December 2009 · Issue 08

EHDN News

EUROPEAN **HUNTINGTON'S DISEASE** NETWORK

Nightly News with Jeff Carroll, Charles Sabine and Ed Wild

FEATURE ARTICLE

2009 World Congress on Huntington's disease

By Ed Wild and Jeff Carroll

The 4th World Congress on Huntington's disease (HD) was held in Vancouver from 12-15th September 2009.

Plenary Sessions

After introductory messages from organisers Michael Hayden and Blair Leavitt, the Congress was opened by inspirational talks from HD gene carriers. 13-year-old **Katie DeLargie** bravely described hearing at the age of ten that her father had HD and she was also at risk. **Jamie Fuller**, a dedicated gay rights campaigner, contrasted her public struggle against prejudice with her personal battle with living at risk of HD. **Thoren Young** challenged the scientists in the audience to share family members' sense of urgency and frustration. **BJ Viau**, whose mother has HD, talked about his annual 'Hoop-a-thon' basketball event (hoopathon.com), which has raised over half a million dollars for HD care.

Katie DeLargie

Jamie Fuller

Julio Montaner

A fascinating series of talks focused on what the HD community can learn from other diseases. **Mike Benatar** summarized the state of clinical trials in ALS (a motor neuron disease), arguing for a need to be systematic in our approach to pre-clinical animal trials and to focus on bringing work done in animals to human trials. **Julio Montaner** showed what we can aspire to, by describing the development of effective therapies for AIDS. Scientists took risks by sharing unpublished data, and the community risked participation in clinical trials that resulted in a dramatic improvement in prognosis. >>

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All photos in this article were kindly provided by Austin Hill.

The final session focused on the road to effective therapeutics for HD.

Robert Pacifici

Gill Bates

Lynn Raymond

Robert Pacifici of CHDI Inc. gave an overview of CHDI's operations. CHDI is the biggest funder of HD research and aims to "rapidly discover and develop drugs that delay or slow Huntington's disease" (chdi-inc.org). CHDI is working on prioritizing and testing the approximately 600 "targets" for drugs that have been proposed from lab experiments. Pacifici launched a major new collaborative web-based research effort: hdresearchcrossroads.org. He ended with the exciting goal of moving "one or more" of their drugs into human clinical trials in the next 18 months. **Gill Bates** talked about one promising target, HDAC inhibitors – drugs that aim to keep the DNA hidden from interference by the HD protein. Her team has carefully studied the different HDAC proteins and concluded that HDAC4 is the most promising target for inhibitor drugs. Finally **Sarah Noonberg** (Medivation Inc.) and **Karl Kieburtz** (Pfizer Inc.) gave an update on the HORIZON study (supported by EHDN and the Huntington Study Group) of dimebon (latrepirdine) as a possible treatment for cognitive problems in HD. The study has recruited 350 subjects in 10 countries.

Science sessions

The first science session focused on biomarkers – tests that can tell us how rapidly someone's HD is progressing. Biomarkers will be essential if we hope to test new treatments, especially in HD gene carriers without symptoms. **Ken Evans** of the Ontario Cancer Biomarker Network gave insights and advice from cancer treatment where biomarkers are widely used. **Stefan Klöppel** reviewed progress in brain imaging techniques, highlighting the large PREDICT-HD and TRACK-HD studies. **Ralf Reilmann** gave an encouraging update on clinical biomarkers, like tongue force measurement, as technological ways of measuring subtle clinical changes in HD. Finally **Julie Stout** talked about her 'toolkit' of cognitive biomarkers in HD and reviewed the important cognitive findings from PREDICT-HD and TRACK-HD.

Patrick Weydt, Marcy McDonald, Ali Khoshnan and **Thomas Moeller** addressed a session on inflammatory and metabolic changes in HD, areas of recent interest which are increasingly seen as important in the search for treatments. Khoshnan has found new links between the inflammatory signaling protein IKK and the crucial neuronal growth factor BDNF – both already known to be important in HD.

Lynn Raymond has studied excitotoxicity (the death of neurons due to excessive excitatory neurotransmission) in HD for several years. Her recent work has begun to dissect which parts of the neuron are important for neuronal firing to become overactive and therefore toxic. She presented work done in collaboration with Mahmoud Pouladi from Michael Hayden's lab that suggests that very specific doses of memantine improved symptoms in the YAC HD model mouse. Memantine can slow neuronal firing and is approved in Europe for the treatment of Alzheimer's disease. Efforts are now underway to begin human clinical trials of memantine in HD patients.

Two major categories of work are underway with stem cells. First, some scientists believe that neurons lost in HD might be replaceable using stem cells. Second, many are working on using stem cells from donors with the HD mutation to make accurate cell models of HD. This latter approach is receiving a big push from CHDI, and **Jamshid Arjomand** gave an overview of their efforts. CHDI is creating banks of stem cells that will be available for any interested researcher to use. **Anselme Perrier, Clive Svendsen** and **Elena Cattaneo** spoke about efforts to use stem cells to replace neurons lost in HD. Because neurons generally do not grow during adulthood, this process is difficult, though exciting progress in animal models was shown.

