvard Medical School, Boston, USA)

### Drugs in the desert: The CHDI therapeutics conference

The desert mountains of Palm Springs provided a dramatic backdrop to some exciting Huntington's disease (HD) news and discussions in February. CHDI's 2011 therapeutics conference was notable for a spirit of openness, with CHDI revealing details of its internal drug discovery efforts.

In welcoming the 230 delegates attending the meeting, Robert Pacifici, the Chief Scientific Officer of CHDI, explained its role, not only as the biggest funder of HD research worldwide, but also as a fully-fledged research organization with its own advanced programmes to develop drugs.

The keynote speaker established the tone of openness in a striking way. 'Gene Veritas', the author of the 'At Risk for Huntington's Disease' blog, revealed his identity publicly for the first time as Ken Serbin. He spoke movingly about his family's struggle with HD and the stigma that made him keep his online persona separate from his everyday life. "You and I – the HD-positive man and the community of HD researchers – stand on the cutting edge of science and of history," he declared. "Because, in conquering HD, you are going to hold out the hope of a world in which disease is vanquished."

### Lowering huntingtin levels

The first of five scientific sessions addressed the hot topic of silencing the *huntingtin (HTT)* gene. If a treatment could stop cells making the harmful protein, there is a good chance that it could slow down the disease, or even prevent the damage caused as a consequence of the mutation. Scientists can design special targeted chemicals that silence the *HTT* gene so that cells produce less of the harmful protein.

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**Scott Zeitlin** (University of Virginia) has bred mice that allow him to control the amount of huntingtin they produce. They may help answer the crucial question of exactly how much huntingtin is needed for a cell to remain healthy. **Karen Chen** of the Spinal Muscular Atrophy (SMA) Foundation shared results from animal trials to alter protein levels in SMA, another genetic nervous system disease. She is hoping for a protein silencing trial in SMA this year. **Andreas Weiss** described the efforts of drug giant Novartis to fight HD by lowering protein levels. He described a lab test that he has developed that is aimed at measuring how much protein is left in patients – a test Novartis intends to make available to HD researchers. Finally, **Doug Macdonald** summarized CHDI's collaborative efforts to make gene silencing a reality. Several teams have succeeded in switching off the gene in animals, producing not only lower levels of huntingtin but also improvements in cells and symptoms. Advances, both in drug design and in technologies to deliver drugs into the brain, are bringing these treatments closer.

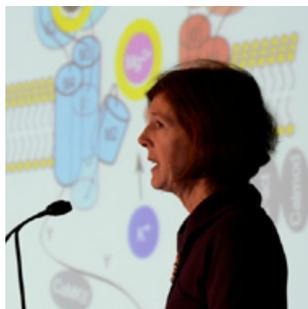
### Neuronal communication

Neurons communicate with each other at specific sites called 'synapses', and the process of communication between neurons is known to be changed in HD. **Lynn Raymond** (University of British Columbia) is trying to understand how brain cells might be over-excited in HD. Low doses of memantine, a drug used in Alzheimer's disease, corrected the over-excitation seen in HD mice.

**Don Faber** (Albert Einstein College of Medicine) found that a drug called retigabine improved neuronal communication in HD.

**Michael Orth** (University of Ulm) studies how the brain controls movement, by using transcranial magnetic stimulation (stimulating neuronal signalling by placing magnets above the head). He has shown that HD patients need more stimulation to cause movement of the hand, suggesting that the surface (cortex) of the brain is underactive.

**Vahri Beaumont**, who heads CHDI's neuronal communication team, announced five different drug development efforts targeting synapses in HD. One of these is a



protein called phosphodiesterase-10. Blocking the action of this protein in HD mice improved most of the changes in synapses. These drugs are exciting new leads in HD. NeuroSearch is the company that developed Huntexil, a drug aimed at improving movements in HD. Clinical trials have suggested that the drug may be effective.

**Nicholas Waters** described how NeuroSearch is trying to understand exactly how Huntexil works, which could help them develop new and better drugs.

### Handling energy problems in cells

The next session focused on how the body uses nutrients from food to produce energy. This is an important topic because it is known that metabolism is abnormal in HD early in the disease.

**Timothy Greenamyre** (University of Pittsburgh) studies mitochondria – tiny organelles inside our cells that process fuel into energy. In HD, they seem to behave like leaky batteries, in that they do not hold their electrical charge as well as normal.

Meanwhile **Sarah Berman** (University of Pittsburgh) described a system for studying the behavior of



mitochondria in neurons that could help us understand the problems in HD. **Hoby Hetherington** (Yale University) presented a brain imaging technique called magnetic resonance spectroscopy imaging (MRSI), which can produce detailed maps of which chemicals are found in different brain areas – this could help determine whether drugs that target energy deficiencies are working. **Leticia Toledo-Sherman** gave details of CHDI's work on such drugs. CHDI is close to starting animal studies of new 'designer' drugs aimed at a protein called pyruvate dehydrogenase kinase, which controls how nutrients are fed to mitochondria in cells. She is optimistic that CHDI will have a suitable drug to test by this autumn.

**Sol Snyder** (Johns Hopkins University) discovered a protein called Rhes that is interesting because it sticks to the huntingtin protein, and does so more strongly when huntingtin is mutated. Rhes might be a clue to why some bits of the brain are more vulnerable than others to damage in HD.



