September 2009 · Issue 07

EHDN News

EUROPEAN HUNTINGTON'S DISEASE NETWORK

Anne Rosser and Stephen Dunnett

CONTENT Click the Page

www.euro-hd.net

FEATURE ARTICLE

The UK Dementias and Neurodegenerative Diseases Research Network (DeNDRoN)

By Anne Rosser and Stephen Dunnett, Cardiff University, Cardiff (UK)

The Dementias and Neurodegenerative Diseases Research Network (DeNDRoN) is a UK initiative designed to improve the speed and quality of clinical research in dementias and neurodegenerative conditions, in particular in Huntington's disease (HD), Parkinson's disease and motor neurone diseases. The overall aim of DeNDRoN is to improve the prevention, diagnosis and treatment of these diseases, and to enable better patient care.

The background to DeNDRoN

In the UK, most healthcare is delivered through the National Health Service (NHS), which over the last 60 years has provided healthcare that is free at the point of delivery and is funded through national taxes. While the system is government-funded, NHS services in England, Northern Ireland, Scotland and Wales are managed separately, although they remain largely similar in their operation. The UK government has long supported research within the NHS and, in order to improve the infrastructure for the delivery of clinical trials, there has been a reorganisation of the way in which this support is delivered. In 2005, the Clinical Research Network (CRN) was established; it now operates under the umbrella of the National Institute for Health Research (NIHR). The CRN supports six topic-specific research networks: DeNDRoN; Medicines for Children; Stroke; Cancer; Diabetes and Mental Health. In addition there is a Comprehensive CRN for other diseases and a Primary Care Research Network. Their general aims are 1) to streamline the support for clinical studies; 2) to help to remove barriers to research within the NHS; 3) to facilitate sharing of resources and methodology; and 4) to strengthen collaboration with industry. >>

Subscribe here to the EHDN Newsletter:
Please go to the URL below and fill out the online form:
http://www.euro-hd.net/html/network/communication/newsletter
Please send us your comments, suggestions and overall feedback:
newsletter@euro-hd.net

Imprint: Editorial Board of the EHDN Newsletter: Prof. Gillian Bates (King's College London School of Medicine, London, UK), Prof. 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).

By Anne Rosser and Stephen Dunnett, Cardiff University, Cardiff (UK)
September 2009 · Issue 07

What is DeNDRoN?

DeNDRoN was established in September 2005. It encourages sharing of resources and methodological expertise between people working on a wide range of disabling long-term neurodegenerative disorders that share common factors. Its core aim is to facilitate high-quality clinical studies for prevention, diagnosis and treatment of these diseases. As well as building on the strengths already present in the UK, it is increasing general capacity in the field of dementia and neurodegeneration. DeNDRoN is coordinated by a consortium from Newcastle University and University College London with a Coordinating Centre that oversees the development and performance management of the seven local research networks. Together these networks cover approximately 70% of England. There is an equivalent network covering Wales and a dementia network in Scotland.

How does DeNDRoN facilitate clinical research?

DeNDRoN aims to support research in a number of practical ways, for example, by encouraging patient and carer engagement, supporting training, and helping to tackle barriers to research by facilitating interactions with NHS research and development offices. DeNDRoN also facilitates interactions with industry, and helps researchers to secure sessions within NHS clinics that they can dedicate to research. A major shared resource is the bank of DeNDRoN study nurses, who are employed by the local research networks and can be 'hired' on a per session basis by research centres engaged in adopted DeNDRoN studies. (Note that any study that has approved peer-reviewed funding, along with commercial studies, can be put up for 'adoption' by the network.) The major value of the CRN approach is that it provides a system whereby assistance (e.g., for patient recruitment) can be hired rapidly and at an appropriate level, as required, thereby avoiding the need to raise funding for individual posts for each project. It also avoids all the associated cost and regulatory issues that go along with establishing new posts. The UK HD network is part of DeNDRoN. With a flexible approach on the part of both the DeNDRoN team and EHDN, this partnership has flourished and provides added value to HD research within the UK. The EHDN initiatives REGISTRY (see page 5 of this issue) and BioRep, amongst others, are studies that have been adopted by DeNDRoN and benefit considerably from the partnership and this additional route of support.

Further information on DeNDRoN is available at www.dendron.org.uk.

DeNDRoN
Dementias & Neurodegenerative Diseases Research Network

How do I contact the network?

If you are a principal investigator working on HD in the UK and you wish to make contact with the network for the first time, you can do this through the Associate Director for HD or directly to the DeNDRoN Co-ordinating Centre (contact details available at www.dendron.org.uk).

How are studies adopted?

Applications for adoption of clinical studies are made directly to DeNDRoN. Studies can be multicentre or single-site, but must be funded by a recognised funding agency. Further advice on study adoption can be obtained from Kris Beicher (kris.beicher@dendron.org.uk).

Elections for the EHDN Executive Committee and the EHDN Scientific and Bioethical Advisory Committee

In 2009, two members of the EHDN Executive Committee, Jan Roth (Czech Republic) and Stefano Di Donato (Italy), will rotate out of office. Four candidates were nominated for these positions: Danuta Ryglewicz (Poland), Sheila Simpson (UK), Alberto Albanese (Italy) and Jean-Marc Burgunder (Switzerland).

