January 2012 · Issue 15

EHDN *News*

EUROPEAN **HUNTINGTON'S DISEASE** NETWORK

Recent LanCo meeting in Rome in December 2011

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FEATURE ARTICLE

Behind the Scenes at EHDN

By Jamie Levey, EHDN Central Coordination, Paris, France, and Robi Blumenstein, CHDI, New York, USA

For most people with HD and their families, the European Huntington's Disease Network (EHDN) means the friendly and caring doctors and site coordinators they see at their annual REGISTRY visit. They may not know that those doctors and nurses are supported by a large group of equally dedicated personnel that do everything from monitoring the quality of data collected to helping translate this newsletter. This is the first in a series of articles that will take you "behind the scenes" at EHDN and introduce you to some of those people and the important work they are doing.

EHDN was born out of a discussion among HD professionals at the Gordon Conference in Italy in 2003. The idea was to build an independent network of HD clinicians, scientists and families that could facilitate collaborative research, speed up clinical trials and improve the clinical care of those affected by HD. 'Fast forward' to 2011. EHDN now has over 1,400 members from the global HD community, and represents over 140 HD centres across 19 countries. Today, there are more than 8,600 participants enrolled in REGISTRY and over 6,200 biosamples have been collected. EHDN is actively involved in important clinical trials (Horizon and MermaiHD are examples), and is working with sponsors on protocol development, site selection, rapid participant recruitment and study site management.

From the outset it was understood that in addition to the clinicians and scientists, who provide their valuable time on a volunteer basis, EHDN would

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By Jamie Levey, EHDN Central Coordination, Paris, France and Robi Blumenstein, CHDI, USA
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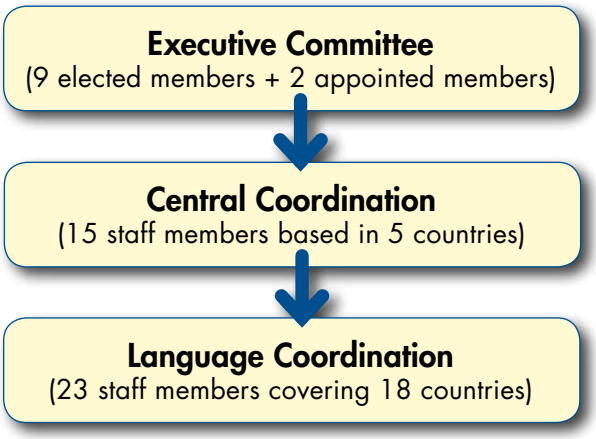
need a full-time staff to take care of all the administrative and logistical tasks involved in running a large network spanning many countries. The operational team of EHDN now numbers more than 40 staff members who work full-time on EHDN activities. At the core of the operations are Central Coordination (CC) and Language Coordination (LC), as overseen by the Executive Committee (EC).



The Executive Committee is responsible for overseeing the activities of EHDN, developing and maintaining the EHDN infrastructure, ensuring funding, evaluating research projects and clinical trials that are recommended by the Scientific Bioethics and Advisory Committee, and convening the bi-annual plenary meeting.

Central Coordination manages the day-to-day activities of EHDN including site management services for REGISTRY and clinical trials, data access, information technology development, and other services such as regulatory affairs and biostatistics. The functional groups at EHDN are Clinical Operations, Science, and Administration.

Language Coordination

Language Coordination is EHDN's 'field' organization of people that support and manage the activities of EHDN at sites within the network. Sites are grouped by common language and are supported by a native language-speaking Language Area Coordinator, or 'LanCo'. The Language Coordination team is comprised of medical doctors, research psychologists, social workers and others from diverse industrial and academic backgrounds.

LanCos spend their time visiting local study sites on a regular basis to ensure that sites are receiving the support they need from the network as well as to ensure that REGISTRY and other studies are operating in line with the Good Clinical Practice (GCP) guidelines published by *The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use* (usually referred to as the ICH) and standard operating procedures (SOPs) that have been adopted by EHDN. This involves making sure that

Saul Martínez and Lisanne Muetze are two of the 23 LanCos

Saul Martínez

My name is Saül Martínez and I'm from Barcelona. I'm a Neuropsychologist specialized in Movement Disorders like Parkinson's and Huntington's disease and I'm currently working for the EHDN as a LanCo in Spain. Besides my work, my other passion is surfing. Since my childhood I'm playing with the waves. Now, after more than 15 years in the sea, traveling and participating in competitions I've got a wish: To allow people with HD to feel the unique experience of surfing. I'm now associated with Play & Train to make this wish come true. www.playandtrain.org