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The huntingtin protein, which is made from the HD gene, interacts with hundreds of other proteins, as it travels around the cell. Many of these other proteins 'tag' huntingtin by adding a small molecule to it. These small molecules can influence where in a cell huntingtin ends up, and what it does when it gets there. **Joan Steffan, Rona Graham** and **Dimitri Krainc** study processes that influence huntingtin by tagging it. Steffan and Graham both described mouse models of HD that have been completely rescued from HD symptoms by changing interactions between huntingtin and other partners. These experiments suggest that interfering with these processes could provide effective treatments for HD.

Late-breaking reports were heard from: **Holly Kordasiewicz** on progress in gene silencing therapies; **Pierre Krystkowiak** on adenosine receptor mutations as delayers of HD onset; **Nellie Georgious-Karistianis** on imaging brain iron content as a possible biomarker; **Simon Brooks**, who presented new ways to assess cognition in HD mouse models; **Juliette Godin**, who has identified a role for the beta catenin protein in HD; and **Alison Lashwood** with an update on the in-vitro fertilisation techniques that enable HD families to have babies born free from the risk of HD.

Care sessions

'Care' sessions ran in parallel to science sessions and provided a wealth of insights and practical advice from family members, carers and health professionals. Among the highlights was **Sandra Kostyk**, who used the video game Dance Dance Revolution to improve walking and balance in HD. **Monica Busse** announced the new EHDN guidelines for physiotherapy in HD. Reporting on juvenile HD, **Oliver Quarrell** said that with an average delay of nine years before diagnosis, many families of juvenile HD feel disbelieved or ignored. **Brynne Stainsby** runs the Young People Affected by HD network (ypahd.ca), which enables young family members to help each other. **Warren Evans** is a motivational speaker who has raised nearly a million dollars in memory of his stepdaughter who died of juvenile HD (laurashope.com). HD mutation-positive researcher **Jeff Carroll** gave a talk describing his personal experiences with HD, finishing with a plea for improved information flow between groups sponsoring HD research and the patient community.

Michael Hayden proposes a toast.

Nightly News

In a first for a World Congress, each day's scientific and care reports were summarized for the entire audience, in understandable language, in the 'Nightly News'. NBC News Correspondent **Charles Sabine** anchored the sessions with reporters **Jeff Carroll** and **Ed Wild** (see front page). Video recordings of the Nightly News sessions, and some other Congress highlights, can be viewed online at www.cmmt.ubc.ca/WCHD2009-News.

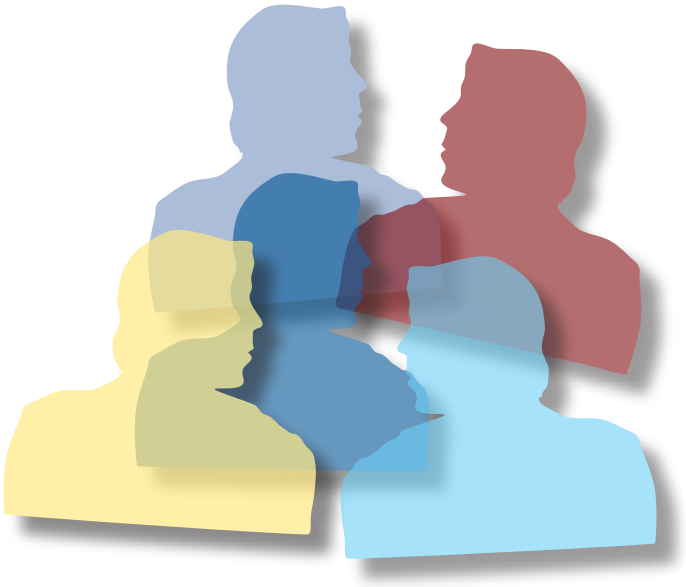
Results of the elections for the EHDN Executive Committee and the EHDN Scientific and Bioethical Advisory Committee

Members of the EHDN Executive Committee (EC) and EHDN Scientific and Bioethical Advisory Committee (SBAC) serve for terms of three years. This year, two members of the EC and three members of the SBAC rotated out of office. In August, the candidates for nomination were presented to the regular membership via the EHDN website and the ballot was open from September 1st to September 15th. Four candidates stood for election to the EC, seven to the SBAC and about 20% of the EHDN Regular Membership took part. **Sheila Simpson**, Aberdeen, UK, and **Jean-Marc Burgunder**, Bern, Switzerland, were elected to the EC and **Ralf Reilmann**, Münster, Germany, **Tiago Fleming Outeiro**, Lisbon, Portugal, and **Raphael M. Bonelli**, Vienna, Austria, were elected to the SBAC.