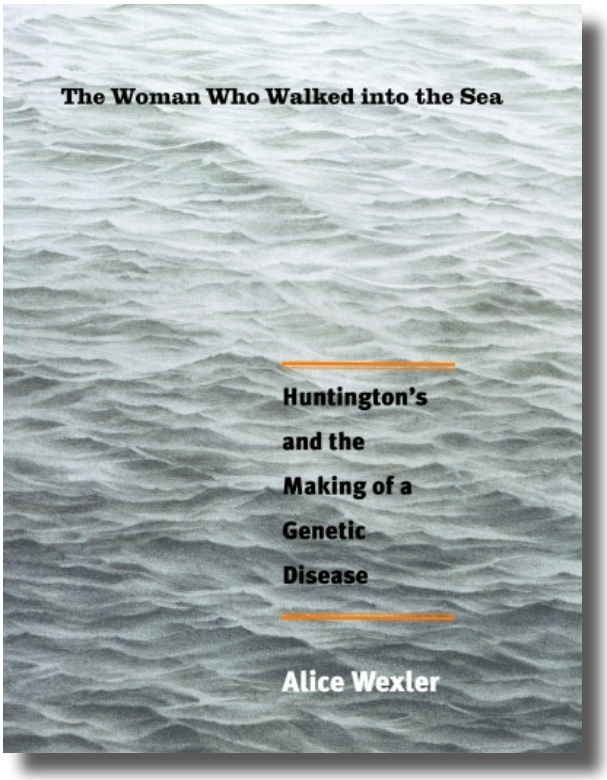
Seven candidates are competing for three positions in the EHDN Scientific and Bioethical Advisory Committee: Raphael Bonelli (Austria), Jean-Marc Burgunder (Switzerland), Tiago Outeiro (Portugal), Paolo Paganetti (Switzerland), Josef Priller (Germany), Ralf Reilmann (Germany) and Ferdinando Squitieri (Italy).

For more details and to cast your votes, please visit https://www.euro-hd.net/html/network/project/voting/vote/001,1/survey_voting09.

The roots of HD's stigma

Huntington's disease (HD) carries a huge stigma. Many families with HD cover it up, and many face discrimination because of it. Surrounded by fear and ignorance, in many ways Huntington's is stuck in the Dark Ages.

For the first time, a new book explores the roots of HD's stigma. Written by historian Alice Wexler, it is titled ***The Woman Who Walked into the Sea: Huntington's and the Making of a Genetic Disease*** (Yale University Press, 2008).



Many will recall Alice as the author of *Mapping Fate: A Memoir of Family, Risk, and Genetic Research* (1995), in which she chronicled her mother's demise because of HD and her dynamic family's quest for a cure. Starting in the late 1960s, her father, the late Milton Wexler, became a national champion of HD research, and her sister Nancy Wexler, a top scientist, helped pioneer the Genome Project and the discovery of the HD gene in 1993.

In *The Woman Who Walked into the Sea*, Alice explores how Americans over the past two centuries dealt with and interpreted HD. Although people in the early 1800s did not know what caused St. Vitus's dance – as HD was then known – they often understood that it ran in families. Some people from families associated with the illness faced prejudice, but others were accepted and even respected. In certain communities, contrary to popular images of the disease, a number of individuals from families associated with St. Vitus's dance achieved local prominence, as Alice explains.

However, today's HD-affected families also will be all too familiar with the portraits and struggles depicted. For example, on a summer night in 1806, Phebe Hedges, a 40-year-old woman from East Hampton, New York, walked into the sea in an act of suicide. Thus instead of following the standard line about heroic researchers, Alice spends much of the book focusing on the challenges faced by the families.

As a result, in this reviewer's opinion, the American physician Dr. George Huntington (1850-1916) appears in the book as a very ambiguous figure. On the one hand, he was the first scientific observer to note that HD involved what would eventually be called "dominant inheritance" – in other words, that once the disease failed to appear in an individual, none of his or her descendants would be affected and the disease disappeared in that branch of a family. After the publication of Dr. Huntington's findings in 1872, the symptoms he described became known as Huntington's chorea – "chorea", of course, meaning the shaking produced by the disease. "Chorea" later gave way to the word "disease" when it became clear that HD also involved cognitive and other problems.

On the other hand, Dr. Huntington used the concept of "insanity" to describe the depression and difficulties in judgment resulting from HD. That emphasis, Alice asserts, "introduced a term with powerful negative associations" and "may have heightened social fears surrounding the disease". Scientists classified HD as a degenerative disease, reflecting not only its neurological reality but beliefs in social Darwinism, survival of the fittest, and the concept of a superior race.

Despite the importance of his discovery, Dr. Huntington showed no interest in carrying out further research, but *The Woman Who Walked into the Sea* teaches us that, in the late 1800s and early 1900s, many other scientists were involved in discussions about HD, both positive and negative. Understanding the disease was a collective, international effort.