Lisanne Muetze

Let me introduce myself, my name is Lisanne Mütze, I am 29 years old and since summer 2011 the new EHDN LanCo for the German-speaking countries. Now working in Ulm, I originally come from Frauendorf in Brandenburg (Eastern Germany), where I was born and raised. After finishing my high school diploma I moved to Bavaria for a vocational training. Afterwards I started to study Medical Documentation and computer science in Ulm. After graduation I joined the EHDN family. In my spare time I like seeing good friends, reading, solving Sudokus and dancing. Apart from that, I try to support my favourite ice hockey-team "ECDC Memminger Indians" as often as possible. If you ever see me, please don't hesitate to talk to me.

project documents are appropriately completed, filed and documented, and liaising with external bodies such as Ethical Review Committees when required. LanCos work very closely with clinical trial sponsors to facilitate the conduct of clinical trials within EHDN from start-up to close-out.

Efficiently conducting HD studies and trials and monitoring them for compliance with GCP and SOPs is very important in generating the data we need to find and evaluate effective treatments for HD. There is no doubt LanCos make a critical contribution to this process.

In the future, LanCos will help support the ENROLL-HD study and other research projects defined by the EHDN Scientific Strategic plan. To learn more about the Language Area Coordination, visit the webpage at www.euro-hd.net/html/network/project/langcoord.

LanCo meeting in Rome, December 2011

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Siena Biotech Starts Phase II Study with Selisistat (SEN0014196) for Huntington's Disease

Goran Westerberg, Clinical Development, Siena Biotech SpA, and Tim McLean, Clinical Operations Manager, EHDN

The Background

Siena Biotech SpA is starting a phase II trial in Europe in Huntington's disease (HD) patients with its selective Sirtuin 1 (SIRT1) inhibitor, Selisistat (SEN0014196). The compound is being developed as a disease-modifying therapy for HD and has previously obtained 'Orphan Drug' status from the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as well as the Australian Department of Health and Ageing (TGA).

Following successful completion of a phase I study in healthy volunteers during 2010, an exploratory pharmacodynamic study of Selisistat in HD patients has recently been completed across six European sites. The study, with the acronym 'PADDINGTON', is being co-funded by the European Commission under the Seventh Framework Programme. It aimed to assess safety and to ascertain SIRT1 modulation by the drug, thereby providing pharmacodynamic data to guide the design of subsequent efficacy studies. The results of this study are currently being analysed and are expected to be available within 2012. An additional study looking at the effect of food on bioavailability of the compound in HD patients in the United States was started in November 2011. This study is expected to be completed by August 2012.

The Current Phase II Study

The current PADDINGTON phase II study has been endorsed by the EHDN and will be conducted at multiple study sites in Germany, UK and Italy to ensure rapid recruitment. This is a randomised, double-blind study to evaluate safety, tolerability, pharmacokinetics and pharmacodynamics of Selisistat at two doses versus placebo. Any short-term clinical effects will also be recorded. A total of 144 subjects will be recruited across approximately 20 EHDN sites. The first patients were enrolled at sites in Germany and Italy during November 2011 and all sites are expected to open for enrollment by early 2012. Treatment duration is 12 weeks, and recruitment to the study should close during the summer of 2012, with effects on the primary outcome measures available by end of 2012.

The Study Drug

Selisistat has been found to be effective in a range of disease-relevant parameters in both *in vitro* and *in vivo* models. Siena Biotech SpA has generated compelling mechanistic data to support the therapeutic application of SIRT1 inhibitors in HD. SIRT1 is a protein deacetylase capable of modulating the acetylation status of mutant huntingtin.

About the Sponsor Company

Siena Biotech SpA (http://www.sienabiotech.com) is a clinical-stage drug discovery company based in Siena, Italy, whose R&D efforts are mainly focused on discovering new drugs for therapeutic intervention against neurodegenerative diseases and cancer. The company has developed an internal portfolio of several R&D projects in three therapeutic areas: Alzheimer's disease, Huntington's disease and cancer. Siena Biotech is the operational arm of the Monte dei Paschi di Siena Foundation operating in the field of scientific research and biotechnology, in line with its founding charter and mission.

