June 2009 · Issue 06

EHDN News

EUROPEAN HUNTINGTON'S DISEASE NETWORK

Over 200 researchers from Europe, North America and Asia joined CHDI's fourth annual scientific meeting in Cannes, France.

FEATURE ARTICLE

Bonnie Lee La Madeleine, CHDI Foundation, Los Angeles (USA)

HD Therapeutics 2009: Cross-fertilization, rediscovery and learning

The paths towards developing treatments for those living with Huntington's disease (HD) have not been easy, but the scientists and clinicians who gathered in Cannes from 27th to 30th April for HD Therapeutics 2009 are at last seeing signs of progress.

HD Therapeutics 2009 was CHDI's fourth annual scientific meeting, and its first in Europe. The goal of the meeting was cross-fertilization, said Robert Pacifici, Chief Scientific Officer at CHDI. "By bringing together scientists who are working at all levels of HD research, new ideas take seed and everyone learns. And we are learning, and getting really good at it," Pacifici said.

To illustrate that point, he referred to a number of community resources that will allow research to progress more efficiently. The HD Community BioRepository (established by CHDI at Coriell, New Jersey) is a repository into which scientists can deposit and withdraw reagents, which will better enable sharing of resources. ResearchCrossroads is a web-based, interactive portal, currently under development, that will bring together ideas and results from numerous scientific outlets. It will ultimately give HD researchers easy access to data and other scientific information about ongoing research.

Hollywood's love affair with Huntington's Disease

Julie Melman put a human face on the science of HD during her keynote address. She had edited together a series of television and film representations of HD and juxtaposed them with real home movies of families living with HD. Contrasting the "dramatic" storylines with the everyday realities brought home the urgency of the work the scientists are doing.

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Imprint: Editorial Board of the EHDN Newsletter: Prof. Gillian Bates (King's College London School of Medicine, London, UK), Dr. Jenny Morton (University of Cambridge, Cambridge, UK), Dr. Diana Raffelsbauer (PharmaWrite, Giebelstadt, Germany), Dr. Jenny Naji (Cardiff University, Cardiff, UK), Christiane Lohkamp (IHA, Stuttgart, Germany), Gabriele Stautner (Artifox Communication Design, Ulm, Germany).

Understanding the biology of HD Pathology

Only recently has technology advanced enough to allow scientists to observe the timing of neuronal changes in the brains of people with HD. The first session of the meeting focused on what we are learning with these powerful tools.

Diana Rosas (Massachusetts General Hospital) and Beth Borowsky (CHDI) presented whole brain imaging and other clinical data from Track-HD (an EHDN-supported study looking at the earliest pathological changes in those with HD). Looking for functional markers of disease progression, David Eidelberg (Feinstein Institute) showed how metabolic brain imaging reveals a distinct pattern that evolves throughout the pre-manifest period. He found that this pattern can be measured in pre-manifest individuals and may be a way of gauging disease progression before diagnosis. Further validation will allow these biomarkers to be used in studies of new therapeutic agents.

Target Identification and Validation

The five presentations during this session, three from academia and two from industry, introduced several promising technologies that are part of CHDI's translational program. After William Yang (UCLA) talked about the insights that proteomics and network analysis might reveal about interactomes in an HD mouse model, Juan Botas (Baylor College of Medicine) and Bob Hughes (Buck Institute) discussed the advantages and limitations of using cellular and invertebrate models to validate targets. Chris Trotta (PTC Therapeutics, Inc.) demonstrated how small molecules might modulate post-translational control of therapeutic targets. Finally, Philip Gregory (Sangamo Biosciences) talked about using zinc finger proteins as designer tools to interrogate possible therapeutic targets and develop therapeutics.

From Target to Proof-of-Concept Molecule

Two programs were introduced to illustrate how CHDI pursues promising targets and develops compounds to test the mechanisms of action for those targets. Gill Bates (King's College London) and Alex Kiselyov (deCODE) introduced the biological and chemical challenges of HDAC modulation. Despite the complexity and challenges of this program, some exciting possibilities are being uncovered. Dirk Winkler (Evotec AG) and Leticia Toledo-Sherman (CHDI) gave a status report on CHDI's kynurenine monooxygenase inhibition program.

How does Viagra benefit HD?

During his featured talk, John Lowe (recently retired from Pfizer, Inc.) demonstrated how the successful development of a drug in one member of a family of targets might benefit other diseases. He did this by showing how a drug that inhibits phosphodiesterase (PDE) 5, and serendipitously improves erectile function, revealed a new mechanism of action for nitric oxide. This success gave his team the opportunity to investigate the rest of the PDE family. Inhibition of PDE4 is currently a promising therapeutic direction for HD.

Poster viewing session

Leveraging Pharma's Tools for HD

Representatives of four pharmaceutical companies explained how each organization approaches drug development, makes decisions about which programs to support and offset risk. Ian Reynolds (Merck & Co., Inc.) demonstrated that Merck's NMDA receptor 2B-antagonist program might have benefits for HD patients, despite having been shelved for people with Parkinson's disease. David Bredt (Eli Lilly) introduced Lilly's effort to use antibodies that flush β-Amyloid from the brain into plasma, thereby reducing the amount of β-Amyloid available to form aggregates as a treatment for Alzheimer's disease.

Also sharing a set of lessons learned, Sam Kongsamut (sanofi-aventis) outlined the 5-hydroxytryptamine 2A antagonist program. The success of the program results from a stress on flexibility, clarity of focus, and the development of simple, reliable and acute assays. Graeme Bilbe (Novartis) presented their HD therapeutics programme, that includes high throughput compound screening, a selective bioassay that can detect mutant huntingtin in blood and CSF, and also a potential drug for the control of L-Dopa induced dyskinesia in Parkinson's disease.

Strategies for Successful Early Clinical Development

The final presentations encapsulated several recurring issues raised throughout the meeting. Alan Holllister (AstraZeneca) proposed a new research paradigm that might reduce the chances of failure in phase 3 trials.