Gene Veritas is gene-positive for Huntington's disease and blogs at www.curehd.blogspot.com.

As the field of medicine modernized in the late 1800s and created the new specialty of neurology, HD was transformed from a "medical curiosity" into an "interesting disease". Because of HD's genetic cause and consistent symptoms, many neurologists came to see it as the "neurological disorder par excellence". Research on HD broke new ground in the history of medicine. It helped to show that Gregor Mendel's newly discovered laws of genetics applied to humans as well as plants and animals. And at a time when it was widely believed that parents could transmit a "weakness" or generalized tendency to illness that could degenerate into any number of diseases, it offered an example of similar inheritance over multiple generations. It also now became clear that a hereditary illness could disappear in one generation and not reappear.

However, exaggerated ideas about scientific progress and "survival of the fittest" helped to foster extreme measures against people with disabilities. Long before Nazi Germany, the United States embraced eugenics, the idea that society should improve its genetic stock by preventing the so-called unfit from having children. In 1907, Indiana passed the first legislation legalizing sterilization of inmates in public institutions. Over the next three decades, the U.S. produced the harshest eugenics laws in the world outside those implemented by the Nazis.

Families with HD were among those who bore the brunt of eugenics. Alice describes the work of Dr. Elizabeth Muncey, an Eugenics Record Office researcher who in 1913 compiled information on more than 4,000 people, past and present, who were allegedly linked to HD. "Muncey was doing science, but also surveillance", Alice writes. "She was scrutinizing certain families, diagnosing and labeling them, and in this manner, setting them apart from their neighbors."

Charles Davenport, a scientist who worked with Muncey and analyzed her data, concluded that "it would be a work of far-seeing philanthropy to sterilize all those in which chronic chorea has already developed". It was the government's job "to investigate every case of Huntington's chorea that appears and to concern itself with all of the progeny of such". A government that failed to prevent the spread of Huntington's was "impotent, stupid" and invited "disaster". And immigrants with Huntington's should not be allowed into the country. Davenport called for developing a predictive test for HD for eugenic purposes.

In the 1930s the Nazis may have forcibly sterilized as many as 3,500 people affected by HD. Tens of thousands of Americans were also involuntarily sterilized between the 1920s and 1960s, some of them perhaps affected by Huntington's. Alice illustrates how the scientific theories of the early 1900s, although eventually rejected, endured in our culture as beliefs held by everyday people. This deepened the stigma of HD. For decades, doctors continued to recommend against marriage for families affected by HD. Sadly, although some doctors sought ways to alleviate the suffering associated with this disease, many others in the scientific and medical communities advocated control of the families.

Alice Wexler has won the 2009 American Medical Writers Association Medical Book Award in the Healthcare Professionals (non-physicians) category for her book.

Fears about HD reached a crescendo in the 1930s and 1940s. New theories emerged, claiming that the original sufferers of the disease had been accused of witchcraft and had even played a part in the famous Salem witch trials of 1692. Both respected scientific journals and the popular magazine *Literary Digest* published articles on the alleged witchcraft connection; the *Digest* referred to HD as "the witchcraft disease". Not until 1969 did others debunk these "historical fictions", as Alice calls them, adding that one perpetrator still clung to them as recently as the 1980s.

The long history of prejudice and misunderstanding about HD reconstructed in *The Woman Who Walked into the Sea* will make you indignant, no matter what your relationship to HD. Alice's book provides important information for scientists, activists, and families involved in the search for treatments and better care for people with neurological diseases. She shows us that disease is not just a question of science and medicine, but also of history and the cultural codes by which we all live.

The Woman Who Walked into the Sea by Alice Wexler
Order the book online (cloth: $30, paper: $20):
http://yalepress.yale.edu/yupbooks/book.asp?isbn=9780300105025

REGISTRY version 3.0

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

REGISTRY version 3.0 is due to be released later this year. The purpose and overall concept of REGISTRY v.3.0 is unchanged from that of REGISTRY v.2.0, with both sharing the same major goals and objectives. The main difference between the two versions is the addition of REGISTRY sub-studies into REGISTRY v.3.0. These have been included to assist with the evaluation of novel assessment tools for HD that can be applied in clinical and research domains. Two further changes to the REGISTRY protocol include 1) permission to collect retrospective clinical data from a participant's medical notes, and 2) minor modifications to the standard REGISTRY assessment.

An overview of the REGISTRY sub-studies component is shown in the table. Forthcoming issues of the EHDN newsletter will feature a more detailed description of the sub-studies, including information on the aims, design, participant characteristics, measures, statistical analysis plan and study coordination, as well as site selection and investigator training. Sub-studies have been designed to help us understand more about specific stages of the disease, e.g. very early ('pre-motor manifest') and late ('advanced') stages of HD, and 'juvenile HD' (for participants with very long CAG repeat lengths). In addition, assessments have been proposed that will capture, more adequately than at present, abnormalities in cognitive and behaviour domains. Disease-specific tools to assess quality of life will also be developed.