The EHDN owes a great deal to **Stefano Di Donato** and **Jan Roth** for the many hours that they have devoted to working for the EC. The EHDN thanks all retiring committee members and those who put themselves forward for election and welcomes the successful candidates.The nomination page is now open on the EHDN website to allow members to nominate candidates for next year's election.

REGISTRY

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



REGISTRY's SUB-STUDIES

REGISTRY version 3.0 will include a series of sub-studies that will fall into three main categories: characterisation of specific HD stages (e.g. advanced-stage HD), characterisation of clinical phenotypes (e.g. neuropsychiatric features), and questionnaires and clinical rating scales for HD-specific domains (e.g. quality of life). The aim of the sub-studies is to determine the sensitivity and reliability of established, as well as not-yet-established, assessments of specific and rare clinical phenotypes that are not presently captured in the existing standardised scales.

This article focuses on the 'characterisation of specific HD stages' category. Validating assessment tools for specific HD stages will help to determine whether or not they are useful for clinical and for research purposes. Current standardised assessment tools in REGISTRY provide an overall indication of the frequency and severity of many features of the disease. While these are useful for gauging a general impression of symptoms, they lack adequate detail to distinguish clinical endpoints for use in clinical trials.

One of the sub-studies falling under this category is the Advanced-HD Scale. Lead proposers of this scale are Anne-Catherine Bachoud-Lévi and Katia Youssov (Créteil, France) and Raymund Roos (Leiden, The Netherlands). The standard Unified Huntington's Disease Rating Scale (UHDRS) and other assessments used in REGISTRY do not adequately capture features characteristic of this stage of the disease. For example, the cognitive assessment component of the UHDRS consists of timed psychomotor tasks that cannot be administered to people in more advanced stages of HD due to their motor impairment and dysarthria. Likewise, communication impairments preclude interview-based behavioural assessments, and items requiring active participation are not informative when patients have severe mobility problems. Finally, other aspects, such as control over bodily functions that contribute greatly to the caregiver burden and the medical needs of advanced-stage HD, are not captured in the standard UHDRS assessment. The Advanced-HD Scale has been designed for individuals with a total functional capacity (TFC) ≤ 5. It aims to evaluate both the current clinical status and the rate of decline of individuals in this stage of the disease. The Advanced-HD Scale includes four components: motor (e.g. frequency of falls, capacity to eat), behavioural (based on caregiver, rater, and family observations), cognitive (e.g. orientation, simple commands) and somatic (e.g. sleeping, incontinence). It takes approximately 30 minutes to administer.

A pilot study at French and Dutch sites (manuscript in preparation) shows promising results that suggest that the scale is more sensitive than the standard UHDRS in individuals with advanced-stage HD and has good inter-rater reliability. The sub-study will seek to validate this scale by replicating these results in a larger European HD population. Note that present guidelines state that this scale should be administered in combination with the UHDRS and will not replace it until the validation is complete.

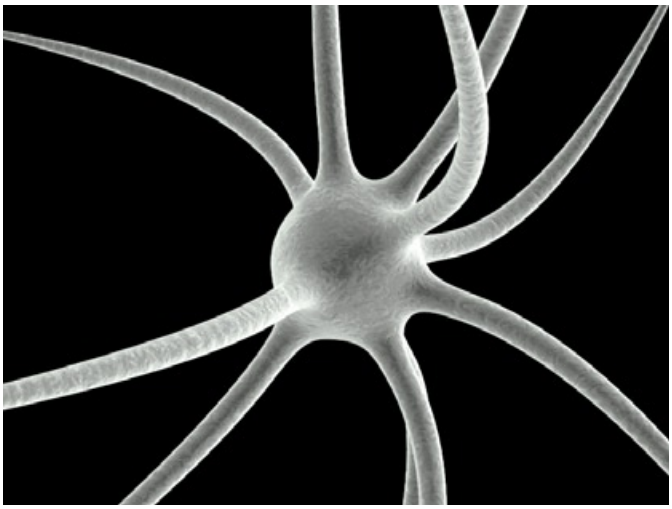
The scale is available in English, French and Dutch. The Advanced-Stage HD Working Group will host a training session for potential raters at a working group meeting in Leiden, The Netherlands (date to be confirmed). For further information, please contact the Sub-Study Development Officer, Marleen van Walsem (marleen.walsem@euro-hd.net).

Neuroprotective Therapy Working Group

By Joaquim Ferreira (Lisbon, Portugal) and
Ralf Reilmann (Münster, Germany)

The concept of neuroprotection

Current therapies for Huntington disease (HD) provide only partial control of some of the distressing symptoms of the disease (e.g. chorea, psychosis and depression). These treatments are described as 'symptomatic', meaning that they only ameliorate the clinical features of the illness. The benefits are temporary and disappear when the treatment is stopped. Unfortunately, there are no therapies available at present that can slow or halt disease progression.