Malek Bajbouj (Charite, Free University, Berlin) showed several imaging techniques that might demonstrate drug effectiveness in trials more precisely. Ken Evans (Ontario Cancer Biomarker Network) outlined a plan to develop functional rating scales for HD, and Mark Guttman (Centre for Movement Disorders, Ontario) proposed developing a new set of diagnostic guidelines.

"Science is a process of rediscovery," said Diana Rosas, echoing Pacifici's opening remarks. This year's meeting was CHDI's largest with over 200 researchers from Europe, North America and Asia. Over the three days, they discovered and rediscovered possible paths for the development of therapeutics for HD and explored the means with which to accelerate this process.

NEWS

Impact of the earthquake in Italy on HD patient care

Paola Zinzi, National Research Council, Rome (Italy)

On April 6th 2009, at 3:30 a.m., a powerful 6.3 magnitude earthquake struck the city of L'Aquila in the Abruzzo region of central Italy. It was the worst earthquake to hit this region in nearly 30 years, and the aftershock was so strong it was felt in Rome, 75 miles away. It levelled or damaged thousands of homes and public buildings in L'Aquila including hospitals, the University, students' residences and historic churches. The death toll was 295, 1,500 people were injured and 55,000 were made homeless, making this the deadliest earthquake to hit Italy since the 1980 Irpinia earthquake. Many people left their homes out of fear amid continuing aftershocks, which caused further buildings to collapse in L'Aquila and the neighbouring towns. Of those who fled, 33,000 are now living in the tent camps that have been set up across the region. Officials aim to have people out of the tent cities before the winter, which can be very cold in the mountainous region of Abruzzo.

The Rehabilitation Home Care "Nova Salus" is located in Trasacco, not far from L'Aquila. The professional staff, Domenico De Angelis, head of administration, Stefano Maceroni, physiotherapist, and Liliana Basmagi, speech therapist, have reassured us that no-one, including the 5 HD in-patients, was injured, and that the structure of the building was not damaged. However, the experience was very frightening for all concerned, and the homes of some of the professional staff living in L'Aquila were destroyed by the earthquake.

Over the years, the region of Abruzzo has invited Italian HD patients to enrol in the rehabilitation pilot project initiated almost ten years ago at "Nova Salus". We sincerely hope that we shall be able to continue our activities, but there is a possibility that local social and medical needs will overload the institution, thus preventing HD patients from other regions from attending the Home Care in the near future. Our immediate goal is to rapidly complete the collection of several years of research data (2003-2008) documenting the effects of a longitudinal intensive rehabilitation programme on a wide range of HD symptoms. Most of this research has been conducted without financial support. In collaboration with the EHDN Physiotherapy Working Group, we are working on the submission of a seed fund proposal to EHDN.

NEWS

EHDN welcomes Russia! ЕХДН встречает Россию!

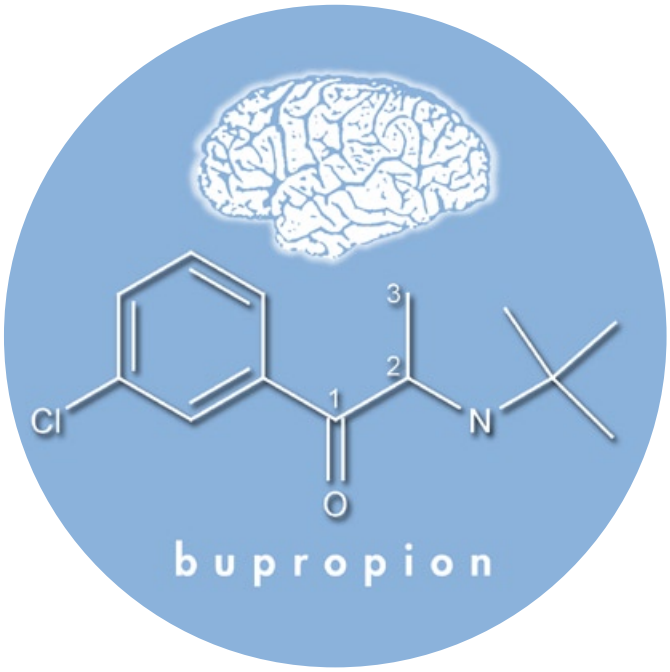
Russian study centres will be joining EHDN and actively participating to REGISTRY. Movement disorder specialists and neurogeneticists from several centres in the Russian Federation (Moscow, St. Petersburg, Samara and Rostov-on-Don) are eager to join EHDN and to enrol consenting patients under their care. Sergey N. Illarioshkin (Vice-Chairman of the National Institute of Neurology, Head of the Section of Neurogenetics and Director of the Brain Institute in Moscow) will host the Language Area Coordinator, Elizaveta Tarasova, MD, who is currently being trained for this position. The Centre in Moscow will be the first study site to become active, with an estimated 300 potential HD mutation carriers (both pre-manifest and manifest).

EHDN clinical trial to assess bupropion as a treatment for apathy in HD

Josef Priller and Harald Gelderblom,
Neuropsychiatry Unit, Dept. of Psychiatry, Charité CCM, Berlin (Germany)

Apathy in Huntington's disease

Apathy is a common behavioural problem in Huntington's disease (HD), especially in the more advanced stages of the disease. It is defined as the primary absence of motivation, lack of initiative and drive, as well as emotional blunting. With a prevalence of 34% to 67% in HD patients, the impact of apathy on their quality of life cannot be underestimated. This is emphasised by the fact that apathy was repeatedly ranked as one of the most pressing problems by EHDN investigators. However, specific treatment options for apathy in HD do not exist. Rather, coexisting depression or the consequences of cognitive impairment are treated with antidepressants or with acetylcholinesterase inhibitors, respectively. While systematic research on specific treatment for apathy has been conducted in Alzheimer's disease, this has not been done for HD.