Participants fulfilling inclusion criteria for the various sub-studies will be invited to take part by selecting the 'Novel Assessment' optional component of the study. The REGISTRY sub-studies provide a new, flexible method to develop novel instruments for HD. This approach will enable robust, data-driven interpretation of the proposed novel assessments. It will take full advantage of the Network inviting many people to participate in the studies through a distributed and coordinated system.

Olivia Handley

Overview of REGISTRY Sub-studies

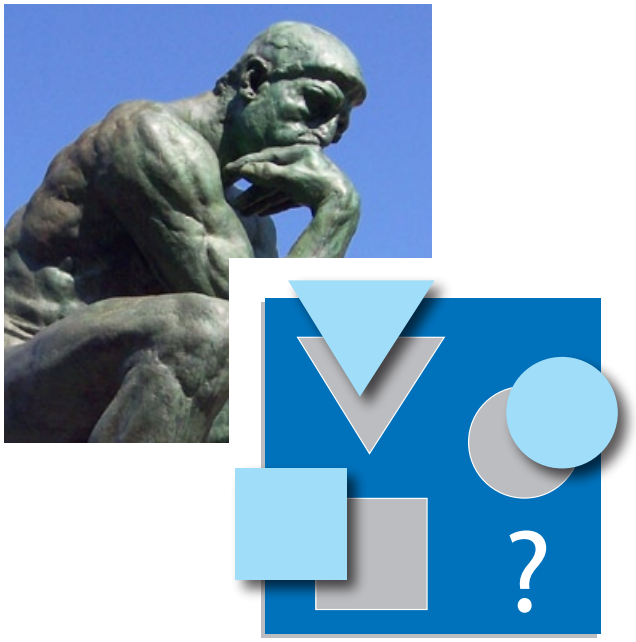
REGISTRY Sub-studies	Assessments
Pre-motor manifest HD	Clinical assessment battery to detect and track specific features in pre-motor manifest HD *
Advanced stage HD	Clinical assessment scale to detect and track specific features of late stage HD
Juvenile HD	Clinical assessment scale to detect and track specific features of juvenile HD
Cognitive Phenotype	Language processing in early HD
	General cognitive impairment
	Finger tapping
	Normative data collection on REGISTRY 3.0 Cognitive Assessment Battery
Behavioural Phenotype	Apathy
	Irritability
	Obsessive-compulsive behaviours
	Frontal behaviours (self-report)
Quality of Life	HD and Carer surveys (self-report)
Physiotherapy	Determining physiotherapy outcome measures
Environmental modifiers	Lifestyle questionnaire

*awaiting outcomes from TRACK-HD

(see page 8 of this issue)

Cognitive Phenotype Working Group

By Anne-Catherine Bachoud-Lévi (Henri Mondor Hospital, Créteil, France) and Jennifer Thompson (Hope Hospital, Manchester, UK)



Why is cognition important?

Unlike the motor symptoms of Huntington's disease (HD), cognitive changes are not visible to other people. Despite this, changes in cognition (i.e. thinking) are an integral feature of HD that are present very early in the course of the illness and become more severe with passing time. People with HD typically become forgetful, have difficulty paying attention and maintaining concentration, and become less efficient and organised in their behaviour. These difficulties, even in the early stages of HD, can have a huge impact on work and everyday life. If treatments for HD are to be successful, then it is important that they address cognitive symptoms as well as the more commonly recognised physical symptoms.

Aims

The main aims of the Cognitive Phenotype Working Group are:

1. to provide an extended cognitive battery to be used in the EHDN REGISTRY study
2. to develop novel assessment tools and evaluate their sensitivity to the progression of HD and potential use as outcome measures in therapeutic trials.

We will also carry out collaborative neuropsychological studies aiming to extend the theoretical understanding of HD and identify targets for therapeutic interventions. The standardisation of cognitive test administration in order to increase data reliability is also an important issue and a key area of focus for the group.

Activities

An extended cognitive battery has been developed for use in the REGISTRY study. We have also developed a detailed instruction manual for administering and scoring the extended battery, which has been translated into the various languages of the Network. Training videos for the cognitive battery are currently under development.