Updating the Predictive Genetic Testing Guidelines

By Rhona MacLeod, Aad Tibben and Marina Frontali
On behalf of the EHDN 'Genetic Testing and Counselling' Working Group

The Genetic Testing and Counselling Working Group (WG) was formed in Dresden in 2007 by Professor Gerry Evers Kiebooms to look at communication in relation to genetic test information and to review the guidelines. The WG comprises psychologists, clinical geneticists, family members, genetic counsellors and laboratory scientists. The 1994 guidelines for predictive testing were discussed and reviewed at the first meeting in Leuven in May 2008. They had not been updated since they were first drawn up by an *ad hoc* committee comprising representatives of the IHA and WFN 17 years ago. Undoubtedly, the guidelines have succeeded in their original aims of setting minimum standards for predictive testing, protecting at-risk individuals and providing a reference point to help with ethical and clinical dilemmas as they arose. Almost two decades on, however, it was felt that a review was essential in order to take into account some of the changes that have occurred since that time. These include new technology such as pre-implantation genetic diagnosis; increased scientific knowledge about HD (for example, understanding of intermediate and reduced penetrance alleles, prodromal signs etc); the debate surrounding the testing of minors; new opportunities to participate in research and data on the experiences of individuals who have undergone testing (such as post-test discrimination).

Process of reviewing the guidelines

The WG established a number of subgroups, each of which had the task of reviewing the literature in relation to one of six sections of the 1994 guidelines. These were: 2.1 Testing of minors; 2.8 Lab standard of accuracy; 4.0 Communication of information; 5.2 Information pertaining to the test; 7.0 'Prenatal Diagnosis' renamed 'Reproductive options'; and 9.0 Post-test counselling. International participants were invited to contribute their expertise on specific topics. The subgroups provided written proposals, which included the rationale for change and the reference material that they had used, which were debated in plenary discussions.

Summary of Proposed Changes

Section 2.1	Recommendation that test be deferred until 18 years or older' (previously 'age of majority') Access to genetic counselling for minors recommended.
Section 2.8	Recommendation that laboratories comply with quality assessment schemes where these exist, for example through certification or accreditation.
Section 4.4	New recommendation regarding access to medical reports. Pre-test discussion may include advice about the potential for discrimination (including family/work, adoption).
Section 5.2	Pre-test genetic counselling should mention all possible test outcomes, including intermediate and reduced penetrance results.
Section 7.0	Renamed 'reproductive options' includes a section on PGD and the recommendation that couples should have opportunities to discuss all reproductive options available to them in their country which may include no tests, PGD, prenatal testing, gamete donation and adoption.
Section 9.0	Access to specialist centers for follow up after predictive test. Opportunities to participate in research as applicable. Discussion of plans for follow-up prior to testing.

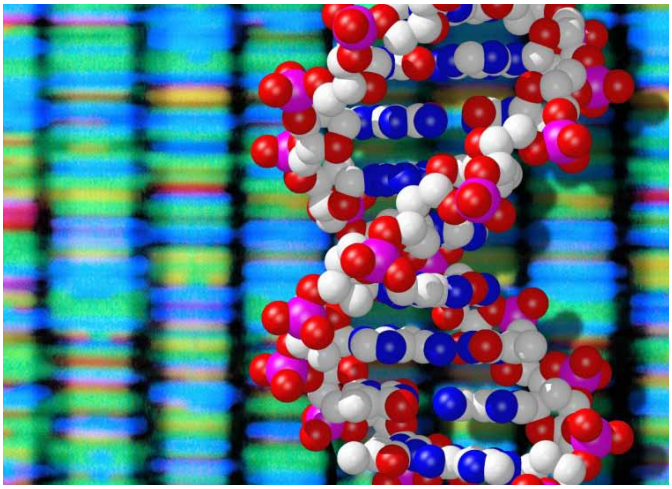
International Consultation

The proposed updates have undergone a lengthy consultation process, first with the European Huntington's Disease Network (EHDN) in June-August 2010, and then more widely through the International Huntington's Disease Association (IHA) and World Federation of Neurology (WFN) between Nov 2010 – June 2011. A Town Hall session at the World Congress on HD in Melbourne, September 2011, outlined the proposals and drew on the experiences of an expert panel from countries including South America, Australia and Canada. Asun Martinez (then Chair of the IHA) confirmed to congress that the updates had been approved by the IHA. Panel members supported the idea of putting a mechanism in place prospectively to regularly review the recommendations for predictive testing and proposed that the review should take place every 2 years in conjunction with the World Congress. A committee, overseen by the Chairs of the IHA and WFN, will be comprised of a rotating membership and will review comments received and research evidence presented in the intervening two years.

Following the WFN meeting in September, Professor Raymund Roos, Chair of the WFN, invited a small international writing committee to make the final edits to the proposed changes, prior to submission to a peer-review journal for publication.