The chemical structure of bupropion (Zyban®)

Bupropion – a promising agent for the treatment of apathy in HD

Apathy has been related to dysfunctions of the frontal lobe, especially in the frontal-subcortical circuits, the cingulate cortex, caudate and pallidum. Dopaminergic fibres projecting from the ventral tegmental area to the frontal lobe of the cortex seem to be important. To date, all these regions are thought to be involved in reward and motivation. Dopamine has been implicated as a key neurotransmitter in reward/motivation pathways. Bupropion is an antidepressant that blocks norepinephrine, and more importantly, dopamine reuptake. The latter function distinguishes bupropion from other antidepressants such as the selective serotonin reuptake inhibitors. This is of particular interest, since the effects of dopamine are regulated by reuptake via norepinephrine transporters in the frontal cortex, which largely lacks dopamine transporters. Thus, bupropion can increase dopamine levels in an area of the brain that is of particular relevance in the generation of apathy. There is evidence to suggest that bupropion may have dopaminergic effects in humans. In addition, evidence exists for the efficacy of bupropion in the management of apathy from clinical trials.

Multi-centre trial on the therapeutic effect of bupropion on apathy in HD

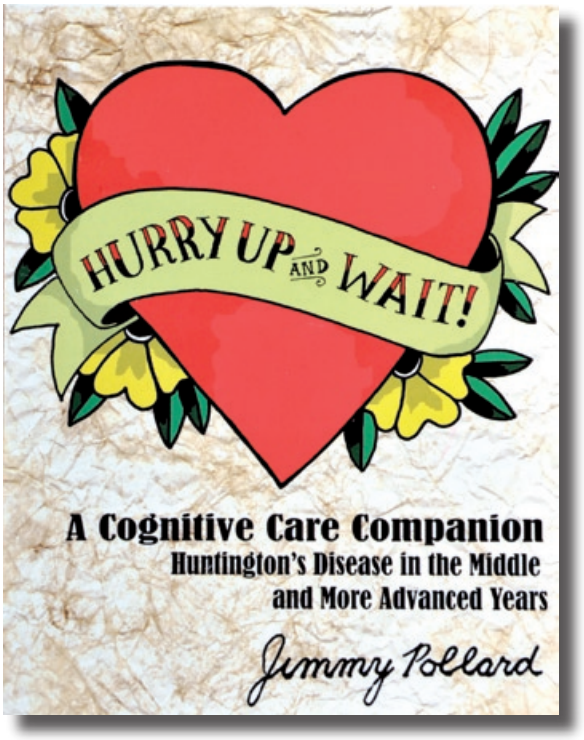
In a multi-centre, double-blind, placebo-controlled study, we shall investigate the effects of bupropion on apathy in HD patients. The trial, which is supported by the HSC (Huntington Society of Canada) and EHDN, will be conducted by three participating sites: Neuropsychiatry Unit, Charité, Berlin (Germany), Cambridge Centre for Brain Repair, Cambridge (UK) and Department of Psychiatry, Leiden (The Netherlands). Apathic HD mutation carriers will be randomised to receive either bupropion or placebo and followed for 12 weeks. Patients with concomitant disorders like depression or severe cognitive impairment, that can cause apathic behaviour, will not be included. Apathy will be graded using apathy scales which have been validated for other degenerative CNS diseases and applied to a larger group of patients with HD by one of the principal investigators of the study. Patient accrual is planned to start in September 2009. For referral of potential study participants, please contact harald.gelderblom@charite.de.

Hurry Up and Wait! by Jimmy Pollard

Huntington's disease (HD) brings changes in the thinking of affected individuals that present a series of ongoing challenges to both family carers and professional carers in nursing homes. To accommodate the cognitive features of HD in both settings, a carer must 'hurry up' because the affected person has difficulty waiting for things, yet at other times, they must patiently 'wait' for the affected person to slowly organise and express their thoughts. A carer's day can therefore be an exhausting mixture of hurrying and waiting, bouncing between these two contrary and demanding activities.

'Hurry Up and Wait!' offers a set of exercises to show what it might feel like to think with HD and to see things from the unique viewpoint of the affected person. Greater understanding of the features of 'thinking with HD' can help us not only to accommodate HD patients better, but also to understand how cognitive dysfunction contributes to the most challenging problems that carers face. Providing care that requires you for many years to hurry up and wait, often at the same time, is both demanding and paradoxical. As Pollard points out, "if done over many days or many years or several decades, this is a most profound act of love." The exercises are also helpful in explaining HD to friends and professionals unfamiliar with our family care challenges.

Jimmy Pollard has given us neither a 'how to' book nor an advice book. Rather, he presents us with ideas, exercises, concepts and observations based on many years spent with a large number of people in the middle and later years of their disease. 'Hurry Up and Wait!' summarises and shares with readers some important lessons that he has learnt from his long-term partnerships with many family carers and his professional colleagues.



About the author

Jimmy Pollard lives in Lowell, Massachusetts, United States. He holds a Master's degree in special education and a nursing home administrator's license. For the last twenty-three years, his career has been dedicated to the care of people in the middle and later years of HD in nursing homes and other extended care settings. He currently works as the director of HD services at Tewksbury Hospital and is an Associate Member of the European Huntington's Disease Network.

Jimmy is well known to people with HD and their families around the world. He has been invited to speak at national HD and caregivers meetings all over Europe, Australia, Canada and the United States. He has toured England and Wales speaking to healthcare professionals for the HD Association of Great Britain. He is a regularly invited speaker at biannual meetings of both the European and International Huntington Associations, the last time being at the World Congress on HD in Dresden, Germany, in 2007.

