

*Fédération Huntington Espoir*



## Nouvelles de la Recherche Novembre 2006

### NOUVEAU CENTRE DE CELLULES SOUCHES HUMAINES

Dans un nouvel effort pour simplifier et augmenter la sécurité dans la recherche sur les cellules souches humaines, Johns Hopkins a créé une “one-stop shop” pour préserver, créer, approvisionner et tester des lignées de cellules de haute qualité pour ses propres chercheurs actuellement, et la grande communauté scientifique ultérieurement.

En tandem avec l’ouverture du nouveau centre, JH a engagé une huitième personne à l’Embryonic Stem Cell Research Oversight (ESCRO), semblable aux autres organisations qui garantissent la sécurité des personnes humaines, et s’assurent que les cellules souches étudiées à l’Université sont saines.

Le Centre et ESCRO vont communiquer avec les experts JH pour tester les lignées de cellules, afin de détecter les altérations ou des mutations qui pourraient compromettre leur qualité ou signaler leur danger.

“Nous sommes convaincus que de tels services vont apporter un niveau formidable de confiance et de sécurité à la recherche sur les cellules souches à Hopkins , tant et plus que les scientifiques vont pouvoir travailler plus rapidement” (Dangs)

“Nous savons bien que beaucoup de chercheurs voudraient s’aventurer dans le domaine de la science des cellules souches, mais ne le font pas à cause des obstacles bureaucratiques considérables pour obtenir l’accès aux contrats et aux transferts matériels des lignées de cellules; le centre fera tout cela pour toute l’Université, et en accès libre”.

Avec une aide au démarrage, dont un don anonyme de 100 million \$, à JHU, au début de l’année, le Centre va stocker une collection de cellules souches d’embryons humains, certaines approuvées par des fondations fédérales et d’autres, non.

Les cellules souches des embryons humains viennent des embryons non utilisés lors des fécondations in-vitro. Comme ces cellules peuvent devenir des cellules de toutes sortes du corps humain, elle peuvent être utilisées pour traiter des maladies telles que Parkinson’s, des diabète I, Huntington,....

(En accord avec le règlement établi par le Président Bush, seules des cellules souches humaines produites avant le 9 août 2001 peuvent être utilisées dans le cadre de la recherche fédérale. Les lignées de cellules qui peuvent avoir cette éligibilité ne peuvent être utilisées dans aucun essai humain, car elles ont été élevées dans des cellules de souris, et peuvent donc héberger des virus spécifiques aux souris.)

## Johns Hopkins University (Baltimore)

Johns Hopkins Medicine

October 24, 2006

From: "Johns Hopkins Medicine" <dro@jhu.edu>

To: "JHU News" <JHU\_News@listproc.hcf.jhu.edu>

Sent: Tuesday, October 24, 2006 1:33 PM

Subject: JHU: stem cell "resource center" (Med 2006-113)

Johns Hopkins Medicine

Media Relations and Public Affairs

Media Contact: Audrey Huang

410-614-5105

audrey@jhmi.edu

October 24, 2006

### **NEW HUMAN STEM CELL CENTER AT JOHNS HOPKINS EXPECTED TO SPEED RESEARCH AND KEEP IT SAFE**

-- New Institutional Board To Oversee, Set Standards for Safety

In a novel effort to simplify and speed up safe human stem cell research, Johns Hopkins has set up a "one-stop shop" to preserve, create, supply and test high-quality cell lines for its own researchers now and the greater scientific community later.

The privately funded Stem Cell Resource Center, housed for now within the School of Medicine's Institute for Cell Engineering on the East Baltimore campus, offers streamlined and centralized handling of cell lines and requests to use them and is expected to cut wait times and paperwork substantially, according to Chi V. Dang, M.D., Ph.D., the school's vice dean for research and head of the institute, known as ICE.

In tandem with the opening of the new center, Johns Hopkins appointed an eight-person Embryonic Stem Cell Research Oversight -- ESCRO -- committee modeled on guidelines set forth in 2005 by the National Academies. Similar to institutional review boards that oversee the safety of human subjects in research, the ESCRO committee's charge is to ensure that all human stem cell experiments conducted at the university are safe.