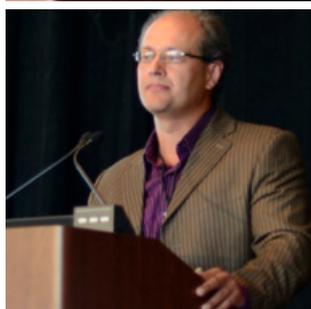


### Growth factors

Growth factors produced in the brain enable neurons to remain healthy. Researchers have wondered whether they might be able to help neurons remain healthy in HD. **Clive Svendsen** (Cedars-Sinai Medical Center) explained that direct infusion of one growth factor (glial-derived neurotrophic factor) into the brains of Parkinson’s disease patients was beneficial. **Moses Chao** (New



York University) reported that a chemical called adenosine can mimic the effects of growth factors. Understanding these effects might allow safer treatments based on growth factors.

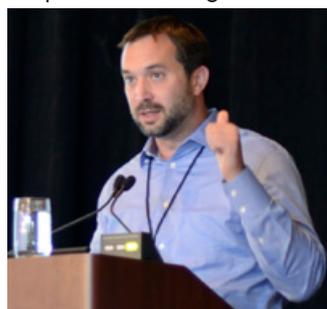


**Jordi Alberch** (University of Barcelona) has found that brain-derived neurotrophic factor (BDNF), another growth factor, can’t move around cells that contain the HD mutation, and says there is an imbalance between two different BDNF receptor molecules, p75 and TrkB. **Alex Kiselyov**

leads a CHDI team trying to correct the imbalance by making drugs to target TrkB receptors, restoring the healthy effects of BDNF.

### CHDI internal programs

The final session featured presentations from CHDI scientists on two of the hottest targets for new treatments. **Ignacio Muñoz-Sanjuan** talked about efforts

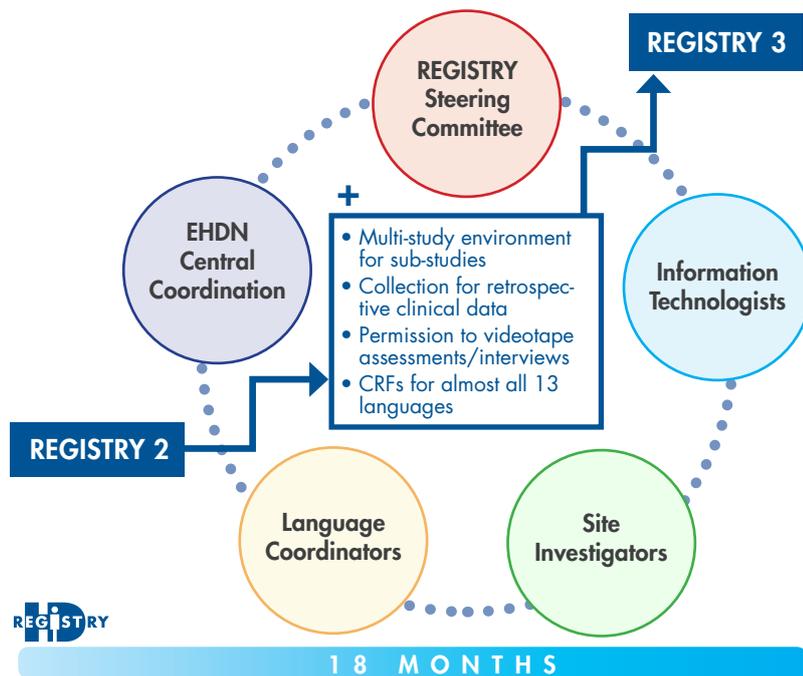


to inhibit a protein called kynurenine 3-monooxygenase (KMO). To understand whether blocking KMO would be helpful for HD, CHDI has led an intense effort to design drugs that target it and now has several tailor-made KMO drug candidates that they are honing further before testing in HD animal models. **Celia Dominguez** specializes in designing drugs to hit specific molecular targets. She is working on drugs to reduce the activity of a protein called HDAC4. If the activity of HDAC4 can be reduced, other genes will be less exposed to the chaos caused by the HD mutation. She is confident that a candidate drug will be tested in HD mice by this summer.

### HDBuzz

The authors of this piece were given the privilege of closing the meeting with a presentation on HDBuzz, a new HD research news web platform, written by scientists, in understandable language. We showcased the contents of the site and interactive features like Twitter and Facebook feeds (follow ‘HDBuzzFeed’). HDBuzz is available in English and Spanish – and we had the audience count down from “Fünf” to “Eins” to help launch the German version. Check out the site at [www.hdbuzz.net](http://www.hdbuzz.net).





## REGISTRY 3: Update and Launch

Olivia Handley, REGISTRY Project Manager, London, United Kingdom

Over the past 18 months, the EHDN Central Coordination, REGISTRY Steering Committee, Information Technologists (IT), Language Coordinators, and Site Investigators have been working hard on preparing for the implementation of REGISTRY version 3. The modified protocol will allow for the conduct of REGISTRY sub-studies, collection of retrospective clinical data (i.e. prior to enrolment into REGISTRY), and permission to videotape assessments and interviews. For an overview of REGISTRY 3 please see the EHDN News of September 2009, and for details of specific sub-studies see the December 2009, March and June 2010, and January 2011 editions. In addition, the standard REGISTRY assessment has been modified to improve characterisation of the onset of HD. It will include extended assessments that we anticipate will be more sensitive to tracking the progression of cognitive and behavioural symptoms.

The IT implementation process of REGISTRY 3 has been complex: all existing REGISTRY 2 data have been migrated into the REGISTRY 3 web portal; monitoring and compensation systems have been upgraded; additional online plausibility checks have been added, and almost all case report forms (CRFs) have been translated into each of the 13 languages used within EHDN.

Crucially, the new web portal hosts a multi-study environment which allows REGISTRY sub-studies to be conducted alongside the standard REGISTRY visit.