You can order the book online for € 13.26 here:
http://www.lulu.com/content/2517713

Deutsche Ausgabe demnächst über die Deutsche Huntington-Hilfe erhältlich: www.huntington-hilfe.de

The Collection of Family History Information in REGISTRY

By Olivia Handley, REGISTRY Project Manager, London (United Kingdom)

Huntington's disease (HD) presents with many different symptoms or phenotypes, and their range can vary considerably from one affected person to another. Whether or not HD just affects different people in different ways, or whether some of the symptoms/phenotypes are inherited within HD families is unknown. The collection of family history information and knowledge of the familial relationships of REGISTRY participants will be critical for identifying which symptoms cluster within families. The REGISTRY Family History Questionnaire, together with DNA samples, permits the analysis of phenotypic and genotypic information, and will allow exploration of the relationships between genetic factors and the effect they may have on altering the clinical features of HD and their treatment response.

The REGISTRY web portal captures family history data using a sophisticated tool to enable the creation and modification of a family tree (see figure). Each family member is represented by a node. The REGISTRY participant is represented as a "**P**". The symbols representing family members who consented to participate in REGISTRY are labelled with their annotated pseudonym (see father of participant in the figure). By using this procedure, biosamples and clinical data of related participants can be linked.

For each node, it is possible to add a spouse, offspring (with known or unknown spouse), mono- and dizygotic twin, and offspring born through ovum/sperm donation. It is also possible to add more than one spousal relationship for a node. The following data are obtained for each family member: gender, year of birth, whether the relative is alive/dead (year and cause of death) and HD gene status. If HD symptoms are already manifest, information relating to age of disease onset, first symptoms, diagnostic and genetic confirmation is also included.

To date approximately half (n = 2,005) of the 4,496 participants enrolled into REGISTRY have family history trees. Coupled with the availability of longitudinal assessment data and a robust biosample repository, REGISTRY will soon be in a position to contribute towards well-powered studies aimed at identifying and exploring the impact of specific genetic variations on the onset and course of heritable HD phenotypes and their treatment response.

Family History Tree (from a test pseudonym)

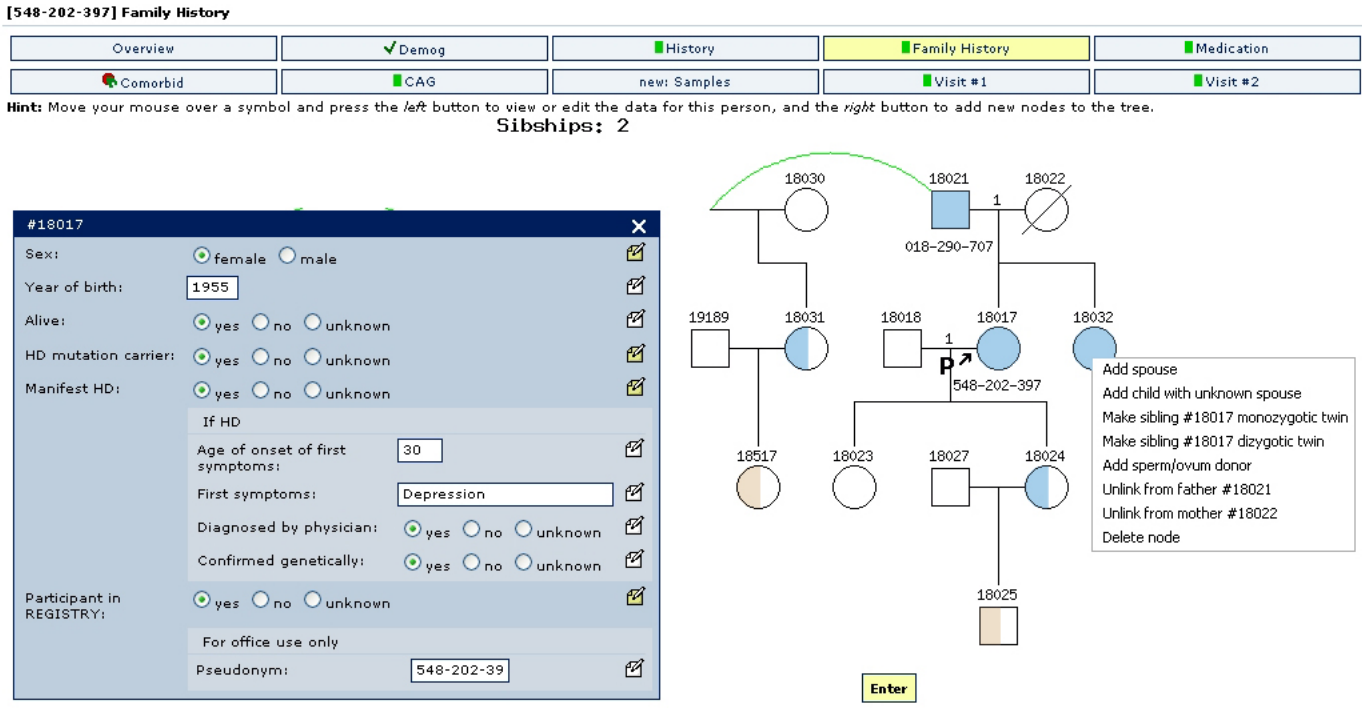
□ = male ○ = female

= Manifest HD

= Premanifest HD, HD mutation carrier

= Non mutation carrier

= Deceased



Surgical Approaches Working Group

By Anne Rosser and Stephen Dunnett,
Cardiff University, Cardiff (United Kingdom)

Alternative Surgical Strategies for Huntington's Disease

For more than two decades there has been interest in surgical treatments for Huntington's disease (HD). Initially, these treatments focused on cell transplantation. More recently, consideration has been given to gene therapies and deep brain stimulation (DBS). Although these approaches involve very different types of implant (cells, viral vectors or electrodes), they have common neurosurgical delivery strategies. The Surgical Approaches Working Group (SWG) was established to evaluate the status of different strategies and to identify areas where EHDN might play a particular role in coordinating clinical trials involving surgical treatments.

Neurosurgeons use a stereotactic frame to position implants (cells, electrodes, gene vectors) in the depths of the brain precisely. The image shows the Leksell Stereotactic System®.