Current projects

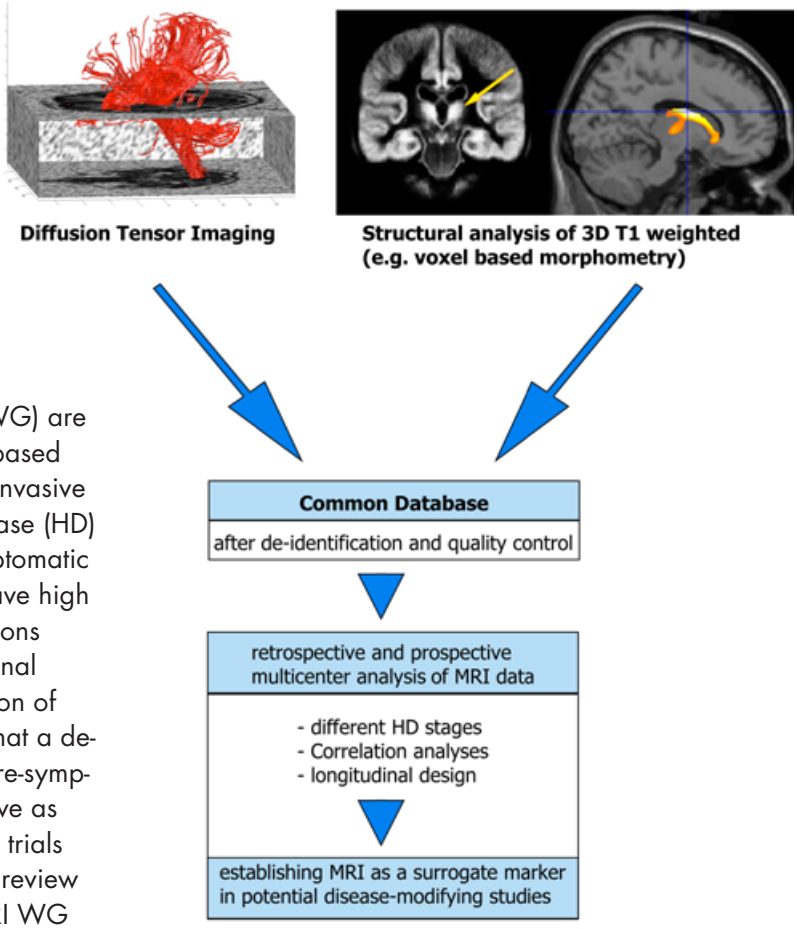
As a result of our working group meeting in Paris in February 2009, we have proposed several research projects as addenda to the REGISTRY protocol. These include a test of syntactic comprehension, an investigation of the sensitivity of the Montreal Cognitive Assessment and an assessment scale which is suitable for use in advanced HD. We will be collecting data on the extended cognitive battery from healthy controls in order to assist in the normalisation of cognitive data across the different languages in the Network. Finally, we are developing a study of cognitive rehabilitation in HD. This project aims to establish whether cognitive strategies or training programmes can improve cognitive function in HD. This is important because it could potentially improve the functioning, confidence and quality of life of people with HD. This project will be a key topic at our meeting in Vancouver in September 2009.

Group membership and meetings

We meet twice a year, typically at the EHDN Plenary Meeting and on one other occasion. Members are encouraged to present work in progress at meetings and to propose collaborative group projects. We encourage scientists and clinicians with an interest in neuropsychological aspects of HD to contact us and get involved in the group! If you are interested please contact:
Anne-Catherine Bachoud-Lévi
(anne-catherine.bachoud-levi@hmn.aphp.fr)
or Jennifer Thompson
(jennifer.thompson@manchester.ac.uk).

Imaging/MRI Working Group

By Jan Kassubek (University of Ulm, Germany), Stefan Klöppel (University of Freiburg, Germany) and Beatriz Gomez-Anson (University of Barcelona, Spain)



Aims

The aims of the Imaging/MRI Working Group (WG) are to explore the usefulness of imaging techniques based on MRI (magnetic resonance imaging) as a non-invasive tool to track the progression of Huntington's disease (HD) both in symptomatic HD patients and in pre-symptomatic mutation carriers. Imaging has been shown to have high potential as a biomarker to depict *in vivo* alterations in brain micro- and macrostructure in cross-sectional studies, and to assess and quantify the progression of HD longitudinally. Imaging studies have shown that a degenerative process is already underway in the pre-symptomatic phase. MRI-based neuroimaging can serve as a ´dry´ surrogate marker in the design of clinical trials – an aspect that has been addressed in a recent review conceptually led by members of the Imaging/MRI WG (Klöppel et al., Neuroscience, Epub). Imaging can help to evaluate the effect of any disease-modifying treatment, as it can visualise a slowing of the degenerative process, even when clinical markers remain unchanged.

Main projects

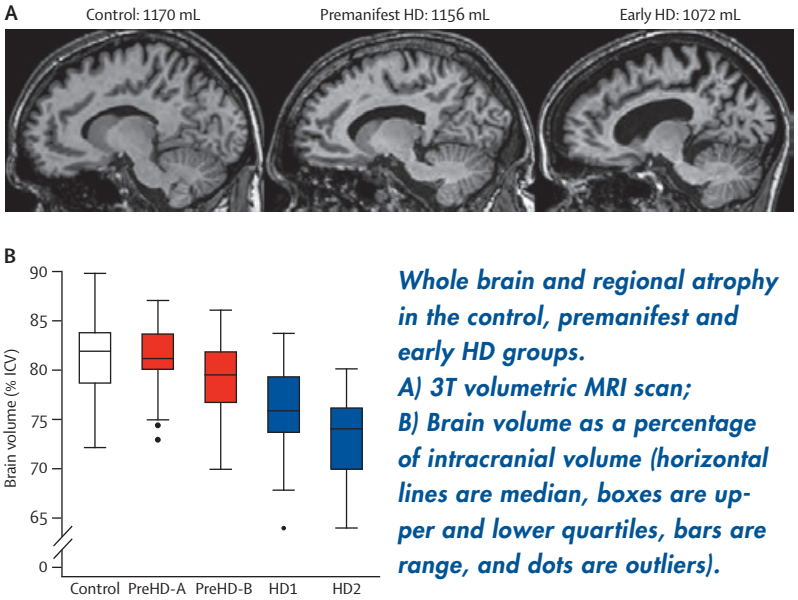
The Imaging/MRI WG acts as a platform to facilitate advanced MRI research by sharing technical expertise and analytical methods within the concept of computational neuroanatomy with input from multiple experts outside the working group. One of our main projects is to standardise the post-processing of MRI data in order to increase the reproducibility of results and thus the validity of data processed at different study sites. This has been demonstrated by a study on voxel-based morphometric analysis of 3D MRI data in a large sample of HD patients, which has examined how varying post-processing parameters may affect the results at a group level. It could be demonstrated that attention to these methodological factors during data analysis is of the utmost importance when such neuroimaging data are to be considered for use as a read-out parameter in a clinical trial context. This project (led by University College London, UK) has been summarised in a manuscript submitted for publication authored by the Imaging/MRI WG.