The IT implementation process has two phases: implementation of the core system followed by implementation of the REGISTRY sub-studies. Language Coordinators received intensive training on the core system during March 2011. The core system release will take place early during the second quarter of this year. The training programme for sites will be conducted via Site Investigator Meetings, Monitoring Visits, and Webinars. Please contact your Language Coordinator for further details on the training options available to your site staff:

[www.euro-hd.net/html/network/project/langcoord](http://www.euro-hd.net/html/network/project/langcoord).

In parallel to the launch of REGISTRY 3, significant efforts are underway to prepare for Enroll-HD, a new global HD study that will merge REGISTRY and COHORT (North American and Australian observational HD study) as well as reach out to other geographical regions (including Latin America and Asia). It is anticipated that many of the features of REGISTRY 3 will be carried into Enroll-HD. Therefore, over the next year, the aim is to have a seamless transition from REGISTRY 3 to the newly offered Enroll-HD. Further details on the progress of Enroll-HD can be found in the article featured on page 5.

## Enroll-HD: A Prospective Registry Study in a Global HD Cohort

Simon Noble (CHDI Foundation, USA) and Olivia Handley (EHDN, London, UK)

Enroll-HD is the new global initiative to conduct an observational study in Huntington's disease (HD) that will be open to HD families in Europe, North America, Latin America, Australia, and Asia. Enroll-HD represents the next phase of the existing HD clinical studies REGISTRY (Europe) and COHORT (North America/Australia) and builds on their many strengths and successes. Importantly, a newly formed, rapidly expanding HD clinical network, Red Latinoamericana de Huntington (RLAH) in Latin America, will join Enroll-HD.

### Main aims

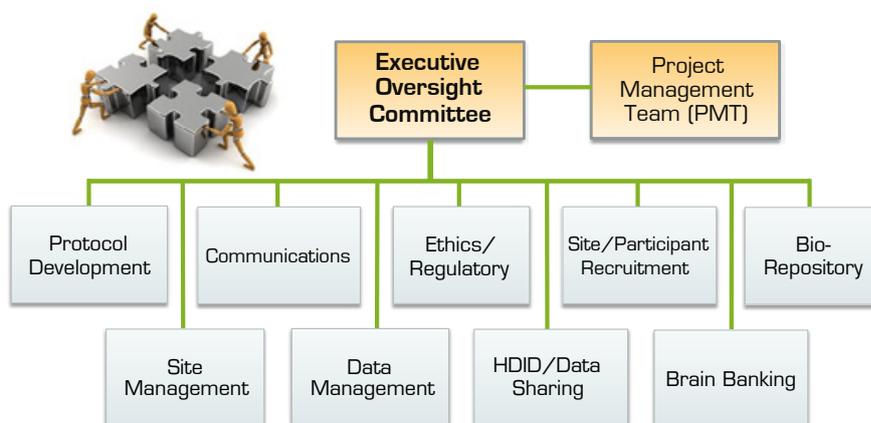
The overarching objective of Enroll-HD is to accelerate the development of therapeutics for HD by (1) compiling uniform clinical data and biological samples to understand better the natural history of HD, (2) building a more comprehensive database — including biological samples — that will be accessible to any HD investigator worldwide, (3) facilitating clinical sub-studies and the development and validation of HD assessment tools, (4) fostering good clinical care and improving health outcomes for both patients and families and (5) expediting recruitment into future global clinical trials of candidate therapeutics.

### Next steps

The start-up and management of Enroll-HD will be in two key stages. The first is a consultation phase to build consensus, the second is an implementation phase. The currently ongoing consultation phase is being managed by the Executive Oversight Committee (EOC) and a series of Working Groups (WGs; see figure). A key criterion defining the Enroll-HD EOC and WGs has been to seek representation from across the broad HD community (clinicians, patients, families, researchers, advocates) whilst also ensuring a balance of regional delegates. The WGs are now established and beginning their work. Anyone wishing to participate should contact Joe Giuliano ([joseph.giuliano@chdifoundation.org](mailto:joseph.giuliano@chdifoundation.org)).

Critical first steps that are now underway include the drafting of the Enroll-HD study protocol and the develop-

## EnrollHD A Prospective Registry Study in a Global HD Cohort



*Management structure that will be used during the period of integration into Enroll-HD. The boxes represent the working groups.*

ment of procedures to ensure best data-sharing practices. This includes data protection, and the storage and safeguarding of biological samples, all in accordance with respective local laws.

A committee comprised of representatives from EHDN, CHDI, HSG (Huntington Study Group) and RLAH was established to select a Contract Research Organisation (CRO) aiming to facilitate the standardisation of data collection and management across the global study, as well as to provide support to sites and the networks. The selected CRO, Outcome Sciences, is an established multinational with expertise in patient registry studies that led the development of the US government handbook "Registries for Evaluating Patient Outcomes: A User's Guide" ([www.outcome.com/ahrq-registries-evaluating-patient-outcome.htm](http://www.outcome.com/ahrq-registries-evaluating-patient-outcome.htm)). They will play an important supportive role throughout the consultation and implementation phases, particularly in project management, protocol development, facilitating Institutional Review Board approvals, supporting the integrated data management system, assisting study transition at sites, data monitoring and assisting with strategies for global recruitment.

The Communications WG will soon begin to issue periodic updates for investigators and the wider HD community. An Enroll-HD website targeted at patients, families and investigators is planned, with an interim site at [www.Enroll-HD.org](http://www.Enroll-HD.org) that will provide upcoming meeting dates and WG charters, memberships, and contact details. You can join the Enroll-HD mailing list at [Info@Enroll-HD.org](mailto:Info@Enroll-HD.org) for future updates.