Cell transplantation

Based on what has proved effective in studies using experimental animals, trials of cell transplantation in HD have all involved implantation of fetal striatal cells into the striatum, to replace those lost in the disease. Several clinical studies have now demonstrated good graft survival and preliminary evidence of efficacy. A major French trial is underway, co-coordinated by Dr Bachoud-Lévi. This trial has sufficient numbers to indicate efficacy and the outcome is keenly awaited. Although at present all trials use fetal cells, the ultimate aim is to use stem cell alternatives. Cell transplantation studies are already well co-ordinated through the European Network for Cell Transplantation and Repair (NECTAR), with whom EHDN co-operates closely.

Deep Brain Stimulation (DBS)

DBS employs electrical stimulation of brain areas via implanted electrodes. There is evidence of efficacy for a variety of conditions, including Parkinson's disease (at a stage that is refractory to, or complicated by drug treatment), although the mechanism of action is not fully understood. There is some evidence from animal models, and limited evidence from isolated HD clinical cases, that DBS may be effective in controlling severe chorea in HD. There are also trials underway to study DBS as a therapy in early HD. The SWG reviewed the existing data and concluded that there is a need to investigate DBS as a symptomatic treatment for poorly-controlled and troublesome chorea. The first pilot studies are planned to determine optimal brain targets appropriate to control chorea. The long-term aim is to support a future multicentre European study of DBS in HD.

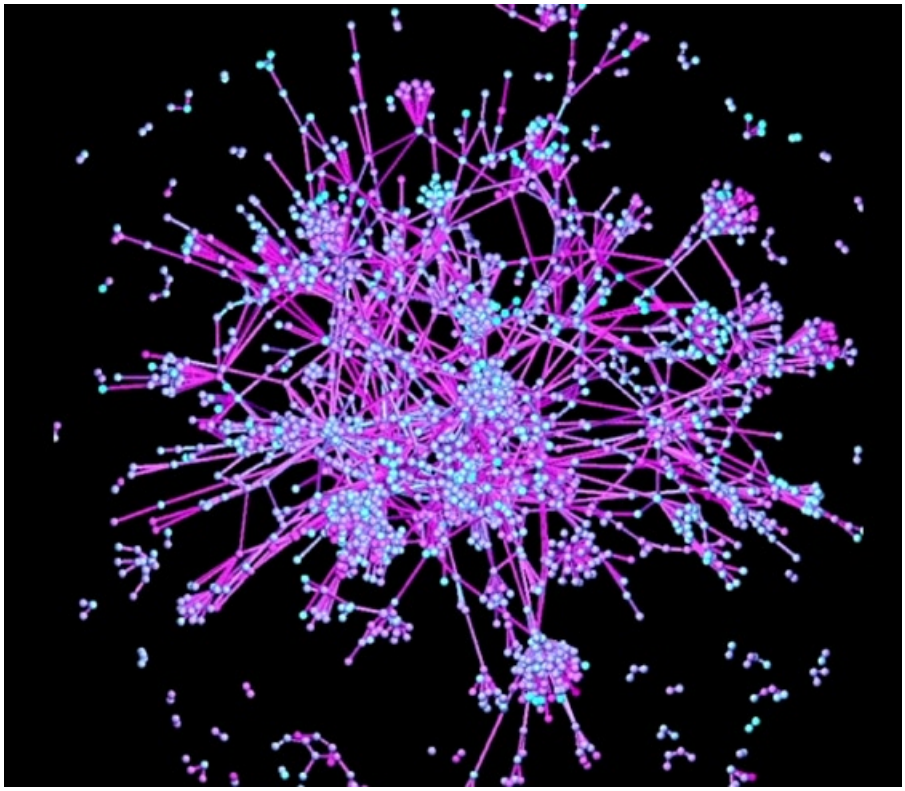
Gene therapy

Two major areas of interest are *HD* gene silencing and the delivery of trophic (growth) factors. Gene silencing by RNA interference aims to reduce the production of huntingtin in the hope that reducing the level of (toxic) mutant protein will slow disease progression. Trophic factors such as BDNF and CNTF may exert a neuroprotective effect on damaged striatal neurones. A number of small clinical trials are already underway to explore the potential of using such factors to slow the progression of HD. Delivery of gene therapy may be achieved either using viruses to transfer the genes into the correct brain targets, or by engineering cells (such as skin cell fibroblasts) to secret the factors at high levels, and then transplanting the engineered cells into the brain.

Development of DBS has become the SWG's major activity, although members of the group are also active in, and continuing to monitor, progress in cell transplantation and gene therapy.

Biological Modifiers Working Group

By Christian Néri, INSERM, Paris (France)



Biological network with modules made of strongly-interconnected and thus functionally-related genes.

What is the goal of the Working Group?

The identification and validation of neuroprotective molecular and cellular pathways that could be targeted for the development of new treatments for Huntington's disease (HD) is of primary importance. Models that recapitulate the features of HD and are amenable to large-scale manipulations have been produced in many different species including yeast *(S. cerevisiae)*, fruit flies *(D. melanogaster)*, nematode worms *(C. elegans)*, and a variety of cultured mammalian cells. Genome-wide analyses (e.g. changes in the expression of all genes or systematically testing the effects of knock-out of all genes on HD phenotypes) in these models have generated very large data sets that have the potential to direct the selection of neuroprotective targets. The goal of our working group is to use network biology for the comprehensive and unbiased integration of these 'omics' data. This may optimise the selection of neuroprotective targets for further validation.

What is network biology?

Network biology is an integrated discipline that combines computational modelling and biological expertise. It relies on the use of gene or protein interaction networks to decode the complex interplay between signalling pathways in modulating biological processes. High-coverage networks (that integrate diverse data sets and allow instructive network biology approaches) are now available. These data sets typically include protein-protein interactions, genetic interactions (see figure), co-expression of genes and/or proteins, and informative co-citation of genes and/or proteins in the scientific literature.