Another major project is a multi-centre study using diffusion weighted MRI applications (diffusion tensor imaging, DTI) which target the directionality of the brain white matter structures and their connectivity. Initial DTI-based studies from a single centre have shown that white matter is specifically affected by HD, and that correlation analyses might help us to understand the pathoanatomical basis of HD-associated clinical symptoms and signs. As a next step, we plan to conduct such studies across imaging centres that will allow the inclusion of far more subjects. For this purpose, an infrastructure will be established to enable sharing of completely anonymised data between imaging centres. Seed funding from the EHDN is currently supporting a project led by Jan Kassubek to optimise the scanning parameters necessary for such an undertaking.
For more details, please contact Jan Kassubek (jan.kassubek@uni-ulm.de).

Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data

Sarah J. Tabrizi et al., Lancet Neurology (2009), 8: 791-801

TRACK-HD identifies sensitive biomarkers and novel assessments that could be used in neuroprotective trials of HD.



Whole brain and regional atrophy in the control, premanifest and early HD groups. A) 3T volumetric MRI scan; B) Brain volume as a percentage of intracranial volume (horizontal lines are median, boxes are upper and lower quartiles, bars are range, and dots are outliers).

Background

TRACK-HD is a multi-national, multi-centre (London, Leiden, Paris and Vancouver), prospective, observational study of premanifest and early stage Huntington's disease (HD). The aim of TRACK-HD is to develop novel assessments that are sensitive enough to detect very early indicators (biomarkers) of gradual change before clinical signs of HD emerge. These biomarkers could be used in clinical trials to measure the effects of potential disease-modifying therapies for HD.

Subjects and methods

Participants were 123 controls, 120 premanifest HD gene carriers and 123 patients with early HD. The premanifest group was subdivided according to whether subjects were predicted to be "further from" (preHD-A) or "nearer to" (preHD-B) clinical onset. The early HD patient group was also subdivided into disease stage 1 (HD1) and 2 (HD2), with stage 2 being more advanced.

Different image analysis techniques were applied on 3 tesla magnetic resonance imaging (3T MRI) data, yielding measurements of whole brain size, caudate nucleus and putamen volumes, as well as cortical thickness. Quantitative motor assessments included finger tapping, tongue force and gait. Cognitive tests targeted recognition of negative facial emotions, visual working memory and odour identification. Neuropsychiatric symptoms were assessed with a short version of the Problem Behaviour Assessment.

Results

MRI brain scans showed shrinkage of the caudate in participants with preHD or early HD compared to controls (see figure). In those groups, volumes of the whole striatum, as well as caudate and putamen volumes (as measure separately) were significantly reduced, even at the preHD-A stage. Whole brain measures showed a stepwise decline across the groups, with significantly reduced volumes in the preHD-B and both HD groups. Cortical thinning was apparent early in the posterior frontal region of preHD-A subjects, and other brain regions were increasingly affected as the disease progressed. Voxel-based morphometry revealed progressive abnormalities of both grey and white matter in all groups.

Finger tapping was a sensitive measure that showed differences between all group pairs. Tongue force variability also increased in a stepwise manner across groups. Gait analysis was however less sensitive than the other quantitative motor measures.

All three cognitive tests performed showed enough sensitivity to make it possible to separate HD patients and preHD subjects from control subjects. Findings from the Problem Behaviour Assessment indicated that apathy and irritability are also sensitive markers, both before and after diagnosis.

Conclusions

Analysis of baseline data from TRACK-HD confirms that specific biological and clinical parameters in HD gene carriers differ markedly from controls and can be detected early, at the premanifest stage. Sensitive readouts include 3T neuroimaging, quantitative motor and cognitive tests. The battery of assessments presented here will be validated in the ongoing longitudinal TRACK-HD analysis, and moves us closer to the much-needed methodology for conducting neuroprotective clinical trials in premanifest and early HD.