The next steps

Overall, the feedback received from the HD community has been positive. It is acknowledged, however, that some people may feel that they did not have sufficient opportunity to participate in the process, and for others the changes have not gone far enough. It is essential therefore that we have a mechanism in place to ensure that recommendations for predictive testing remain current and clinically relevant. This way, we can build on the excellence of the 1994 guidelines and continue to educate a new generation of doctors and specialists in the field. Whilst recommendations of practice are undoubtedly important – they help to provide safety parameters within which we, as professionals, work – nevertheless they tell us little about the nuances of counselling and how our approaches are tailored to the individual. It is hoped that the publication of the updates this year will succeed in generating new research questions and encourage clinicians to share more of their day-to-day practice as well as the counselling theory and skills upon which they draw. A final point is to note the central importance of family members in helping to develop these recommendations, as well as their vital contribution to research and debates on the subject of predictive testing.



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SEED FUND APPLICATIONS

Submission Dates 2012

1st March

1st July

1st November

Summary by Diana Raffelsbauer, Freelance Medical Writer, PharmaWrite, Germany
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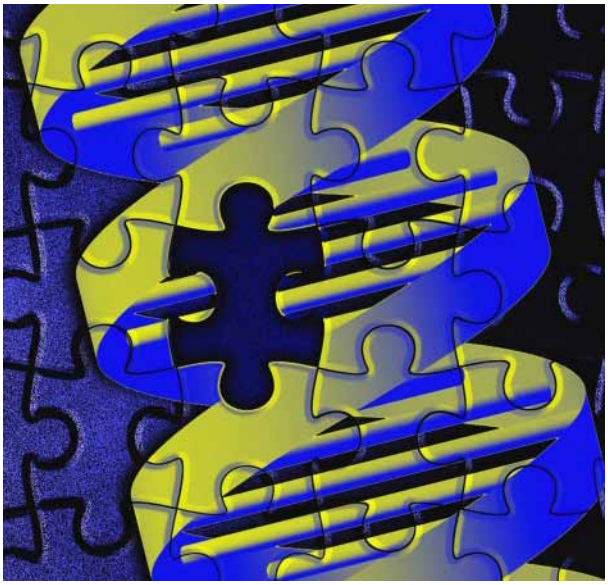
Discrepancies in reporting the CAG repeat lengths for Huntington's disease

Oliver W. Quarrell et al., *European Journal of Human Genetics* 2012; 20: 20-6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This study assessed the accuracy of CAG repeat number reports from local laboratories in 15 European countries within EHDN.

Background

Huntington's disease patients who participate in the REGISTRY study may opt to have their CAG repeats in the *huntingtin* gene determined by a central laboratory, BioRep, based in Milan, Italy. The regenotyping results can then be compared to those obtained from local genetics laboratories in the patient's home country.

Subjects and Methods

Blood samples from 1,326 REGISTRY participants were available for regenotyping and comparison with the original results from 121 laboratories in 15 countries. Duplicate results were compared by subtracting the BioRep result from that obtained from the local laboratory for both the disease causing (upper) and normal (lower) alleles. Discrepancies were considered in the light of acceptable measurement errors proposed by both the American College of Medical Genetics (ACMG) and the Draft European Best Practice Guidelines (BPG).

Results

For the upper allele, 49% of the results were identical and 51% were discrepant (31% by one CAG, 12% by two CAGs and 8% by three or more CAGs). The discrepancies were in both directions (55% increase and 45% decrease). When the proposed ACMG and BPG acceptable measurement errors were applied, the discrepancy rate fell from 51% to 13.3% and 9.7%, respectively. In 52 (4%) patients, the discrepancy was clinically significant. Of these, in 36 cases the repeat length moved from the reduced-penetrance range (36-39 CAGs) to the fully-penetrant range (≥ 40 CAGs) and in 11 cases from the fully-penetrant to reduced-penetrance range. A potential misdiagnosis occurred in five cases, as the change in results crossed the ≤ 35 CAGs critical boundary.

Discrepancies were noted in the results from 71% of the laboratories. Of these, 40% were outside the acceptable errors proposed by ACMG and 34% outside that proposed by BPG. Of the 121 laboratories, only 45 participated in the 2009 external quality assessments (EQA) organised by the European Molecular Genetics Quality Network. There was no correlation between the frequency of discrepancies and the time when local genotyping was performed.