What is the added value of combining data integration with network-based analysis in HD target selection?

It is premature to expect that we can model HD at the computational level and predict how HD pathogenesis will develop in a whole organism. However, the current data sets are sufficiently diverse to allow us to identify (1) how conserved pathways and processes might respond to mutant huntingtin expression in models of HD, and conversely (2) how HD-related phenotypes might respond to the manipulation of conserved pathways and processes. Biological networks provide a basis for sensitive and discriminative data integration. In this context, the selection of networks and sub-networks that are highlighted by different models as targets and/or modifiers of mutant huntingtin activity may provide a strong basis to develop neuroprotective strategies relevant to various stages and features of HD.

Is the 'proof-of-concept' available for establishing the potential of network biology for enhancing target discovery?

There are a number of studies, both published and unpublished, that demonstrate that the integration of genome-wide information using biological networks is complementary to hypothesis-driven approaches. Therefore, these approaches provide us with a unique potential for prioritising genes and pathways of importance in modifying the symptoms or progression of HD.

Mobility and falls in people with Huntington's disease

Monica E. Busse et al., J. Neurol. Neurosurg. Psychiatry (2009), 80:88–90

This pilot study assessed the frequency of falls in a small group of HD patients and identified two scales that could be used to recognise individuals at high risk of falling.

Background

Motor disorders in Huntington's disease (HD), particularly chorea, bradykinesia and dystonia, affect posture, balance and gait. These may result in:

- reduced mobility
- decreased functional ability
- increased dependence on others for performance of daily tasks
- decline in quality of life
- increased risk of falls
- higher fracture and mortality risks (e.g. due to head injury).

Although people with HD are at risk of falls, and do fall, fall rate has not yet been investigated in detail.

Study design

The aim of this observational study was to estimate the frequency of falls in people with HD and to make a preliminary assessment of tools appropriate for assessing the risk of falling.

Twenty-four HD patients were assessed using the following scales:

- **Balance:** Berg Balance Scale (BBS; in which lower scores mean worse balance) and Timed "Up & Go" Test (TUG; in which higher scores mean worse performance)
- **Gait:** Walking speed over 10 metres, and monitoring of walking activity for 7 days
- **Motor Performance and Functional Capacity:** Unified Huntington's Disease Rating Scale (UHDRS): Motor, Functional Assessment Scale, Independence Scale and Total Functional Capacity.

Data about stumbles and falls within the last 12 months were collected using a questionnaire.

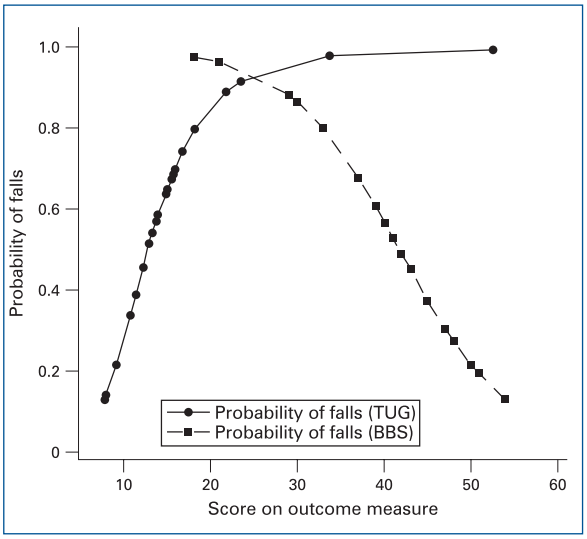
Study participants were divided into two groups, one comprised of recurrent fallers (with ≥ 2 falls/year) and the other comprised of non-fallers (with ≤ 1 fall/year). Use of anti-choreic, hypnotic, sedative or anti-depressive medication was not an exclusion criterion.

Photo kindly provided by Paola Zinzi

HD patient during a gait and balance training (walking on a straight or zigzag line) at the Rehabilitation Home Care "Nova Salus" (Italy).

Results

Ten patients (41.7%) reported ≤ 1 fall and 14 patients (58.3%) ≥ 2 falls in the previous 12 months. Recurrent fallers did not walk as far, and walked more slowly than non-fallers. Their balance was worse and their TUG scores were higher. These differences were statistically significant ($p < 0.01$ in all outcomes). Logistic regression identified the parameters TUG and BBS as significant predictors of falls (see figure below). HD patients had increased risk of falls if TUG scores were ≥ 14 seconds or BBS scores ≤ 40. The median UHDRS motor score was 48.



Reproduced from M. E. Busse et al., J. Neurol. Neurosurg. Psychiatry (2009), 80:88–90, with permission from BMJ Publishing Group Ltd.

The risk of falls increases with increasing TUG scores or decreasing BBS scores.

Conclusion

Recurrent falls are common in HD patients. The BBS and TUG tests seem to be useful tools for assessing the risk of falls and may enable a better management of the risk of falling in HD. However, it should be noted that the TUG test is susceptible to cognitive impairment, and this may limit its applicability in HD.

Summary by Diana Raffelsbauer, PharmaWrite, Giebelstadt (Germany)
June 2009 · Issue 06

Automatic detection of preclinical neurodegeneration

Stefan Klöppel et al., Neurology (2009), 72:426–431

This work, conducted in collaboration with the PREDICT-HD Study Group, assessed the usefulness of a fully automatic image classification method to separate structural MRI brain scans of presymptomatic HD gene mutation carriers from those of controls with different levels of *a priori* information.

Background

Previous studies have shown that neurodegeneration occurs in the presymptomatic phase of Huntington's disease (HD) before clinical diagnosis. HD primarily affects the striatum, causing gross atrophy of the putamen and in particular of the caudate nucleus, which can be detected 15 years before the predicted onset of disease symptoms. It is estimated that, at the time of clinical diagnosis, a striatal atrophy of 50% has already occurred.