The ultimate goal of EHDN is to facilitate the development of therapeutic strategies to prevent, slow or stop the onset and progression of HD. Treatments that postpone or slow the progression of a neurodegenerative disease are known as 'neuroprotective'. However, this concept is controversial and restrictive, because it describes a mechanism of action rather than the consequence of an intervention. A broader term that is widely accepted by the scientific community is 'disease-modifying'. When applied to HD, the 'disease-modifying' concept may describe an intervention that favourably interferes with the genetic aetiology or neuronal pathogenesis and forestalls the disease onset (in pre-symptomatic gene carriers) or slows functional decline (in manifest HD patients). Potential disease-modifying agents have been identified through basic research and are currently under investigation in pre-clinical trials. Thus, this is a crucial time for defining the best methodology for clinical trials that will allow us to target a disease-modifying effect.

Aims

1. To improve knowledge of how to select pharmacological agents to be entered at different stages of clinical development
2. To improve knowledge of how to design and conduct clinical trials to demonstrate a disease-modifying effect in HD and make recommendations for future trial designs
3. To stimulate and facilitate the design, execution and analysis of disease-modifying trials in HD
4. To make information available to scientists and the general public
5. To stimulate collaboration with partners in research and the pharmaceutical industry.

Activities

Under the auspices of the EHDN, the Neuroprotective Therapy WG organised a task force to elaborate a comprehensive review of methodological aspects relevant for the design of trials of potential disease-modifying treatments. The first meeting took place in Lisbon on the 9th and 10th of October 2009. The main topics were the concept of disease-modifying treatments in HD, target population, study design, study duration, proposed statistical analysis, meaningful outcomes, biomarkers and surrogate endpoints. All EHDN working groups active in fields relevant for this discussion (Behavioural Phenotype, Biomarkers, Motor Phenotype, Cognitive Phenotype, Imaging and Functional Ability) were invited to actively participate through their lead facilitators. The working groups agreed that only the most robust scientific data available should be applied to the design of disease-modifying trials in HD. The final recommendation will result from a consensus between the task-force members and will be presented to partners in research and the pharmaceutical industry. We shall also model the different rates of disease progression of clinical relevant outcomes for disease-modifying trials at different stages of disease based on prospective REGISTRY follow-up data.

For more information, please contact Joaquim Ferreira (joaquimjferreira@net.sapo.pt) or
Ralf Reilmann (r.reilmann@uni-muenster.de).

Behavioural Phenotype Working Group

David Craufurd (Manchester, UK), Matthias Dose (Taufkirchen, Germany) and Marlene van Walsem (Oslo, Norway)

Behavioural problems such as depression, anxiety, irritability and apathy are common in Huntington's disease (HD) and often cause more distress to patients and their families than the movement and cognitive changes. Behavioural symptoms are also important in this context because they respond to treatments that are currently available.

Aims

The primary aim of the Behavioural Phenotype WG is to develop and validate suitable assessment tools. This is important because most existing psychiatric measures were developed for use in other populations and may not be reliable or valid when administered to someone with a progressive neurodegenerative disorder. We also aim to investigate the behavioural phenotype and to promote better symptomatic treatments.