Summary by Diana Raffelsbauer, PharmaWrite, Giebelstadt, Germany
September 2009 · Issue 07

Delayed onset of the diurnal melatonin rise in patients with Huntington's disease

N. Ahmad Aziz et al., Journal of Neurology (2009), Epub ahead of print, DOI 10.1007/s00415-009-5196-1

This study shows that the timing of the evening rise in melatonin levels is significantly delayed in HD patients compared to controls. Despite similar mean levels in both groups, the average melatonin concentrations correlate inversely with both motor and functional disability in individuals affected by HD, suggesting that melatonin secretion is likely to decrease with disease progression.

Background

Sleep disturbances are prevalent in Huntington's disease (HD) patients and may substantially affect their quality of life. They include difficulty in falling asleep and maintaining sleep, reduced rapid eye movement sleep, increased motor activity during sleep and daytime sleepiness.

Daily cyclic activities are regulated by the hypothalamic suprachiasmatic nucleus (SCN) – the 'biological clock' – via several routes, including modulation of the secretion of the hormone melatonin. Previous studies have shown a considerable dysfunction of the SCN in both HD patients and transgenic mice. Based on these findings, Aziz and colleagues postulated that disturbed SCN function in HD might result in abnormal melatonin secretion.

Subjects and methods

Plasma melatonin levels of nine early-stage HD patients and nine matched control subjects were measured over 24 h. Symptoms were assessed with the UHDRS motor and total functional capacity subscales to investigate a possible correlation between melatonin secretion and clinical phenotype.

Results

Mean 24 h melatonin levels were not significantly different between HD patients and control subjects (see table). However, melatonin onset time was significantly delayed in HD patients by approx. 90 min (see figure). Since melatonin offset time was similar in both groups, there was a tendency towards a shorter duration of the nocturnal melatonin plateau in HD patients. Interestingly, in HD patients, mean melatonin levels significantly correlated with UHDRS motor score ($r = -0.70$, $p = 0.036$), total functional capacity ($r = +0.78$, $p = 0.013$) and independence score ($r = +0.88$, $p = 0.002$), but not with CAG repeat length ($r = +0.18$, $p = 0.645$).

Melatonin secretion profiles in HD patients versus controls.

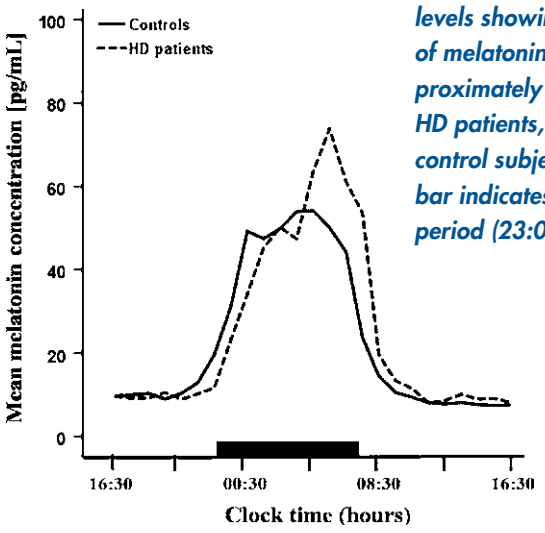
	HD patients	Controls	*p* value
Mean 24 h levels (pg/ml)	24.8 ± 5.4	22.7 ± 2.8	0.601
Onset time (hh:mm)	00:30 ± 00:22	22:52 ± 00:40	0.048*
Offset time (hh:mm)	07:30 ± 00:48	08:22 ± 00:21	0.478
Nocturnal duration (h)	7.0 ± 1.0	9.5 ± 0.8	0.063

* statistically significant

Conclusions

Delayed onset of melatonin secretion in HD patients is reminiscent of a delayed sleep phase syndrome-like circadian rhythm disorder involving alterations in melatonin and cortisol secretion. These disturbances are likely to stem directly from pathology within the SCN molecular oscillation caused by toxic effects of mutant huntingtin locally and/or by dysfunction of brain circuitry innervating the SCN.

Treatment of HD patients with melatonin and bright light may help to ameliorate sleep disturbances by advancing the biological clock. Moreover, melatonin has been shown to reduce oxidative neurotoxicity in cell and animal models of HD, and may be neuroprotective in HD patients as well.



Mean 24 h melatonin levels showing a delay of melatonin rise of approximately 1:30 h in HD patients, compared to control subjects. The black bar indicates the dark period (23:00–7:30 h).

Summary by Diana Raffelsbauer, PharmaWrite, Giebelstadt, Germany
September 2009 · Issue 07

CAG expansion in the Huntington disease gene is associated with a specific and targetable predisposing haplogroup

Simon C. Warby et al., Amer. Journal of Human Genetics (2009), 84: 351-366

Analysis of genetic diversity in the *HD* gene reveals that there are DNA sequences close to the gene that predispose to CAG repeat instability. These sequences are more frequently found in individuals carrying the HD mutation.