Methods

This study applied a method called support vector machine (SVM) to automatically identify presymptomatic HD gene mutation carriers and distinguish them from control subjects. Analysis was performed using the grey matter segment of magnetic resonance imaging (MRI) scans in the absence of, or with different levels of *a priori* information.

SVMs are supervised machine-learning techniques used for classification and regression. From a set of training data, they learn to separate diagnostic groups and apply this knowledge to new data. This method was used to separate different HD diagnostic groups from controls according to their estimated time to clinical disease onset, which was calculated based on current age and CAG repeat length (see table).

Subjects were 96 presymptomatic HD gene carriers (PSCs) recruited from the PREDICT-HD Study. They were stratified into three sub-groups: near, mid and far from disease onset (see below). 95 age- and sex-matched control subjects were also enrolled.

n	Gene status	Probability of disease onset in the next 5 years	Sub-group
32	PSC	> 33%	near
32	PSC	10%–33%	mid
32	PSC	< 10%	far
95	non-carrier	0	control

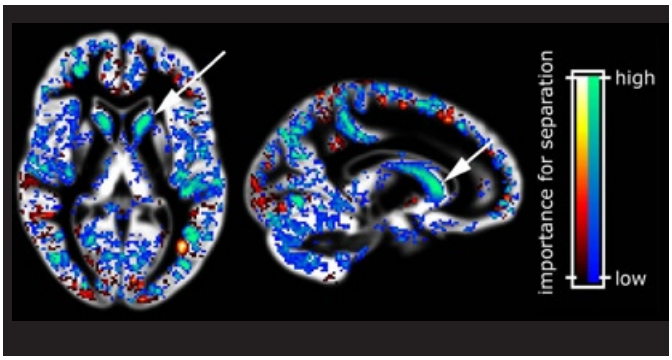


Image kindly provided by Stefan Klöppel

Brain regions most relevant for separating HD gene mutation carriers from controls. Blue to green dots indicate areas of reduced grey matter volume in mutation carriers. The arrows point to the caudate, which is known to be most severely affected in HD. Scattered red to yellow dots show regions where mutation carriers have more grey matter, which most likely reflects noise in the data.

Results

Subjects from the near sub-group were correctly identified as HD gene carriers 69% ($p = 0.002$) of the time. This rate was improved to 83% ($p < 0.001$) by using the weighted voxel-based morphometry procedure. This is similar to preselecting the caudate and putamen. By contrast, subjects far from disease onset were assigned to the PSC group by chance. As shown in the figure (green area), the striatum was critical for the correct separation of mutation carriers from controls, but the insula and parietal cortex were also important.

Conclusion

Disease-modifying treatments for neurodegenerative disorders are likely to be more effective in the early stages of the disease, when drugs may prevent neurodegeneration and brain atrophy. Hence, there is a pressing need for methods that are less labour- and time-intensive than those currently used, and that are capable of screening a large number of subjects and of identifying suitable candidates for clinical trials. Accurate presymptomatic diagnostic tools are crucial in this process. While the availability of a reliable genetic test for HD limits the usefulness of procedures aimed at the separation of gene mutation carriers from non-carriers, techniques such as the one presented here could prove valuable in separating patients with certain symptoms (e.g. rigidity or psychiatric symptoms) from those without. This method may also be useful as a putative state biomarker of disease progression, in addition to motor, cognitive and behavioural scales. Moreover, this strategy may be further developed to identify preclinical phases in other neurodegenerative disorders, such as Alzheimer's disease.

Summary by Diana Raffelsbauer, PharmaWrite, Giebelstadt (Germany)
June 2009 · Issue 06

Intrabodies binding the proline-rich domains of mutant huntingtin increase its turnover and reduce neurotoxicity

Amber L. Southwell et al., J. Neuroscience (2008), 28:9013–9020

This study investigated the consequence of targeting intrabodies to different domains of the huntingtin protein on Huntington's disease pathology.

Background

Huntington's disease (HD) is caused by the expansion of a polyglutamine (polyQ) tract close to the beginning of the huntingtin protein in the part encoded by exon 1 of the HD gene. Although the polyQ tract alone is toxic to neurones, it is thought that the protein context surrounding this tract contributes to the differential neuronal susceptibility between the various polyQ neurodegenerative diseases. For instance, the non-polyQ domains in the HD exon 1 protein (HDx-1) are known to modulate the toxicity of mutant huntingtin, although the mechanisms by which this occurs are not well understood. The structure of HDx-1 is shown in the figure below.

Methods

This work used **intrabodies** to study the function of different domains of mutant HDx-1 (mHDx-1). Intrabodies are intracellular, recombinant, single-chain antibody fragments containing the specific heavy and light antigen-binding domains, connected by a linker, that bind to their target protein.

Two types of intrabodies were used. Their binding sites on HDx-1 (see figure) were:

1. the first 17 amino acids: **V_L12.3**
2. the proline-rich region (PRR):
   2.1. both polyproline (polyP) tracts: **MW7**
   2.2. the proline-rich domain: **Happ1** and **Happ3**.

The effects of the intrabodies were assessed in a cultured cell model and a rodent brain slice model of HD.