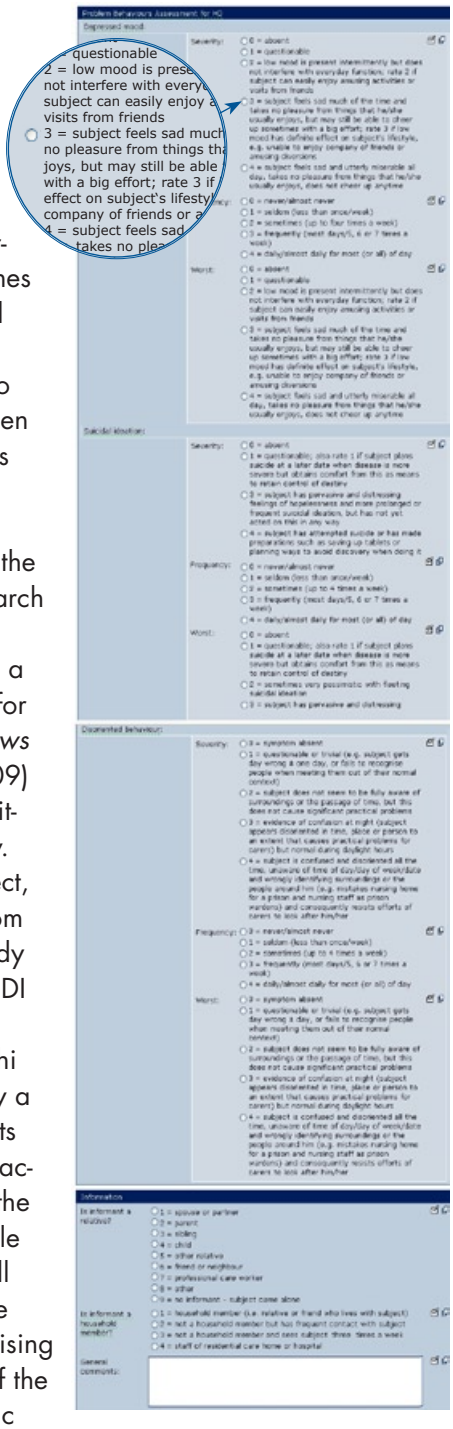
Projects

Our first project was to improve the Unified Huntington's Disease Rating Scale (UHDRS) behavioural assessment. The new short version of the Problem Behaviours Assessment interview (the PBA-s) has similar items to the UHDRS, but uses more explicit scoring criteria from the original PBA for HD to improve reliability and ease of use. We have also introduced better training for raters. In TRACK-HD, the PBA-s showed very good inter-rater reliability in the three languages used in the study (Dutch, English and French). Translation into other languages is now well advanced, and all sites in REGISTRY version 3 will switch to the PBA-s once their behavioural rater has been trained. Certification for raters will be based on correctly scoring three recorded interviews, as is currently required for motor raters, but from 2011 we shall also ask behavioural raters to upload one of their own interviews for re-scoring.

We are working on self-report measures. Hugh Rickards and Jenny Keylock (Birmingham, UK) compared the Beck Depression Inventory (BDI / BDI-II) and Hospital Anxiety and Depression Scale (HADS) in HD patients against a 'gold standard' interview measure of depressive illness. The HADS performed better than the BDI/BDI-II and will be the recommended self-report measure of affective symptoms in REGISTRY v.3. Measures of irritability and apathy are under development.

Symptomatic treatment

The published evidence base for symptomatic treatments for HD is negligible, and surveys of the medicines that are prescribed show great variation from country to country and between specialties. There is an urgent need for more research. In collaboration with the Symptomatic Research and Therapy WG, we have proposed a trial of bupropion for apathy (EHDN *News* Issue 06, June 2009) that will start recruiting subjects shortly. Another joint project, with colleagues from the Huntington Study Group and the CHDI Foundation, is using a formal 'Delphi process*' to survey a panel of HD experts about their own practice and views on the efficacy of available treatments. This will be used to produce guidelines summarising the current 'state of the art' for symptomatic treatment of behavioural problems in HD.



Online form 'Problem Behaviours Assessment for HD'

Membership

We have about 30 active members (80 in total) and usually meet twice a year, at the EHDN plenary meeting and in March. If you are interested, please contact David Craufurd (david.craufurd@manchester.ac.uk), Matthias Dose (m.dose@iak-kt.de) or Marleen van Walsem (marleen.walsem@rikshospitalet.no).

*The Delphi Method is based on a structured process for collecting and distilling knowledge from a group of experts by means of a series of questionnaires interspersed with controlled opinion feedback.

Summary by Diana Raffelsbauer, PharmaWrite, Giebelstadt (Germany)
December 2009 · Issue 08

Normal and mutant *HTT* interact to affect clinical severity and progression in Huntington disease

N. Ahmad Aziz et al., Neurology (2009), 73: 1280-1285

The normal allele of the HD gene (*HTT*) may be involved in HD pathogenesis.

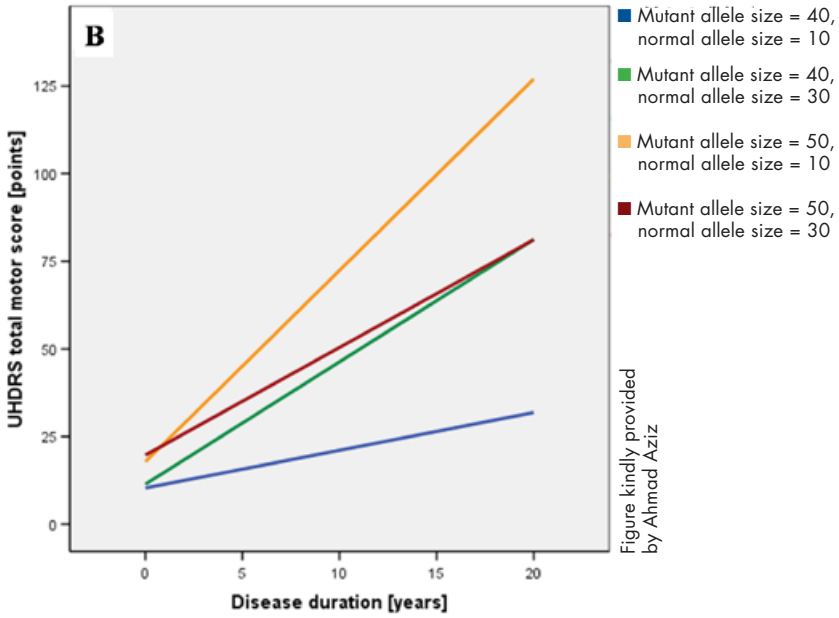
Background

Besides determining the age of onset of Huntington's disease (HD), the length of the mutant CAG repeat has been reported to correlate directly with the rate of disease progression. An interaction between mutant and normal *HTT* alleles has also been described to modulate disease onset. The present study examined whether this interaction influences age of onset, disease severity and progression in manifest HD patients, as well as brain pathology in premanifest HD mutation carriers.