"It's frankly astonishing that no other place has done the much-needed, head-to-head comparison of the existing stem cell lines to fully describe them and make sure they're safe to use," says Dang. "This isn't the 'sexy' part of stem cell work, but it's critical because this research aims at developing stem cell treatment for use in people, and ESCRO is going to make sure to every extent possible that such use at Hopkins is safe."

The center and ESCRO will call on Johns Hopkins experts to screen all cell lines for alterations or mutations that might compromise their quality or signal danger. For example, scientists from Johns Hopkins' McKusick-Nathans Institute of Genetic Medicine and the Center for Epigenetics of the Institute of Basic Biomedical Sciences will examine DNA sequences and chromosomes in each cell line for alterations that look like cancer or other inherited diseases.

Last year, a team led by researchers at the McKusick-Nathans Institute of Genetic Medicine at Johns Hopkins reported that human embryonic stem cell lines accumulate changes in their genetic material over time. Cells grown in the lab longer were worse off, containing the wrong number of chromosomes, changes in the marks that control genes, or changes in the DNA sequence. While the precise effects of these changes aren't known, some resemble those seen in cancer cells. Whether the changes affect the stem cells' abilities to become other cell types also is unknown.

Within the center, experts in the study of genes and their functions (genomics) will develop molecular toolkits for turning on or off genes that coax stem cells to develop into specific cell types, and experts in microscope imaging will create and test better ways to mark the cells so that they can be observed and followed as they grow and develop.

"We're convinced that such services will bring a stunning level of confidence and security to stem cell research at Hopkins, so much so that scientists will be able to work more quickly," Dang says. With plans to apply for funds from Maryland's new stem cell initiative, Dang adds, the center hopes to open its services to non-Hopkins scientists in the state and more widely next year.

Beyond researcher convenience and safety, centralization of services within the center should mean economies of scale that will lead to better use of dollars and time, Dang notes. "These are core operations that can't always be done by a single lab, and now that lab doesn't have to reinvent every wheel to do important work," he says.

The center's scientists also will establish new cell lines and study how they change over time and when or under what conditions they lose genomic integrity, Dang says.

"We know of many researchers who would like to venture into stem cell science but don't in great measure because of the immense bureaucratic burden of paperwork required to gain access to individual cell lines by contract or material transfer agreements," he says. "The center will do all that for the entire university, so that as far as any individual investigator can tell, it will be free access."

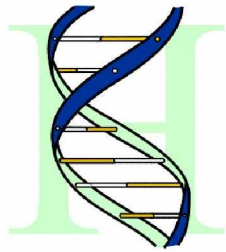
With start-up support from a small portion of a \$100 million anonymous gift to The Johns Hopkins University earlier this year, the center first will store a collection of adult and embryonic stem cell lines, some approved for studies that have federal funding and some not. The center also will keep tabs on the funding used to support research on all the cells it provides to ensure compliance with federal laws.

Human embryonic stem cells are obtained from extra embryos created during in vitro fertilization. Because the cells can become any type of cell in the body, they may one day treat or cure diseases such as Parkinson's disease or type I diabetes. According to policy established by President Bush, only human embryonic stem cell lines created before 9 p.m. ET, Aug. 9, 2001, can be used in federally funded research. The cell lines that currently meet that eligibility requirement are not suitable for use in any future human trials because they were initially grown on mouse cells and therefore might harbor mouse-specific viruses.

As the new center ramps up its services, the new ESCRO committee will set university-wide standards on experiments performed at Johns Hopkins under the leadership of Jeremy Sugarman, M.D., professor in Johns Hopkins' Berman Bioethics Institute, and Carol Greider, Ph.D., the Daniel Nathans Professor and director of molecular biology and genetics in the Institute of Basic Biomedical Sciences and recent winner of the Lasker Award for her work on chromosomes.

On the Web:

<http://www.hopkinsmedicine.org/ice/index.html>



## **FORME JUVENILE DE LA MALADIE DE HUNTINGTON**

### **LE RETARD D'ELOCUTION ET DE LANGAGE**

NEUROLOGY 2006;67:1265–1267 G. Yoon, MD, FRCP(C); J. Kramer, PsyD; A. Zanko, MS; M. Guzijan, MS; S. Lin, MSW; A. Foster-Barber, MD, PhD; and A.L. Boxer, MD, PhD

On estime entre 5% et 7% parmi tous les cas MH, le nombre de malades juvéniles, (typiquement définis comme ayant des symptômes avant 20 ans). Moins d'1% sont diagnostiqués avant 10 ans, et leur état clinique diffère notablement de celui des premières attaques des adultes.