Results

The results of different assays performed in this study are summarised in the table below. All four intrabodies reduced aggregation of mHDx-1, levels of insoluble mHDx-1, cytotoxicity and neurodegeneration. However, there were differences between V_L12.3 and the PRR binding intrabodies (MW7, Happ1 and Happ3) as follows:

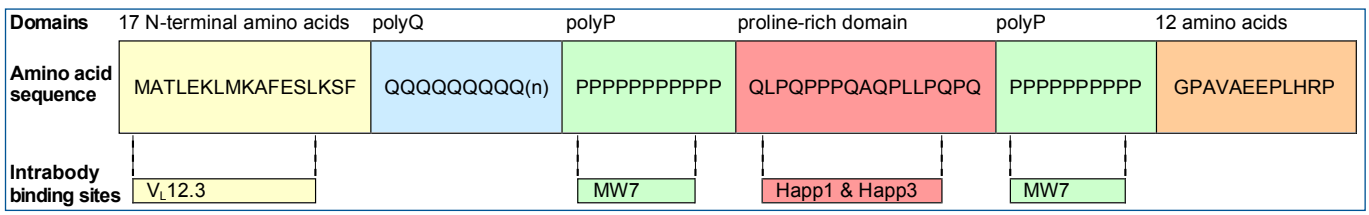
- V_L12.3 increased the amount of mHDx-1 in the cell nucleus, whereas the remaining intrabodies did not alter intracellular protein localisation.
- The PRR binding intrabodies increased mHDx-1 turnover and reduced the levels of soluble mHDx-1, whereas no such effects were observed with V_L12.3.

Effect	V_L12.3	MW7	Happ1	Happ3
Binding site	N-terminus	PolyP tracts	P-rich domain	P-rich domain
Protein aggregation	reduced	reduced	reduced	reduced
Neurotoxicity	reduced	reduced	reduced	reduced
Neuro-degeneration	moderately reduced	slightly reduced	strongly reduced	
Intracellular localisation	increased nuclear mHDx-1	no effect	no effect	no effect
Levels of insoluble mHDx-1	reduced	reduced	reduced	reduced
Levels of soluble mHDx-1	no effect	reduced	reduced	reduced
mHDx-1 turnover	no effect	increased	increased	increased

Effects of intrabody binding on protein aggregation, toxicity, localisation and stability.

Conclusion

Although V_L12.3 and the anti-PRR intrabodies counteract neurotoxicity of mHDx-1 in cell culture and brain slice models of HD, they act by different mechanisms and with different efficacy. Both the anti-polyP (MW7) and anti-P-rich intrabodies (Happ1 and Happ3) reduce aggregation and toxicity by making mHDx-1 less stable and increasing its turnover, reducing the levels of soluble protein and causing a shift away from the aggregated state. On the other hand, the intrabody V_L12.3 seems to reduce neurotoxicity by disrupting cytoplasmic versus nuclear trafficking of mHDx-1. These different mechanisms may offer clues to the specific functions of the intrabody target domains. Understanding how the non-polyQ domains contribute to the toxicity and specificity of mHDx-1 could lead to new therapeutic strategies for HD.



Structure of HDx-1 showing its different domains and the binding sites of the intrabodies.

Upcoming Meetings 2009

Jun 5-7	Huntington's Disease Society of America (HDSA) 24th Annual Convention, Phoenix, AZ, USA http://www.hdsa.org/national-convention/convention.html
Jun 9-14	International Behavioural Neuroscience Society 18th Annual Meeting, Nassau, The Bahamas http://www.ibnshomepage.org/annualmtg09.htm
Jun 7-11	13th Movement Disorder Society (MDS), Paris, France; International Congress of PD and Movement Disorders http://www.movementdisorders.org/congress/congress09/
Jun 20-24	19th European Neurological Society (ENS), Milan, Italy http://www.akm.ch/ens2009/
Jun 22-26	Spanish Society of Neurology (SEN) and Association of British Neurologists (ABN), Liverpool, UK http://www.theabn.org/meetings/annual-meeting.php
Jun 28-Jul 2	9th World Congress of Biological Psychiatry, Paris, France http://www.wfsbp-congress.org/
Jul 11-16	Alzheimer's Association International Conference on Alzheimer's Disease, Vienna, Austria http://www.alz.org/icad/overview.asp
Aug 27-30	1st International Congress on Clinical Neuroepidemiology, Munich, Germany http://www.neuro2009.com/
Aug 31-Sep 2	British Society for Human Genetics Conference, University of Warwick, UK www.bshg.org.uk/2009BSHG.htm
Sep 12-15	4th World Congress on Huntington's Disease, Vancouver, BC, Canada http://www.worldcongress-hd.net
Sep 12-15	13th European Federation of Neurological Societies (EFNS) Congress, Florence, Italy http://efns2009.efns.org/
Sep 12-16	22nd European College of Neuropsychopharmacology (ECNP), Istanbul, Turkey http://www.ecnp.eu/emc.asp?pageId=1196
Sep 23-26	82nd Congress of the German Society for Neurology (DGN), Nuremberg, Germany http://www.akmcongress.com/dgn2009/
Oct 11	23rd Annual Symposium on Etiology, Pathogenesis, and Treatment of Parkinson's Disease and Other Movement Disorders (HSG/PSG/MDS) Baltimore, MD, USA http://www.parkinson-study-group.org/PSG23rdAnnlSymposia.asp
Oct 17-21	Neuroscience 2009 - 39th Annual Meeting of the Society for Neuroscience, Chicago, IL, USA http://www.sfn.org/am2009/
Oct 20-24	American Society of Human Genetics (ASHG), Honolulu, HI, USA http://www.ashg.org/2009meeting/
Oct 24-30	19th World Congress on Neurology, Bangkok, Thailand http://www.wcn2009bangkok.com/
Nov 21	3rd Huntington Disease Clinical Research Symposium (venue to be confirmed) http://www.huntington-study-group.org/NewsEvents/EventsUpcomingMeetings/HuntingtonDiseaseClinicalResearchSymposium/tabid/62/Default.aspx
Dec 3-6	4th International Congress on Brain and Behaviour & 17th Thessaloniki Conference, Thessaloniki, Greece http://www.isbb.gr/
Dec 13-16	XVII World Federation of Neurology Congress on Parkinson's Disease and Related Disorders, Miami Beach, FL, USA http://www2.kenes.com/parkinson/Pages/Home.aspx

Upcoming Meetings 2010

Feb 28-Mar 2	18th EPA European Congress of Psychiatry (EPA 2010), Munich, Germany http://www2.kenes.com/epa/Pages/home.aspx