To assess the reliability of the BioRep results, the DNA from 348 cases was reanalysed at an accredited laboratory in Germany. The results were identical to those of BioRep in 100% of the cases once the ACMG or BPG error rates were applied. BioRep also correctly measured the CAG repeat size in six reference samples supplied by the US National Institute for Standards and Technology.

Conclusions

This study shows that discrepancies in CAG repeat number assessment is a current and widespread problem across Europe that needs to be recognised and addressed. The authors strongly recommend that (1) laboratories provide an error rate for their measurement, (2) they participate in EQA schemes and (3) use reference materials regularly to adjust their internal standards. Knowledge of the discrepancy in CAG repeat size measurement within REGISTRY may be important for those conducting research based on CAG repeat length data pooled from multiple laboratories.

Functional gene expression profiling in yeast implicates translational dysfunction in mutant huntingtin toxicity

Eran Tauber et al., *Journal of Biological Chemistry* 2011; 286: 410-9

This study adds genes involved in translation to the list of modulators of mutant huntingtin toxicity with drug target potential.

Background

Yeast has proven to be a useful model organism with which to study various cellular and molecular features of Huntington's disease (HD). In a previous study[1], Giorgini et al. identified 28 gene deletions that suppressed toxicity of a mutant huntingtin (HTT) fragment in yeast. One of these suppressors was Bna4, the yeast homolog of the enzyme kynurenine 3-monooxygenase, which has been implicated in HD pathophysiology and now represents a promising drug target. In another study[2], expression of mutant *HTT* was sufficient to induce transcription of the kynurenine pathway in yeast, and this induction was abrogated by impairing the activity of the histone deacetylase Rpd3. This work also identified many other genetic suppressors of mutant HTT toxicity through gene expression analysis in yeast strains harbouring wild-type *HTT* versus mutant *HTT*. In the present study, data from this experiment were reanalysed and expanded to identify new candidate drug targets for HD.

Results

Using DNA microarrays, gene expression analysis was performed in yeast strains expressing either a wild-type (Htt25Q) or an expanded HTT fragment with 103 glutamines (Htt103Q). In comparison to wild-type cells, expression of 226 genes was up-regulated in Htt103Q-expressing cells, whereas expression of 244 genes was down-regulated. Up-regulated genes were involved in the stress response, protein folding, modification and degradation, whereas down-regulated genes were involved in ribosome biogenesis and rRNA metabolism.

Gene expression profiling was also examined in three strains of yeast expressing Htt103Q, each of which also had a deletion in a gene that suppresses mutant Htt toxicity (*BNA4*, *MBF1* and *UME1)*. This approach identified more than 400 differentially expressed genes, of which 15 were similarly altered in all three suppressor strains compared to the wild-type strain, supporting the existence of common mechanisms for the suppression of mutant HTT toxicity. These 15 genes are involved in translation (including three tRNAs), stress response, lactate metabolism and mitochondrial function.

In total, 380 of the identified genes were tested for their ability to suppress Htt103Q toxicity when overexpressed in yeast via growth assays. Of these, 12 genes were found to suppress mutant Htt toxicity (see table). Most of these genes are down-regulated in Htt103Q-expressing cells, suggesting that their overexpression suppressed toxicity by rescuing the depletion of a critical factor in the mutant Htt background. Of the 12 novel suppressors, 6 are involved in ribosomal RNA (rRNA) processing, and 7 have human orthologs. Finally, the authors showed through network analysis that these genes are functionally interconnected.

Conclusions

Genes involved in rRNA processing and ribosome biogenesis and assembly play a role in mutant Htt toxicity. These data suggest that translational dysfunction underlies HD pathogenesis and that drugs targeting this process might be beneficial.

DEGs = Differentially Expressed Genes

TABLE 3
DEGs in Htt103Q-expressing cells modulate mutant htt toxicity

	Ortholog(s)[a]	Expression[b]	Function
Suppressor			
BUD23	+	Down	rRNA processing
CSE2	−	Up	RNA polymerase II transcription
DBP2	+	Down	rRNA processing
ENT3	+	Up	Golgi-endosome transport
IPI3	−	Down	rRNA processing
JJJ3	−	Down	HSP40 chaperone
NSA2	+	Down	rRNA processing
PRM7	−	Down	Pheromone response
RAS1	+	Down	G-protein signaling
RRP9	+	Down	rRNA processing
UTP9	−	Down	rRNA processing
YOR1	+	Down	ABC transporter
Deletion suppressor			
mbf1Δ	+	Up	Transcriptional coactivator
Deletion enhancer			
apj1Δ	+	Up	HSP40 chaperone

[a] Human orthologs determined via the Ensembl Genome Browser. Orthologs may be either one-to-one, one-to-many, or many-to-many. *BUD23*, *ENT3*, *NSA2*, *RRP9*, and *MBF1* have one-to-one orthologs in humans that could potentially be targeted for therapeutics.
[b] Direction of differential expression in Htt103 versus Htt25Q cells.