## The Standard of Care Working Group: an Update

By Sheila Simpson and Daniela Rae (NHS Grampian/University of Aberdeen, UK)

Since the first article about this group in June 2008, there have been exciting developments in the Huntington's disease (HD) field, including the further evolution of the EHDN. However, HD remains a relentlessly progressive and incurable familial neurodegenerative disease, and families continue to need appropriate care. Some of the outcomes of the disease can be managed with some success, but there remains no cure as yet.

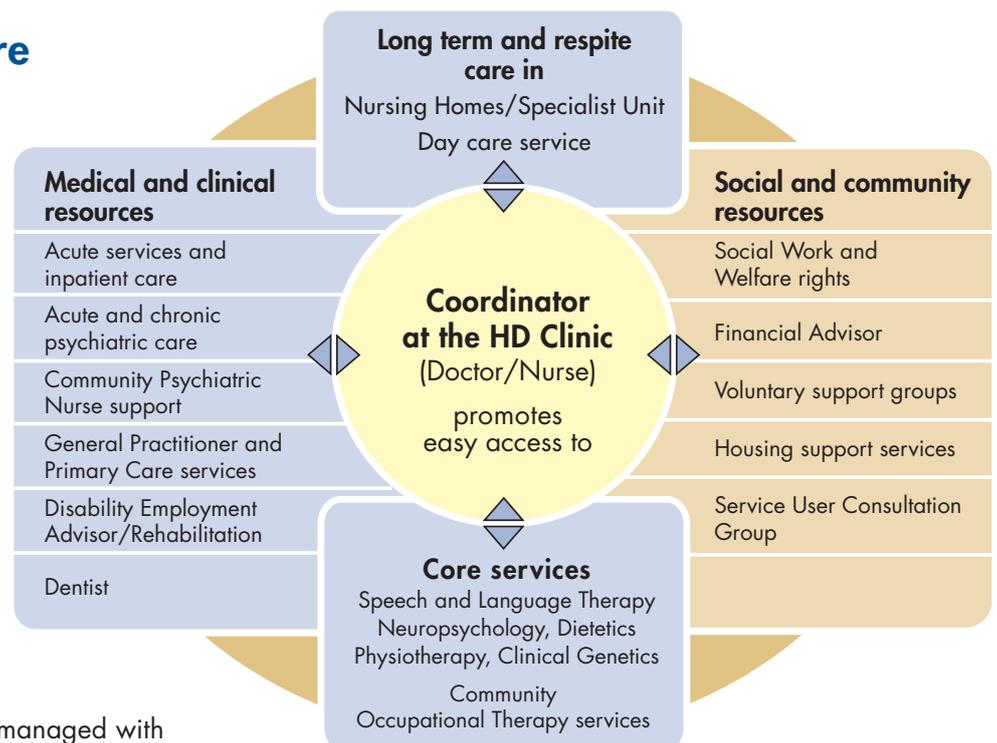
'This man has Huntington's disease; there is nothing more I can do' has been seen in patients' hospital notes on a regular basis, but there is much that can be done to improve the quality of life of the HD patient and his or her family, and the Standards of Care group have collated recommendations from experts in their fields to guide us.

### Why a Standard of Care?

The evidence for best practice is still lacking. In part, this reflects the fact that in many countries there are no specialist clinics for this patient group, and statistically significant data about care from large patient groups are still needed. Throughout the world, the care provided for HD families varies widely. Indeed, the impact of HD goes beyond the immediate symptoms experienced by the person who is ill. It affects the whole family: the person living at risk, the carer, the person in receipt of an unfavourable test result as well as the symptomatic patient. Due to its complexity, HD requires a multi-disciplinary approach involving a range of services that are required at each differing stage of a person's life with the disease. The Standards of Care Group has reviewed and amended its Managed Care Network Pathway accordingly.

### How was it achieved?

The Standards of Care (SoC) group comprises clinicians from various disciplines and many different countries within Europe as well as the USA. Family group mem-



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### *The revised Managed Care Network (MCN): the model developed by the Standards of Care Working Group for integrating different specialised services for HD patients*

bers, doctors and specialist nurses from psychiatry, clinical genetics and neurology, physiotherapists, occupational therapists, dietitians, speech and language therapists and dentists have all contributed. The first step for the groups was to gather information about the different approaches to the management of HD and to perform a rigorous and systematic review of the existing literature on the care of HD in the many disciplines involved. Relevant publications were identified, categorised and graded in accordance with SIGN<sup>1</sup> methodology. This process highlighted a paucity of scientific evidence base for the management of the condition. Thus, although the guidelines used all available evidence, they were created largely on the basis of expert consensus.

### The Subgroups

We quickly realised that for the SoC to operate successfully we needed to divide into different disciplines:

#### **Physiotherapy**

The progressive motor impairment in HD leads to a loss of mobility with individuals eventually requiring assistance with all activities of daily living. The Working Group developed guidelines for physiotherapy evalu-

<sup>1</sup>Scottish Intercollegiate Guidelines Networks "Guideline Developers handbook" (<http://www.sign.ac.uk/guidelines/fulltext/50/index.html>)

ations and interventions by describing current and best practice, and evaluating appropriate, standardised outcome measures relevant to physiotherapy and to the needs of patients ([www.euro-hd.net/html/network/groups/physio](http://www.euro-hd.net/html/network/groups/physio)).

### **Dietetics**

Nutritional screening together with the delivery of good nutritional care is fundamental to the care of an individual with HD. Individuals affected with Huntington's disease will need dietary intervention at some point. The aim of the Dietitians group was to develop nutritional guidelines to facilitate optimal nutritional screening, assessment and management of individuals throughout all stages of HD, including early referrals for a preventative approach to weight management and comprehensive nutritional assessment and management with timely reviews.