Les caractéristiques connues de la MH Juvénile sont : rigidité, dysfonctionnement moteur oral, troubles du comportement, démence, dysfonctionnement cérébral, peurs et appréhensions.

Les manifestations caractéristiques de la forme juvénile de la MH ne sont pas très bien comprises.

Nous avons étudié trois patients qui ont présenté les symptômes de la MH avant l'âge de 10 ans et dont le premier symptôme était un retard d'élocution. Chez ces enfants, les retards d'élocution ont précédé les symptômes moteurs d'au moins deux ans, et leur langage était réduit à des textes formels.

Il est particulièrement important de détecter les retards d'élocution chez les enfants dont les familles ont des membres atteints par la MH.

**Speech and language delay are early manifestations of juvenile-onset Huntington disease.**

Neurology. 2006 Oct 10;67(7):1265-7.

PMID: 17030763 [PubMed - in process]

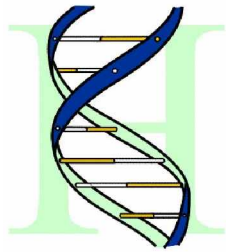
Yoon G, Kramer J, Zanko A, Guzijan M, Lin S, Foster-Barber A, Boxer AL. Division of Medical Genetics, Department of Pediatrics, University of California, San Francisco, CA 94143-1207, USA.

The neurocognitive features of juvenile-onset Huntington disease (HD) are not well understood. We present three patients with onset of HD symptoms before age 10 years in whom speech delay was the first symptom. Speech delay predated motor symptoms by at least 2 years, and language function was consistently impaired on formal testing. Screening for speech delay is particularly important in children with a family history of HD.

Many consider appearance of the first motor symptom to establish onset of JHD, but features such as behavioral problems, dementia, dysarthria, depression, and epilepsy have also been recognized as presenting symptoms. We describe three cases of JHD with onset of clinical symptoms before age 10 years, in whom early speech delay and persistent language deficits were consistent findings (and preceded motor impairment).

Discussion. Speech and language delay is an early feature of JHD that can precede motor symptoms. Speech delay predated motor symptoms by at least 2 years, and language impairments persisted past the onset of other motor and behavioral abnormalities.

These findings highlight the importance of screening for speech delay in children with a family history of HD, as early recognition of speech and language impairment may provide an opportunity for earlier diagnosis and therapeutic intervention for JHD.



*Fédération Huntington Espoir*



## **MECANISMES PATHOGENES DANS LA MALADIE DE HUNTINGTON**

### **MECANISME POSSIBLE POUR LES DOMMAGES DANS LE CERVEAU MH.**

<http://www.sciencedaily.com/releases...1006072450.htm>

Des chercheurs de Mass General Institute (MIND) ont identifié un mécanisme possible soulignant comment la mutation génétique responsable de la MH mène à la dégénération et à la mort de cellules du cerveau. Ils ont montré que la forme anormale de la protéine huntingtine, produit de la mutation, interfère avec la production d'une protéine critique pour le métabolisme énergétique cellulaire.

Cette découverte est la première qui permet de relier deux processus que l'on pense impliqués dans la pathologie de la MH : conversion d'information génétique en protéine et production d'énergie dans les cellules.

Ces travaux montrent (évidence spécifique et mécanismes) que des déficits d'énergie contribuent à la neuro dégénération dans la MH et suggèrent qu'augmenter l'énergie dans le cerveau peut avoir un rôle neuro protecteur. On recherche de nouveaux composés qui peuvent corriger la dérégulation PGC et inverser potentiellement la rupture du métabolisme énergétique dans la MH.

"Our work provides specific, mechanistic evidence that energy deficits contribute to neuro-degeneration in HD and suggests that enhancing energy production in the brain may be neuroprotective. We are beginning to search for new compounds that could correct PGC-1 $\alpha$  dysregulation and potentially reverse the disruption of energy metabolism in HD".