Background

Huntington's disease (HD) is a dominantly inherited neurodegenerative disorder caused by the expansion of a CAG repeat in the *HD* gene. Previous studies have identified a few single nucleotide polymorphisms (SNPs) in the region of the *HD* gene and found correlations between these specific markers and disease chromosomes. Here, Warby et al. present a comprehensive analysis of genetic diversity in the *HD* gene of individuals with expanded alleles (> 35 CAGs) that cause HD, intermediate alleles (27-35 CAGs) that are unstable but do not cause HD, and normal alleles (< 27 CAGs).

Subjects

DNA samples for direct sequencing were extracted from Canadians of European origin (65 HD patients, 66 carriers of intermediate alleles and 58 normal subjects). A replication cohort of 203 HD patients was used to confirm the SNP associations with CAG expansions. Data from the HapMap Project were included which originated from US residents with European ancestry, the Yoruba people (Nigeria) and individuals from both Beijing and Tokyo.

Results

A total of 190 SNPs were identified across the *HD* gene. Because many of these SNPs are always grouped together on a chromosome (linkage disequilibrium), all of the genetic diversity could be sampled by tracking 22 of them as 'tagging' SNPs (tSNPs). Of these, 12 tSNPs were significantly associated with disease chromosomes, some of them having a single allele that was a highly sensitive marker of CAG expansion. The haplotypes were divided into three groups (A, B and C). Disease chromosomes belonged almost exclusively (95%) to haplogroup A. Similarly, chromosomes with intermediate alleles were enriched (83%) for haplogroup A. Haplogroup C, however, was very common on normal chromosomes (41%), but completely absent from disease chromosomes. Therefore, people carrying haplogroup C seem to be protected from CAG expansion.

Haplogroup A was present on almost all CAG-expanded chromosomes but only 50% of normal chromosomes. Haplogroup A can be divided into five haplogroup variants (A1–A5), 55% of which belong to variant A1. Chromosomes with variant A1 are 6.5 times more likely to carry a CAG expansion, whereas variants A4 and A5 are unlikely to carry the expansion. These data suggest an enrichment of specific haplotype variants on disease chromosomes. Variants A1 and A2 confer the highest risk for having a CAG-expanded chromosome, whereas A4 and A5 appear to protect from CAG expansion. The Asian and African cohorts lack the risk variants and are enriched for the protective ones.

Conclusions

This study identified a subset of tSNPs that are highly associated with disease chromosomes of European descent. Many of the SNPs are sensitive markers of disease chromosomes and are strongly linked to CAG expansion. They form a cluster of similar haplotypes (haplogroup A) found on 95% of disease chromosomes and are significantly enriched on chromosomes with intermediate alleles. These data support a stepwise model for CAG expansion into the affected range (> 35 CAGs) and identify specific variants associated with repeat instability that are not present in populations with a lower prevalence of HD (African and Asian). The strong association between specific SNPs and CAG expansion lays the foundation for allele-specific gene silencing in HD. Nevertheless, many technical challenges remain to be resolved until this technology can be translated in clinical practice.

Allele is one of the two copies of each gene or genetic marker in organisms with two sets of chromosomes. Single nucleotide polymorphism (SNP) is a DNA sequence variation occurring when a single nucleotide in the genome differs between two chromosomes. Haplotype is a set of SNPs on a single chromosome. Haplogroup is a group of similar haplotypes with the same SNPs.

Upcoming Meetings 2009/2010

Sep 12-15	4th World Congress on Huntington's Disease, Vancouver, BC, Canada http://www.worldcongress-hd.net
Sep 12-15	13th Congress of the European Federation of Neurological Societies (EFNS), 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.dgn2009.de/
Oct 8-11	The 3rd World Congress on Controversies In Neurology (CONy), Prague, Czech Republic http://www.comtecmed.com/cony/2009/
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/
Oct 17-21	Neuroscience 2009 – 39th Annual Meeting of the Society for Neuroscience, Chicago, IL, USA http://www.sfn.org/am2009/
Oct 20-24	59th Annual Meeting of the American Society of Human Genetics (ASHG), Honolulu, HI, USA http://www.ashg.org/2009meeting/
Oct 24-30	19th World Congress of Neurology, Bangkok, Thailand http://www.wcn2009bangkok.com/
Nov 21	3rd Huntington Disease Clinical Research Symposium, Baltimore, MD, USA 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 of the South-East European Society for Neurology & Psychiatry, Thessaloniki, Greece http://www.isbb.gr/
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

Feb 8-11	5th Annual CHDI Huntington's Disease Therapeutics Conference, Palm Springs, USA
Feb 28-Mar 2	18th EPA European Congress of Psychiatry, 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 09-13	10th International Conference on Alzheimer's and Parkinson's Diseases, Barcelona, Spain http://www.kenes.com/adpd/
Mar 10-13	25th International Conference of Alzheimer's Disease, Thessaloniki, Greece http://www.adi2010.org/
Apr 10-17	2010 Annual Meeting of the American Academy of Neurology, Toronto, Canada http://www.aan.com/go/am10
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 (ENS), Berlin, Germany http://www.congrex.ch/ens2010/
Sept 2-5	6th Bi-Annual Plenary Meeting of the European Huntington's Disease Network, Prague, Czech Republic