### **Speech and Language Therapy**

An especially distressing clinical feature of HD is the emergence of difficulty with speech and swallowing. It is clear that supportive and therapeutic intervention at an early stage can help to preserve clear speech for longer and to support safe swallowing. The ability to communicate with others and to state one's opinion or decision is a skill which ought to be preserved for as long as possible.

### **Dental Care**

There are no innate dental features of HD which make an individual more susceptible to dental caries or periodontal disease. However, there are several contributory factors that may affect detrimentally the oral health of people with HD, such as nutrition, PEG feeding, medication, oral hygiene, the movement disorder affecting the oral cavity as well as access to and provision of dental care. Oral care should be planned throughout the disease process and should not require crisis management in the final phase of the condition.

### **Occupational Therapy**

Occupational Therapy aims to promote independence for the individual with HD, their carers and family, and to maximise quality of life for these groups. The OT group has set out to identify some clinically useful assessment tools and provides interventions and rationales for possible difficulties which may be experienced by a person with HD in the areas of self-care, leisure and



*The Speech and Language Therapy Group at work*

productivity. Guidance also addresses seating, mobility and the safety of the affected person and their carer.

We have now submitted 6 papers from the WG for publication. These have recommended guidelines for management within their discipline, and we are pleased with this progress. However this is only the start of the journey.

### **Future Project Aims**

#### **1. Extensive dissemination and Implementation of the guidelines**

There is no purpose in developing guidelines that are not implemented into clinical care. We will use an evidence based framework to get the SoC WG guidelines into everyday use so that HD care can be enhanced across Europe and beyond. In order to translate the benefits of these guidelines into optimal care, it is necessary to widely disseminate them, not only through online publication, but in a summarised format to lay organisations, governments, professional bodies, health care professionals and carers. The systematic approach allows for the development of a data collection system facilitating data analysis and research in areas where knowledge is currently lacking. Engaging patients and carers in this process, to meet their respective needs, increases awareness of EHDN activities and encourages trial participation.

#### **2. Further development and evaluation of the SoC WG guidelines**

The SoC WG guidance is not all inclusive of those within the Managed Care Network, and so several aspects of care have not been addressed by the group, such as social work and pharmaceutical treatments. We are aiming to work with new partners within EHDN, especially members of existing working groups to address these. Evaluating the implemented care strategies using appropriate outcome measures will add valuable evidence supporting the consensus statements of the group.

## Observing Huntington's disease: the European Huntington's Disease Network's REGISTRY

Michael Orth and the European Huntington's Disease Network, *PLoS Currents* (2010), 2: RRN1184

**The first analysis of data collected through REGISTRY evaluates the variability of Huntington's disease (HD) phenotypes across Europe in relation to biological and environmental factors. It also examines potential predictors of functional capacity.**

### Background

EHDN's core study REGISTRY is a multi-centre, multi-national, prospective observational study of HD. It aims to study the natural history of HD, collect clinical data and biosamples, identify subjects for clinical trials, develop novel assessment tools to track disease progression and improve existing ones. REGISTRY enrolls manifest HD patients, pre-manifest HD gene mutation carriers, individuals at risk for HD, non-mutation carriers from HD families, and control subjects. This paper reports data from the enrolment visit of the first 1,766 participants at 66 EHDN study sites in 13 European countries.

### Methods

Data collection followed a standard protocol using electronic case report forms in the appropriate language. Participants were assessed using the following rating scales: UHDRS<sup>1</sup> '99 Behaviour, Cognitive, Motor and Total Functional Capacity, Becks Depression Inventory, Hamilton Depression Rating Scale, SF-36, Caregiver Burden Inventory and Client Service Receipt Inventory. Data on medical history, comorbid conditions, concomitant medication, family history and CAG repeat length were also collected. Statistical analysis of the data was performed by standard methods.

### Results

HD genotypes and phenotypes were similar across Europe. From the dataset of participants with manifest HD, 48% had motor signs at onset, while 20% had a psychiatric onset, 8% had cognitive signs, and 13% had a mixed onset. Behavioural abnormalities, including depression, apathy and irritability, were present in 87% of the cases. About 40% of the patients had a life-time history of severe psychiatric symptoms, which

included psychosis, aggression and suicidal ideation. In all, 58% of participants were taking medications. Most commonly, these were anti-dyskinetics (to treat motor symptoms), anti-depressants, anti-dementia drugs and nutritional supplements. Anti-dyskinetics and anti-depressants were used more frequently in Southern Europe and Poland ( $p < 0.0001$ ) than in other regions.

UHDRS motor scores increased (became worse) with higher biological disease burden (calculated from a subject's age and CAG repeat length). Cognition and total functional capacity also declined with higher disease burden. No such correlation was found for the total behavioural score, or its subscores, except for apathy, which showed a very weak association.

As disease burden alone was not enough to explain the variation found in the behavioural, cognitive and motor scores, the authors assessed the extent to which biological (age and CAG repeat length) and environmental factors (European region, medication and comorbidity) contributed to this variability. They found correlations between:

1. higher motor scores (decreased motor function) and the use of anti-dyskinetic medication, trauma, increasing age and increasing CAG repeat length
2. higher behavioural scores (poorer behavioural function) and the use of anti-depressants and anti-dyskinetics, as well as endocrine disorders
3. lower cognitive scores (worse cognitive performance) and the use of anti-dyskinetics, increasing CAG repeats and increased age
4. higher cognitive scores (better cognitive performance) and the use of nutritional supplements and other medications.

In addition to assessing phenotype, the authors developed a model to predict disease stage based on the parameters motor score, European region and cognitive score. The model accurately classified more than 80% for each individual stage (apart from the disease stage 2 – early-stage HD) with an accuracy of about 75%.