Subjects and methods

The study population consisted of 921 HD patients enrolled in REGISTRY with data on age of onset and CAG repeat length for both alleles. Assessment of clinical severity and disease progression was performed in 512 patients based on UHDRS[1] data (motor, cognitive, behavioural and total functional capacity scales) and body weight from two or more annual visits. Basal ganglia volumes from magnetic resonance images were determined in 16 premanifest HD mutation carriers from the Leiden University Medical Center.

The influence of mutant and normal CAG repeat size interaction on age of onset in manifest subjects and on brain pathology (as assessed by magnetic resonance imaging) in premanifest subjects was analysed using multiple linear regression with the age of onset or basal ganglia volumes, respectively, as dependent variables. The mutant and normal CAG repeat sizes and their interaction were the independent variables. The effect of this interaction on disease progression was examined using linear mixed-effects models with the clinical scores as dependent variables, and disease duration, the sizes of both alleles as well as their interaction as independent variables.



Interaction between mutant and normal CAG repeat sizes on progression of motor symptoms in HD

Results

The interaction between mutant and normal *HTT* alleles significantly affected age of onset ($p = 0.001$). The higher the number of CAGs in the normal repeat, the weaker the influence of the mutant CAG repeat size on age of onset. The interaction between both alleles also correlated with motor, cognitive and functional decline (all $p < 0.05$), but not with the severity of behavioural symptoms or body mass index. Similarly, the higher the number of CAGs in the normal allele, the weaker the effect of the mutant allele on disease progression (shown in the figure for total motor scores). For subjects with mutant CAG expansions in the low range, increasing the size of the normal repeat correlated with more severe symptoms and faster disease progression, whereas for those subjects with mutant expansions in the high range, increasing size of the normal repeat correlated with less severe symptoms. In premanifest subjects, the interaction effect was significantly associated with the putamen and total basal ganglia volumes (both $p < 0.05$).

Conclusions

Increasing the CAG repeat size of the normal *HTT* allele decreases the influence of the mutant allele on disease onset, severity and progression. The underlying mechanism may involve a competitive interaction between the polyglutamine domains of mutant and normal huntingtin mutually or with other proteins, mitochondrial function, gene transcription or protein aggregation. The precise pathways remain to be elucidated.

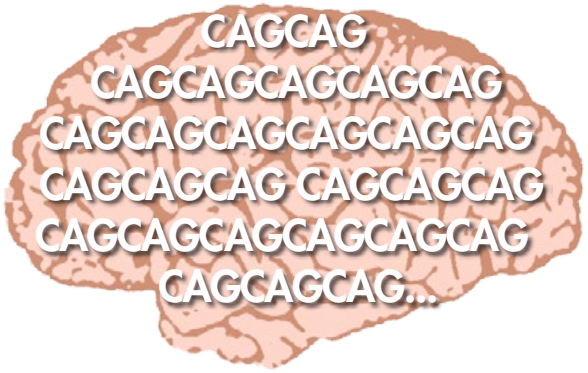
[1] Unified Huntington's Disease Rating Scale

Summary by Diana Raffelsbauer, PharmaWrite, Giebelstadt (Germany)
December 2009 · Issue 08

Somatic expansion of the Huntington's disease CAG repeat in the brain is associated with an earlier age of disease onset

Meera Swami et al., Human Molecular Genetics (2009), 18: 3039-3047

This study examined the relationship between the length of the CAG repeat within the *HTT* gene in the cerebral cortex of HD patients *post mortem* and age of disease onset. Somatic instability of the repeat correlated with age of onset, with larger repeat expansions seen in earlier onset cases.



Background

There is a negative correlation between CAG repeat length and the age of onset for Huntington's disease (HD). However, the CAG repeat length accounts for only 50-70% of the variability in age of onset, which is also influenced by additional genetic and environmental factors.

Previous studies have shown that, in HD, the expanded CAG repeat is somatically unstable. That is, the repeat length changes size in body cells over time, with a propensity to increase. This instability is tissue-specific and pronounced in striatum and cortex, brain regions most affected in HD. The authors of this paper asked whether somatic instability of the CAG repeat in brain contributes to HD pathogenesis as a modifier of age of onset.