1 *Nat. Genet.* 2005; 37:526-31
2 *J. Biol. Chem.* 2008; 283:7390-400

A natural antisense transcript at the Huntington's disease repeat locus regulates *HTT* expression

Daniel W. Chung et al., *Human Molecular Genetics* 2011; 20: 3467-77

This study confirms that the antisense strand of the *Huntingtin (HTT)* gene is transcribed and proposes a model of repeat length-dependent regulation of *HTT* expression.

Background

Little is known about the genomic features of the antisense strand of the *HTT* locus, although evidence for its transcription has been reported in the past. Antisense transcripts have been implicated in the pathogenesis of many other repeat expansion disorders. This has led the authors to investigate the expression of the *HTT* antisense strand in brain tissues from HD patients as well as cell models made using various gene constructs.

Results

To detect expression of the *HTT* antisense strand *(HTTAS)*, strand-specific RT-PCRs[1] were performed using RNA extracted from the frontal cortex of HD and control brains. *HTTAS* transcripts were found in the brain of both HD patients and control subjects. *HTTAS* transcription can initiate from four alternative sites (see figure). Two *HTTAS* splice variants were detected in HD brains. These splice variants contained either exons 1 and 3 *(HTTAS_v1)* or exons 2 and 3 *(HTTAS_v2)*. Short open reading frames exist in exons 2 and 3, but neither the predicted peptides nor parts of them were found in protein databases. The *HTTAS_v1* transcript is expressed in multiple tissues types, including different brain structures, and the activity level of its promoter in cell lines corresponded to 10-15% of that of the *HTT* promoter.

The addition of expanded CAG repeats to the gene constructs reduced *HTTAS* transcription *in vitro*, suggesting that CAG repeat expansion inhibits antisense promoter activity. These findings were replicated in human cortical samples: the levels of *HTTAS_v1* transcript were substantially lower in HD brains than in control brains. Furthermore, the longer the CAG repeat, the lower the amount of *HTTAS_v1* transcript found. In cell lines, a decrease in *HTTAS_v1* transcription (caused by the use of small interfering RNA molecules) increased *HTT* expression, whereas overexpression of *HTTAS_v1* decreased *HTT* transcription. This suggests that *HTTAS_v1* negatively regulates *HTT* expression. The effect of *HTTAS_v1* on *HTT* expression *in vitro* was at least partly dependent on the RISC[2] pathway involving *Dicer*.

Taken together, these findings suggest that cells with an expanded CAG repeat produce fewer *HTTAS* transcripts, which in turn increase *HTT* transcription. However, the level of *HTT* expression is similar in both HD and control brains. This is because the CAG repeat expansion itself has a second (and counteracting) effect on *HTT* expression. Using different minigene constructs in GFP[3] reporter assays, the authors found that the longer the repeat, the lower the *HTT* expression. Therefore, CAG repeat length and *HTTAS_v1* interact to regulate *HTT* expression, with the net effect being that *HTT* transcript levels remain constant across all repeat lengths.

Implications

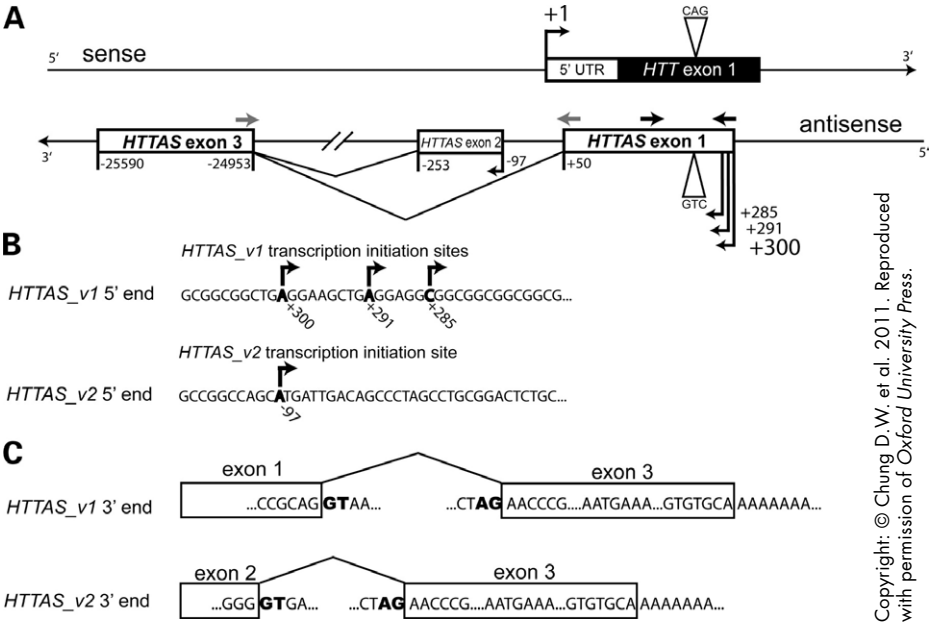
Increasing the levels of the antisense transcript to reduce *HTT* transcription and consequently the production of mutant HTT protein may have therapeutic potential in HD.