### Conclusions

The large collection of clinical data and biological samples within REGISTRY will allow research projects to be conducted on an unprecedented scale. This study will expedite the search for modifiers of disease onset and progression that can be harnessed for the development of novel treatments for HD.

<sup>1</sup>Unified Huntington's Disease Rating Scale

## Biological and clinical changes in premanifest and early stage Huntington's disease in the TRACK-HD study: the 12-month longitudinal analysis

Sarah J. Tabrizi et al., *The Lancet Neurology* (2010), 10: 31-42

**Follow-up data from TRACK-HD reveals that brain atrophy, cognitive decline and worsening of motor function are measurable over 12 months in individuals with premanifest and early-stage Huntington's disease.**

### Background

Several imaging, cognitive and motor measures have been proposed as candidates for tracking disease progression in premanifest and early-stage Huntington's disease (HD), but so far most studies have relied on cross-sectional data. Longitudinal studies are therefore essential to identify biomarkers, particularly over time-frames suitable for clinical trials.

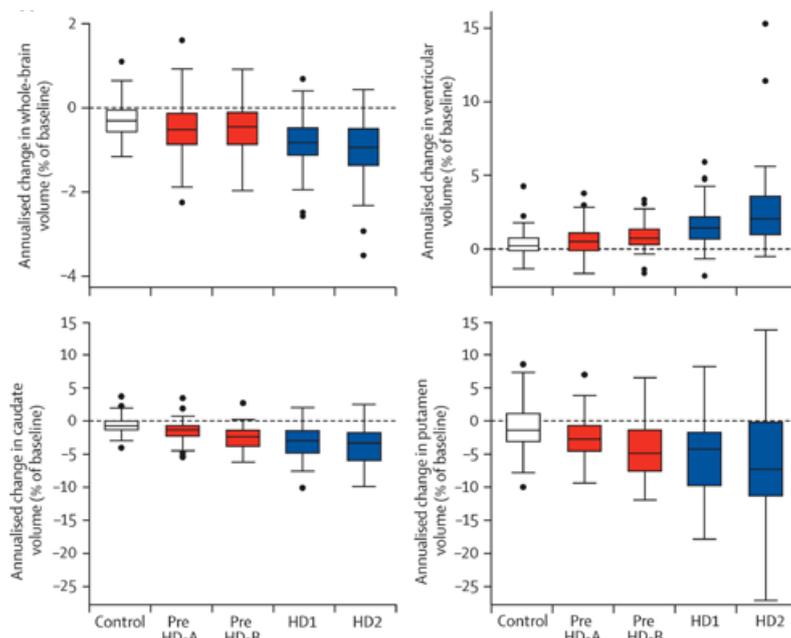
TRACK-HD is a multi-centre, prospective, longitudinal, observational study of premanifest and early-stage HD that aims to develop novel assessments to detect very early indicators of disease onset and progression. Baseline data were reported in 2009 (see Article of the Month 07/2009 in EHDN News issue 7). This paper reports findings from the analysis of the 12-month follow-up data.

### Subjects and methods

Premanifest HD gene mutation carriers were divided at the group median for predicted years to diagnosis into preHD-A (further from predicted diagnosis) and preHD-B (nearer). Early HD patients were divided into two subgroups based on UHDRS<sup>1</sup>-TFC<sup>2</sup> scores at baseline into HD stage 1 (HD1) and HD stage 2 (HD2). Control subjects were matched for age and sex. Methods included detailed demographic and clinical assessments, UHDRS-99, 3-tesla brain MRI<sup>3</sup>, cognitive, quantitative motor, oculomotor, neuropsychiatric and quality of life measures.

### Results

A total of 345 subjects completed the 12-month follow-up assessments. Participants in the preHD-B, HD1 and



**Annualised changes (as percentage of baseline values) in whole-brain volume, ventricular volume, caudate volume and putamen volume.**

HD2 groups had significantly higher 12-month whole-brain atrophy rates compared with controls (see figure). In all pre-HD and HD groups, caudate and putamen volumes showed faster rates of atrophy compared with controls, which increased with disease progression. Quantitative imaging outcomes correlated with both disease burden and UHDRS-TFC.

Several assessments showed significant differences ( $p \leq 0.05$ ) between early-stage patients and control subjects. However, only a circle tracing task, chorea position index and UHDRS-TMS<sup>4</sup> were able to detect changes in premanifest HD subjects compared to control subjects. Interestingly, outcomes of the chorea position index task correlated with both UHDRS-TMS chorea score and whole-brain atrophy. None of the neuropsychiatric measures was sufficiently sensitive to show changes over 12 months in either the preHD or HD group.

### Conclusions

TRACK-HD clearly shows that it is possible to detect disease progression over a period of 12 months in premanifest and early-stage HD. Quantitative brain imaging measures are the most sensitive outcomes. These measures correlate with functional, quantitative motor and cognitive outcomes, providing evidence of a link between structure and function.

<sup>1</sup> Unified Huntington's Disease Rating Scale

<sup>2</sup> Total Functional Capacity

<sup>3</sup> Magnetic Resonance Imaging

<sup>4</sup> Total Motor Score

## Matrix metalloproteinases are modifiers of huntingtin proteolysis and toxicity in Huntington's disease

John P. Miller et al., *Neuron* (2010), 67: 199-212

This study aimed to identify new proteases that cleave mutant huntingtin into fragments that are toxic to nerve cells.