Subjects and methods

CAG somatic instability was studied in the brains of 48 individuals affected by HD whose age of disease onset deviated the most from that predicted by the lengths of their constitutive mutant *HTT* CAG repeat, thus representing extremely young and extremely old onset cases (24 subjects each). CAG repeat length was quantified by small-pool PCR amplification of genomic DNA isolated from frontal cortex. Constitutive *HTT* CAG repeat lengths were determined from cerebellar DNA, in which they are somatically stable.

Results

The mutant *HTT* CAG repeat showed various degrees of somatic instability in cortical samples from all 48 individuals. In most cases, this instability took the form of repeat length expansion (see table).

Frequency of mutant *HTT* CAG repeat length changes in cortex of 48 HD patients

Event	Change in CAG numbers	Frequency
Reduction	< 0	14.6%
No change	0	34.6%
Expansion	≥ 1	50.8%
	≥ 5	22.1%
	≥ 10	11.1%
	≥ 20	5.23%
	≥ 40	0.38%

Adapted from Table 2 of the original publication

There were no differences between the extreme young and extreme old groups in the mean expansion size, total expansion frequency or expansion frequency of ≥ 10 CAG repeats. However, there was a marked difference in the magnitude of the average maximum expansion for each group (extreme young: mean 42 CAGs, range 24-68 CAGs; extreme old: mean 29 CAGs, range 12-44 CAGs). Statistical analysis confirmed that larger somatic expansions were significantly associated with earlier disease onset, independent of any effects of constitutive CAG repeat length on either somatic instability or onset age.

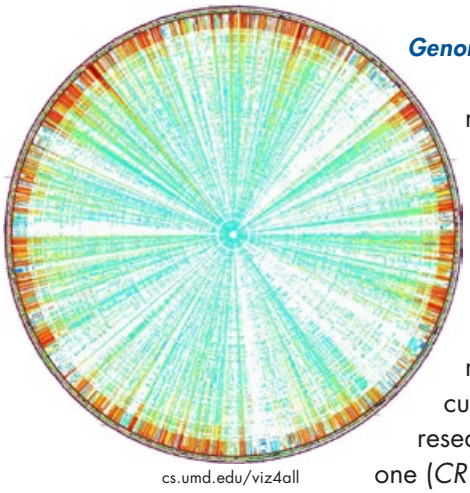
Conclusions

Somatic CAG repeat instability may be a modifier of HD pathogenesis, beyond the role of the constitutional CAG repeat length. Therefore, factors that determine somatic instability in HD patients may modify disease pathogenesis, and conversely, disease modifiers may also influence somatic instability. Genes that are predicted to alter somatic instability could be investigated as potential age of onset modifiers in association studies.

Summary by Diana Raffelsbauer, PharmaWrite, Giebelstadt (Germany) December 2009 · Issue 08

Genome-wide association study identifies variants at *CLU* and *PICALM* associated with Alzheimer's disease

Denise Harold et al., Nature Genetics (2009), 41: 1088-1093



cs.umd.edu/viz4all

Genome diagram

Genome-wide association study identifies variants at *CLU* and *CR1* associated with Alzheimer's disease

Jean-Charles Lambert et al., Nature Genetics (2009), 41: 1094-1099

Milestone in dementia research: three new genetic risk factors for developing Alzheimer's disease identified in genome-wide association studies.

Background

Alzheimer's disease (AD) is the most common form of dementia in the elderly, characterised by the deposition of amyloid plaques and neurofibrillary tangles in the brain. The genetic basis of AD susceptibility is complex. Three genes have been found that, when mutated, cause the rare familial early-onset form of the disease. These are amyloid precursor protein, presenilin 1 and presenilin 2. The gene encoding apolipoprotein E (*APOE*) has been identified as a risk factor for the more common late-onset form of AD and was the only modifier gene known for this form. The identification of additional modifier genes for AD has been limited by small sample sizes and the inability to replicate initial findings. More powerful genome-wide association studies (GWAS) are required to identify genetic risk factors that have modest effect sizes.

Subjects and results

Harold et al. (Cardiff University, UK) performed a GWAS involving a consortium of 80 researchers at 11 institutions in Europe and the US. They included 4,000 AD cases and 8,000 control subjects in the first analysis. These were genotyped with DNA chips containing 530,000 single nucleotide polymorphisms (SNPs). The best hits from this round were checked in a separate replication set of 2,000 AD cases and 2,300 controls. Besides *APOE*, the study detected two genes significantly associated with AD: *CLU*, that encodes clusterin (also called apolipoprotein J), and *PICALM*, that encodes the phosphatidylinositol-binding clathrin assembly protein. Just below the cut-off for genome-wide significance, the researchers also spotted 13 SNPs, of which one (*CR1*) encodes complement receptor 1.

The second GWAS by Lambert et al. was a European study led by INSERM, the Pasteur Institute and the University of Lille (France). They used 2,000 AD cases and 5,300 controls in the 'discovery set', whilst the replication set included 4,000 AD cases and 3,300 control samples from 15 centres in Europe. Using a DNA chip with 540,000 SNPs, this study also revealed *CLU* and *CR1* as genetic risk factors for AD.