### **Study Identifies Possible Mechanism For Brain Damage In Huntington's Disease**

<http://www.sciencedaily.com/releases...1006072450.htm>

Researchers from the MassGeneral Institute for Neurodegenerative Disease (MIND) have identified a possible mechanism underlying how the gene mutation that causes Huntington's disease (HD) leads to the degeneration and death of brain cells. In the Oct. 6 issue of *Cell*, they show that the abnormal form of the huntingtin protein, the product of the HD gene mutation, interferes with the production of a protein critical to cellular energy metabolism. The discovery is the first to bring together two processes believed to be involved in the pathology of HD -- the conversion of genetic information into proteins and the production of energy within cells.

"Our study indicates that these two pathogenic mechanisms are linked, in that disruption of gene transcription by mutant huntingtin leads to abnormal energy metabolism, which affects energy-dependent cellular processes and results in neurodegeneration," says Dimitri Krainc, MD, PhD, of MIND and the MGH Department of Neurology, who led the research team. "The role of mitochondria [subcellular structures that produce the cells' energy] in the process of nerve cell dysfunction and death is an emerging theme in neurodegenerative disorders, but the mechanism behind HD has been elusive."

HD causes the degeneration and death of cells in the basal ganglia -- an area deep within the brain -- particularly in a structure called the striatum. Although the precise function of the huntingtin protein is still unknown, recent studies have suggested that the mutant form directly interferes with transcription of neuronal genes. Evidence also has pointed to disruptions in cellular energy metabolism as key factors in HD. As a result, the MIND team focused on a protein called PGC-1 $\alpha$ , which is known to regulate energy in cells throughout the body. Their previous research had shown that mice in which the PGC-1 $\alpha$  gene had been knocked out developed brain lesions in the striatum.

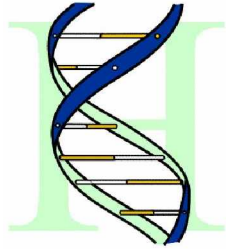
To investigate the possible effect of the HD mutation on PGC-1 $\alpha$ , the researchers first examined brain tissue samples from presymptomatic HD patients and found that levels of the protein were significantly reduced in the portion of the striatum first affected by the disorder. Examination of the brains of PGC-1 $\alpha$  knockout mice found decreased activity in metabolic pathways known to be involved in mitochondrial function -- pathways also downregulated in human HD -- and brain samples from HD patients also showed reduced expression of mitochondrial genes.

Within the striatum HD causes degeneration of medium spiny neurons, the most common cells within the structure. The researchers found that PGC-1 $\alpha$  levels in those particular neurons were much lower among mice with the HD mutation than in normal mice. In contrast, levels of the protein were dramatically higher in striatal cells not affected by HD, suggesting that PGC-1 $\alpha$  may protect against neurodegeneration. Analysis of striatal cells from the HD mice also showed significant underexpression of both PGC-1 $\alpha$  and key mitochondrial genes, further linking decreased protein levels with deficits in energy metabolism.

Additional experiments indicated that mutant huntingtin interferes with the production of PGC-1 $\alpha$  by occupying the regulatory region of the PGC-1 $\alpha$  gene and inhibiting its transcription. Delivery of a viral vector expressing PGC-1 $\alpha$  into the striatum of mice with the HD mutation resulted in significantly less degeneration of neurons that expressed the injected PGC-1 $\alpha$  than of other striatal cells, suggesting that it may be possible to restore the protein's protective effects.

"Our work provides specific, mechanistic evidence that energy deficits contribute to neuro-degeneration in HD and suggests that enhancing energy production in the brain may be neuroprotective. We are beginning to search for new compounds that could correct PGC-1 $\alpha$  dysregulation and potentially reverse the disruption of energy metabolism in HD," says Krainc, who is an assistant professor of Neurology at Harvard Medical School.

Co-authors of the Cell paper are lead author Libin Cui, PhD, Hyunkyung Jeong, MS, and Fran Borovecki, MD, PhD, of MGH Neurology; and Christopher Parkhurst and Naoko Tanese, PhD, of New York University School of Medicine. The research was supported by grants from the National Institutes of Health and a Fulbright fellowship.



## **STRIOSOMES ET DYSFONCTIONNEMENT DE L'HUMEUR DANS LA MH**

Brain. 2006 Oct 17; [Epub ahead of print]

PMID: 17040921 [PubMed - as supplied by publisher]

Tippett LJ, Waldvogel HJ, Thomas SJ, Hogg VM, van Roon-Mom W, Synek BJ, Graybiel AM, Faull RL.