### Background

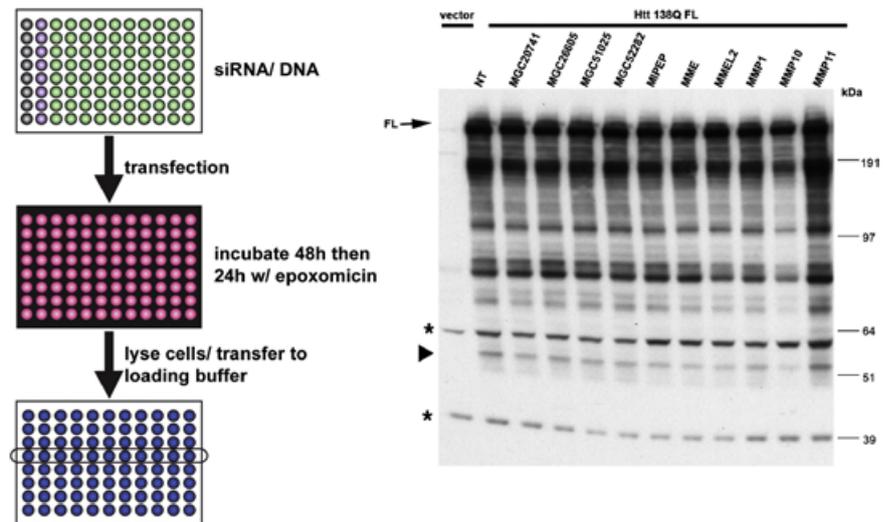
Huntington's disease (HD) is caused by a CAG expansion in the gene coding for a protein called huntingtin (Htt). The mutant protein has a corresponding expanded stretch of glutamines at its N terminus. Mutant Htt is cleaved by enzymes called proteases, and the resulting N-terminal fragments are involved in HD pathogenesis. Hence, inhibition of mutant Htt cleavage has been shown to reduce toxicity in cell and animal studies of HD. A number of proteases that cleave Htt have been identified so far, most prominently caspases and calpains.

### Methods

The authors of this study developed an assay to rapidly screen the generation of small N-terminal Htt fragments based on the western blot method in a 96-well format. A pool of 514 small interfering RNAs (siRNAs) targeting all known human protease genes was used to silence expression of each of these genes. If a particular siRNA knocked down the production of a protease involved in Htt cleavage, the amount of a certain cleavage product (an N-terminal Htt fragment of 55 kDa molecular weight) would be reduced, and this could be seen on a western blot using an antibody that targeted the polyglutamine stretch (see figure). Candidate proteases were tested for toxicity in an HD cell model and characterised further in biochemical and cellular assays, as well as in animal models of HD.

### Results

In the first screen, the authors detected 41 genes that reduced the levels of the small Htt fragment by at least 30%. Retesting of these hits confirmed that 11 genes consistently decreased the production of the Htt cleavage product. The identified proteases included members of the calpain family, the kallikrein family and the matrix metalloproteinase family (MMP-10, MMP-14 and MMP-23B).



**Western blot screen for protease siRNAs that reduce Htt cleavage. The bands range from full-length (FL) Htt to the 55-kDa fragment of interest (arrowhead). Asterisks mark non-specific bands.**

MMPs are thought to degrade the extracellular matrix (the part of animal tissues outside of cells that provide support and anchorage for cells), but may have other substrates as well.

Nine of the 11 proteases modulated Htt toxicity in a second assay of cell death in a mouse striatal cell line expressing the mutant protein (*Hdh*<sup>111Q/111Q</sup> cells). MMP-10 and MMP-14 are expressed in this cell line and are significantly more active here than in control cells. MMP enzymatic activity is also increased in the striatum of two HD mouse models expressing full-length mutant Htt (YAC128) and a fragment of mutant Htt (R6/2) in comparison to control mice. This activation was not observed in another polyglutamine disease (SCA7). MMP-10, but not MMP-14, cleaves both wild-type and mutant Htt at amino acid 402. This was demonstrated *in vitro* and *in post mortem* brain samples. Htt and MMP-10 co-localise, i.e., they are found together forming particular structures inside the cells. Furthermore, reducing the expression of MMP and four other proteases in an HD *Drosophila* model compensates for the toxic effects of mutant Htt that cause motor dysfunction and degeneration of photoreceptors in the fly eyes.

### Conclusions

These data suggest that MMPs are involved in mutant Htt cleavage and modulation of its toxicity in cell and animal models of HD. This protease family is an interesting therapeutic target for HD, particularly because pharmaceutical inhibitors of MMPs are already available.