Conclusions

These studies have identified three new genes as risk factors for developing AD. CLU is a multifunctional chaperone implicated in the regulation of ß amyloid aggregation, deposition and clearance that can also suppress complement activation. PICALM is involved in clathrin-mediated endocytosis, an essential step in the intracellular trafficking of proteins and lipids, such as nutrients, growth factors and neurotransmitters. CR1 is a complement receptor and its identification, together with CLU, provides further evidence that inflammation and the innate immune response play a primary role in AD and other neurodegenerative diseases.

Implications for HD research

These studies confirm that GWAS is a powerful tool for identifying genes that act as disease risk factors and underline the importance of large sample sizes. Interestingly, increased levels of clusterin have been found in plasma and cerebrospinal fluid samples of Huntington's disease (HD) patients (Dalrymple et al., J. Prot. Res. 2007, 6: 2833-40). The blood samples that are collected as part of REGISTRY will provide DNA for an HD GWAS that is being funded by the CHDI Foundation and coordinated through the Genetic Modifiers Working Group in collaboration with our colleagues in the US. Between 2,000 and 3,000 samples from Europe will be genotyped in the first part of the study.

Upcoming Meetings 2009/2010

Dec 3-6	4th International Congress on Brain and Behaviour & 17th Thessaloniki Conference of the South-East European Society for Neurology & Psychiatry, Thessaloniki, Greece http://www.isbb.gr/
Dec 10	Meeting of the EHDN Surgical Approaches Working Group/Subgroup Deep Brain Stimulation, Amsterdam, The Netherlands http://www.euro-hd.net/html/network/groups/surgicalapproaches
Dec 10-11	Meeting of the EHDN Standard of Care Working Group/Subgroup Occupational Therapy, Edinburgh, UK http://www.euro-hd.net/html/network/groups/care
Dec 13-16	XVIII World Federation of Neurology Congress on Parkinson's Disease and Related Disorders, Miami, FL, USA http://www2.kenes.com/parkinson/Pages/Home.aspx

	2010
Jan 14-19	Keystone symposia on Molecular and Cellular Biology, RNA Silencing: Mechanism, Biology and Application, Keystone, CO, USA http://www.keystonesymposia.org/Meetings/ViewMeetings.cfm?MeetingID=1062
Feb 8-11	5th Annual CHDI Huntington's Disease Therapeutics Conference, Palm Springs, USA http://campaign.constantcontact.com/...
Feb 27-Mar 2	18th European Congress of Psychiatry of the European Psychiatric Association, Munich, Germany http://www2.kenes.com/epa/Pages/home.aspx
Mar 06-10	41st Annual Meeting of the American Society for Neurochemistry, Santa Fe, NM, USA http://asneurochem.org/2010Meeting/ASN2010.htm
Mar 10-13	25th International Conference of Alzheimer's Disease, Thessaloniki, Greece http://www.adi2010.org/default.aspx
Apr 10-17	2010 Annual Meeting of the American Academy of Neurology, Toronto, Canada http://www.aan.com/go/am10
May 15	Parkinson Study Group/Huntington Study Group Symposium, Irving, TX, USA http://www.huntington-study-group.org/NewsEvents/EventsUpcomingMeetings/PS-GHSGSymposium/tabid/89/Default.aspx
May 17-21	Australian and New Zealand Association of Neurologists, Annual Scientific Meeting, Melbourne, Australia http://www.anzan2010.com/
June 13-17	14th International Congress of Parkinson's Disease and Movement Disorders, Buenos Aires, Argentina http://www.movementdisorders.org/congress/congress10/
Jun 19-23	20th Meeting of the European Neurological Society, Berlin, Germany http://www.congrex.ch/ens2010/
June 25-27	National Convention of the Huntington's Disease Society of America, Raleigh, NC, USA http://www.hdsa.org/events/index.html?month=6&year=2010
Aug 28-Sept 1	23rd Congress of the European College of Neuropsychopharmacology, Amsterdam, The Netherlands http://www.ecnp.eu/emc.asp?pageId=1516
Sept 3-5	6th Bi-Annual Plenary Meeting of the European Huntington's Disease Network, Prague, Czech Republic https://www.euro-hd.net/html/ehdn2010
Sept 5-6	13th Bi-Annual Meeting of the European Huntington Association, Prague, Czech Republic
Sept 25-28	14th Congress of the European Federation of Neurological Societies, Geneva, Switzerland http://efns2010.efns.org/
Oct 23-24	Convention of the German Huntington Help, 40th Anniversary of the German Huntington Self-support Group, Duderstadt, Germany
Nov 13-17	40th Annual Meeting of the Society for Neuroscience, San Diego, CA, USA http://www.sfn.org/am2010/