1 Reverse Transcriptase Polymerase Chain Reaction

2 RNA-Induced Silencing Complex

3 Green Fluorescent Protein

Genomic structure of HTTAS showing transcription start sites (numbers are relative to the transcription start site of HTT), the three exons and their splicing sites.



Pridopidine for the treatment of motor function in patients with Huntington's disease (MermaiHD): a phase 3, randomised, double-blind, placebo-controlled trial

Justo G. de Yébenes et al., *Lancet Neurology* 2011; 10:1049-1057

Pridopidine is well-tolerated and improves voluntary motor symptoms of HD.

Background

Previous research suggests that glutamate and dopamine neurotransmission are affected in Huntington's disease (HD), and that the mechanism by which dopamine modulates glutamate-induced excitation in the basal ganglia and the cortex might be disrupted.

Pridopidine belongs to a new class of drugs called 'dopaminergic stabilisers'. These compounds can either enhance or antagonise dopamine-dependent behaviours by acting primarily at dopamine type 2 receptors. In animal studies, pridopidine has been shown to normalise dysregulated psychomotor functions, while having only subtle effects on normal psychomotor activity. Data from a phase 2 clinical trial showed that pridopidine might improve voluntary motor symptoms in HD patients without worsening chorea.

Subjects and Methods

A total of 437 HD patients from 32 EHDN sites in 8 European countries were randomly assigned to receive either pridopidine at 45 mg or 90 mg per day, or placebo for 6 months. The primary endpoint was a modified motor score (mMS) derived from UHDRS-TMS[1] and designed to measure 10 items relating to voluntary movements. The full UHDRS-TMS scale, clinical global impression, cognition, behaviour, functional capacity as well as safety and tolerability were also assessed. Both patients and investigators were blinded to treatment assignment.

Results

In the full-set analysis, the difference in mean mMS was –0.99 point (p = 0.042) for the group receiving 90 mg pridopidine vs. placebo and –0.36 point (p = 0.456) for the 45 mg group vs. placebo. These values suggest some improvement in voluntary motor symptoms without reaching the pre-specified threshold of statistical significance (p < 0.025). The difference was more pronounced in the per-protocol analysis (that included only patients who completed all study visits and had drug compliance higher than 70%), which showed a reduction in mMS scores of –1.29 points (p = 0.014) for the 90 mg group vs. placebo. On the UHDRS-TMS, the difference between the 90 mg group and the placebo group was –2.96 points and reached statistical significance (p = 0.004). The main drivers of this improvement were changes in dystonia, eye movements, hand movements, gait and balance (see table). Pridopidine had no effect on non-motor endpoints. The drug was well-tolerated and had an adverse events profile similar to that of placebo.

Conclusions

Pridopidine was effective on some items of the UHDRS-TMS that were not included in the mMS scale. The drug might improve HD symptoms for which there are currently no treatments (i.e. dystonia and abnormalities in eye movements, hand coordination, gait and balance). Further clinical studies are needed to confirm these effects. A larger, global phase 3 trial is currently planned to start in 2012. This trial will aim to replicate the previous findings and to explore whether or not a higher dose of pridopidine (135 mg/day) has a greater therapeutic effect.

	Difference (95% CI)	p value
Eye movements*	–1·07 (–1·85 to –0·30)	0·007
Dystonia	–1·03 (–1·64 to –0·42)	0·001
Chorea	0·14 (–0·67 to 0·95)	0·74
Hand movements†	–0·70 (–1·26 to –0·14)	0·015
Gait and balance‡	–0·35 (–0·66 to –0·04)	0·028

*Equivalent to the sum of unified Huntington's disease rating scale total motor score (UHDRS–TMS) items 1–3 (ocular pursuit, saccade initiation, and saccade velocity). †Equivalent to the sum of UHDRS–TMS items 6–8 (finger taps, pronate and supinate hands, and Luria fist–hand–palm sequencing). ‡Equivalent to the sum of UHDRS–TMS items 13–15 (gait, tandem walking, and retropulsion pull test).