## Upcoming Meetings 2011

<b>Apr 22-24</b>	XIII International Meeting of the Polish HDA Members and HD Conference, Warsaw, Poland, <a href="http://www.huntington.pl/">http://www.huntington.pl/</a>	<b>July 7-8</b>	British EHDN Site Investigators Meeting, Birmingham, UK
<b>May 4-7</b>	9 <sup>th</sup> European Association Neuroscience Nurses Congress, Blankenberge, Belgium <a href="http://www.eann2011.com/">http://www.eann2011.com/</a>	<b>Sept 3-7</b>	24 <sup>th</sup> Congress of the European College of Neuropsychopharmacology, Paris, France <a href="http://www.ecnp.eu/emc.asp?pageld=1686">http://www.ecnp.eu/emc.asp?pageld=1686</a>
<b>May 10-11</b>	EHDN Site Investigators Meeting of the Nordic Countries, Stockholm, Sweden	<b>Sept 11-14</b>	5 <sup>th</sup> World Congress on Huntington's Disease, Melbourne, Australia <a href="http://www.worldcongress-hd2011.org/">http://www.worldcongress-hd2011.org/</a>
<b>May 12-13</b>	Deep Brain Stimulation in Movement Disorders – MDS programme, Kiel, Germany <a href="http://www.movementdisorders.org/education/dbs/kiel/">http://www.movementdisorders.org/education/dbs/kiel/</a>	<b>Sept 24</b>	Russian EHDN Site Investigators Meeting, venue to be confirmed
<b>May 13-15</b>	Molecular Mechanisms of Neurodegeneration (5 <sup>th</sup> Meeting), Milan, Italy <a href="http://users.unimi.it/triplet/2011/">http://users.unimi.it/triplet/2011/</a>	<b>Oct 6-8</b>	21 <sup>st</sup> Alzheimer Europe Conference, Warsaw, Poland <a href="http://www.alzheimer-europe.org/EN/Conferences/Warsaw-2011">http://www.alzheimer-europe.org/EN/Conferences/Warsaw-2011</a>
<b>May 15-16</b>	Italian EHDN Site Investigators Meeting, Milan, Italy	<b>Oct 9-14</b>	14 <sup>th</sup> European Congress of Neurosurgery, Rome, Italy <a href="http://www2.kenes.com/eans/Pages/home.aspx">http://www2.kenes.com/eans/Pages/home.aspx</a>
<b>May 18-19</b>	EHDN Site Investigators Meeting of German speaking countries, Günzburg, Germany <a href="https://www.euro-hd.net/html/network/news">https://www.euro-hd.net/html/network/news</a>	<b>Oct 11-15</b>	12 <sup>th</sup> International Congress of Human Genetics, Montreal, Canada <a href="http://www.ichg2011.org/">http://www.ichg2011.org/</a>
<b>May 25-28</b>	25 <sup>th</sup> International Symposium on Cerebral Blood Flow, Metabolism and Function & 10 <sup>th</sup> International Conference on Quantification of Brain Function with PET, Barcelona, Spain <a href="http://www2.kenes.com/brain/pages/home.aspx">http://www2.kenes.com/brain/pages/home.aspx</a>	<b>Oct 13-16</b>	5 <sup>th</sup> World Congress on Controversies in Neurology, Beijing, China <a href="http://comtecmed.com/cony/2011/">http://comtecmed.com/cony/2011/</a>
<b>May 26</b>	Nutrition and HD, Italian HD Association AICH-Roma Onlus, Rome, Italy <a href="http://www.aichroma.com/">http://www.aichroma.com/</a>	<b>Oct 20-22</b>	1 <sup>st</sup> European Neurorehabilitation Congress, Merano, Italy <a href="http://www.enrc2011.eu/">http://www.enrc2011.eu/</a>
<b>May 28-31</b>	21 <sup>st</sup> Meeting of the European Neurological Society, Lisbon, Portugal <a href="http://www.congrex.ch/ens2011">http://www.congrex.ch/ens2011</a>	<b>Oct 20-23</b>	7 <sup>th</sup> International Congress on Vascular Dementia, Riga, Latvia <a href="http://www2.kenes.com/vascular2011/Pages/home.aspx">http://www2.kenes.com/vascular2011/Pages/home.aspx</a>
<b>May 28-31</b>	European Human Genetics Conference 2011, Amsterdam, The Netherlands <a href="https://www.eshg.org/eshg2011.0.html">https://www.eshg.org/eshg2011.0.html</a>	<b>Nov 3</b>	Portuguese EHDN Site Investigators Meeting, Lisbon, Portugal
<b>June 4</b>	Annual Meeting of the Portuguese HD Association, Portimão, Portugal	<b>Nov 5</b>	5 <sup>th</sup> Annual Huntington Disease Clinical Research Symposium, Indianapolis, IN, USA <a href="http://www.huntington-study-group.org/NewsEvents/EventsUpcomingMeetings/HuntingtonDiseaseClinicalResearchSymposium/tabid/62/Default.aspx">http://www.huntington-study-group.org/NewsEvents/EventsUpcomingMeetings/HuntingtonDiseaseClinicalResearchSymposium/tabid/62/Default.aspx</a>
<b>June 5-9</b>	15 <sup>th</sup> International Congress of Parkinson's Disease and Movement Disorders, Toronto, Canada <a href="http://www.movementdisorders.org/congress/congress11/">http://www.movementdisorders.org/congress/congress11/</a>	<b>Nov 12-16</b>	Neuroscience 2011: Annual Meeting of the Society for Neuroscience, Washington, DC, USA <a href="http://www.sfn.org/am2011/">http://www.sfn.org/am2011/</a>
<b>June 5-10</b>	The Gordon Research Conference on CAG Triplet Repeat Expansion Disorders, Il Ciocco, Italy <a href="http://www.grc.org/programs.aspx?year=2011&amp;program=cag">http://www.grc.org/programs.aspx?year=2011&amp;program=cag</a>	<b>Nov 12-17</b>	20 <sup>th</sup> World Congress of Neurology, Marrakesh, Morocco <a href="http://www2.kenes.com/wcn/Pages/Home.aspx">http://www2.kenes.com/wcn/Pages/Home.aspx</a>
<b>June 21-25</b>	14 <sup>th</sup> European Conference on Clinical Neurophysiology, Rome, Italy <a href="http://www.oic.it/eccn2011/">http://www.oic.it/eccn2011/</a>	<b>Dec 11-14</b>	XIX World Federation of Neurology World Congress on Parkinson's Disease and Related Disorders, Shanghai, China <a href="http://www2.kenes.com/parkinson/Pages/Home.aspx">http://www2.kenes.com/parkinson/Pages/Home.aspx</a>
<b>June 24-26</b>	26 <sup>th</sup> Annual National Convention of the Huntington's Disease Society of America, Minneapolis, MN, USA <a href="http://www.hdsa.org/national-convention/convention.html">http://www.hdsa.org/national-convention/convention.html</a>		