Department of Psychology, The University of Auckland, Auckland, New Zealand.

Dans la maladie de Huntington l'humeur et les symptômes cognitifs s'expriment de façons diverses, accompagnés des symptômes moteurs,.

Il y a aussi une dégénération neuronale aléatoire dans les deux parties du striatum, les striosomes et la partie extrastriosomale.

Pour déterminer si cette variabilité de phénotype dans HD est liée au comportement, nous avons fait une étude en double aveugle sur 35 patients HD, dans laquelle nous avons utilisé un récepteur GABAA pour analyser l'état du striosomes

Résultats: Il existe une relation significative entre les dysfonctionnements de l'humeur et la perte de récepteurs GABAA dans le striosome du striatum.

## **Striosomes and mood dysfunction in Huntington's disease.**

Brain. 2006 Oct 17; [Epub ahead of print]

PMID: 17040921 [PubMed - as supplied by publisher]

Tippett LJ, Waldvogel HJ, Thomas SJ, Hogg VM, van Roon-Mom W, Synek BJ, Graybiel AM, Faull RL.

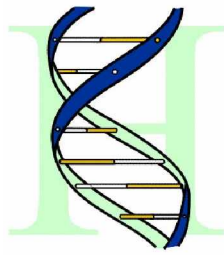
Department of Psychology, The University of Auckland, Auckland, New Zealand.

Variable phenotype is common in neurological disorders with single-gene inheritance patterns. In Huntington's disease, mood and cognitive symptoms are variably co-expressed with motor symptoms. There is also variable degeneration of neurons in the two major neurochemical compartments of the striatum, the striosomes and the extrastriosomal matrix.

To determine whether the phenotypic variability in Huntington's disease is related to this compartmental organization, we carried out a double-blind study in which we used GABAA receptor immunohistochemistry to analyse the status of striosomes and matrix in the brains of 35 Huntington's disease cases and 13 control cases, and collected detailed data on the clinical symptomatology expressed by the patients from family members and records.

We report here a significant association between pronounced mood dysfunction in Huntington's disease patients and differential loss of the GABAA receptor marker in striosomes of the striatum. This association held for both clinical onset and end-stage assessments of symptoms. The cases with accentuated striosome abnormality further exhibited later onset age, lower disease grade and lower CAG repeat length in the HD gene. We found no independent association, however, between CAG repeat length or age of onset and mood dysfunction.

We suggest that variation in clinical symptomatology in Huntington's disease is associated with variation in the relative abnormality of GABAA receptor expression in the striosome and matrix compartments of the striatum, and that striosome-related circuits may modulate mood functioning.



*Fédération Huntington Espoir*



## QUESTIONS ÉTHIQUES

### TESTS GÉNÉTIQUES SUR LES MINEURS

Recensement des politiques à suivre et des positions émises.

Borry P, Stultiens L, Nys H, Cassiman J-J, Dierickx K.  
Clin Genet 2006; 70: 374–381. # Blackwell Munksgaard, 2006 P Borry a, L  
Stultiensa, H Nysa, J-J Cassiman b and K Dierickxa aCentre for Biomedical Ethics  
and Law

L'objectif de cette étude est de passer en revue les aspects éthiques et cliniques ainsi que des positions émises concernant les tests génétiques pré symptomatiques et prédictifs sur les mineurs.

Les données sont extraites de 31 différentes organisations, pour les périodes 1991-2005.

Conclusion : Le bénéfice direct pour le mineur d'un test génétique pré symptomatique et prédictif peut être une intervention médicale ou des mesures préventives. S'il n'y a pas d'urgence médicale, toutes les recommandations convergent vers la remise des tests jusqu'à ce que l'enfant y consente plus tard, en tant qu'adolescent ou adulte.

Il reste une ambiguïté concernant les désordres apparaissant dès l'enfance, pour lesquels des mesures préventives ou thérapeutiques ne sont pas accessibles, et pour le rythme et la durée d'évaluation des premières attaques de la maladie.

Quoique les recommandations concernant les test génétiques pré symptomatiques et prédictifs pour les mineurs s'accordent fortement sur le fait que l'objectif d'amélioration est la principale justification pour effectuer les tests, il subsiste un manque de consensus dans le cas des troubles apparaissant dès la petite enfance et pour lesquels il n'existe pas de traitements préventifs ou thérapeutiques.