Table 4: **Between-group differences (90 mg per day pridopidine *vs* placebo) for the change from baseline to week 26 in groups of items from the UHDRS-TMS**

1 Unified Huntington's Disease Rating Scale – Total Motor Score

Upcoming Meetings 2012

Feb 22-23	8th Annual Update Symposium on Clinical Neurology and Neurophysiology, Tel Aviv, Israel http://www.isas.co.il/neurophysiology2012/
Feb 27-Mar 1	7th Annual HD Therapeutics Conference of CHDI, Palm Springs, CA, USA http://www.regonline.com/builder/site/Default.aspx?EventID=1027835
Mar 3-6	20th European Congress of Psychiatry, Prague, Czech Republic http://www2.kenes.com/epa/Pages/home.aspx
Mar 7-10	27th International Conference of Alzheimer's Disease, London, UK http://www.adi2012.org/de/home.aspx
Mar 8-11	6th World Congress on Controversies in Neurology, Vienna, Austria http://comtecmed.com/cony/2012/
Mar 10	Meeting of HD-affected families in Spain, Centro de Referencia Estatal de Atención a Personas con Enfermedad de Alzheimer y otras Demencias, Salamanca, Spain
Mar 21-25	9th World Congress on Brain Injury, Edinburgh, UK http://www.internationalbrain.org/
Mar 22-25	2nd International Congress on Neurology and Epidemiology, Seville, Spain http://www.neuro-conference.com/2012/
Mar 23-24	5th Singapore International Parkinson's Disease and Movement Disorders Symposium http://www.nni.com.sg/5th+PDMD.htm
Apr 21-28	64th Annual Meeting of the American Academy of Neurology, New Orleans, LA, USA http://www.aan.com/go/am12
May 3-6	8th International Congress on Mental Dysfunction & Other Non-Motor Features in Parkinson's Disease, Berlin, Germany http://w3.kenes-group.com/mailshot/congress/mdpd2012/ms4.htm?ref4=db1
May 10-13	EFNS Academy 2012, Spring School for Young Neurologists, Staré Splavy, Czech Republic http://www.efns.org/EFNS-Academy-2012.255.0.html
May 16-19	7th World Congress for Neurorehabilitation, Melbourne, Australia http://www.dcconferences.net.au/wcnr2012/
June 4-8	13th Asian Oceanian Congress of Neurology, Melbourne, Australia http://www.aocn2012.com/
June 8-10	27th Annual National Convention of the Huntington's Disease Society of America, Las Vegas, NV, USA http://www.hdsa.org/national-convention/convention/index.html
June 9-12	22nd Meeting of the European Neurological Society, Prague, Czech Republic http://www.congrex.ch/ens2012
June 17-21	16th International Congress of Parkinson's Disease and Movement Disorders, Dublin, Ireland http://www.mdscongress2012.org/
June 21-24	Meeting of young adults from HD-affected families in Spain, Burgos, Spain http://www.euro-hd.net/html/network/news
June 23-26	European Human Genetics Conference 2012, Nurnberg, Germany https://www.eshg.org/eshg2012.0.html
Sept 8-11	16th Congress of the European Federation of Neurological Societies (EFNS), Stockholm, Sweden http://www2.kenes.com/efns/pages/home.aspx
Sept 14-16	EHDN 2012, 7th EHDN Plenary Meeting, Stockholm, Sweden http://www.euro-hd.net/html/network/news
Oct 4-6	22nd Alzheimer Europe Conference, Vienna, Austria http://www.alzheimer-europe.org/Conferences/Vienna-2012
Oct 13-17	Neuroscience 2012, Annual Meeting of the Society for Neuroscience, New Orleans, LA, USA http://www.sfn.org/index.aspx?pagename=annualmeeting
Oct 19-21	Meeting of HD-affected families in Spain, Centro CREER, Burgos, Spain http://www.euro-hd.net/html/network/news
Nov 6-10	62nd Annual Meeting of the American Society of Human Genetics, San Francisco, CA, USA http://www.ashg.org/2012meeting/
Nov 8-10	2nd International Congress on Neurology and Epidemiology, Nice, France http://www.neuro-conference.com/2012/