ÁREA: NEUROCIENCIAS

Grupos:

Grupo de Neurología

Responsable: José M. Serratosa Fernández
IP: Marina Sánchez García
Investigación: Básica y Clínica

Grupo de Psiquiatría y Salud Mental

Responsable: Enrique Baca García
Investigación: Clínica

Grupo de Señalización Mitocondrial del Calcio

Responsable: Jorgina Satrústegui Gil-Delgado
Investigación: Básica

III REUNIÓN ANUAL DEL ÁREA DE NEUROCIENCIAS DEL IIS-FJD

(8 de junio 2021)

Nos complace invitarles a la sesión del Área de NEUROCIENCIAS del Instituto de Investigación Sanitaria Fundación Jiménez Díaz, que se celebrará el día 8 de junio del 2021 mediante la plataforma Microsoft Teams.

PROGRAMA Y PRESENTACIONES:

14:00 – 14:05: Presentación de la jornada y moderación
José María Serratosa Fernández / Enrique Baca García

14:05 – 14:15:
Título: "Enfermedad de Huntington".
Ponente: Pedro García Ruiz-Espiga
Grupo: Neurología

14:15 – 14:25:
Título: "Enfermedad de Lafora".
Ponente: José María Serratosa Fernández
Grupo: Neurología

14:25 – 14:35:
Título: "Correlaciones clínico-genéticas en demencias familiares".
Ponente: Estrella Gómez Tortosa
Grupo: Neurología

14:35 – 14:45:
Título: "Esclerosis Múltiple".
Ponente: Irene Pilar Moreno Torres
Grupo: Neurología

14:45 – 14:55:
Título: "Monitorización de conducta".
Ponente: Alejandro Porras Segovia
Grupo: Psiquiatría y Salud Mental

14:55 – 15:05:
Título: "Papel fisiopatológico de Aralar/AGC1, el transportador mitocondrial de aspartato-glutamato, en cerebro".
Ponente: Beatriz Pardo Merino
Grupo: Señalización Mitocondrial del Calcio

15:05 – 15:10: DISCUSIÓN Y PREGUNTAS.

15:10: Clausura de la jornada.

Av. Reyes Católicos, 2. Madrid-28040 NIF: G 85874949 www.iis-fjd.es

ÁREA: NEUROCIENCIAS

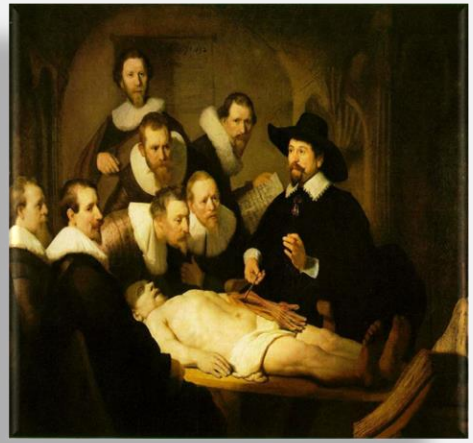
ENFERMEDAD DE HUNTINGTON AVANCES Y ESPERANZAS

Pedro J. Garcia Ruiz-Espiga

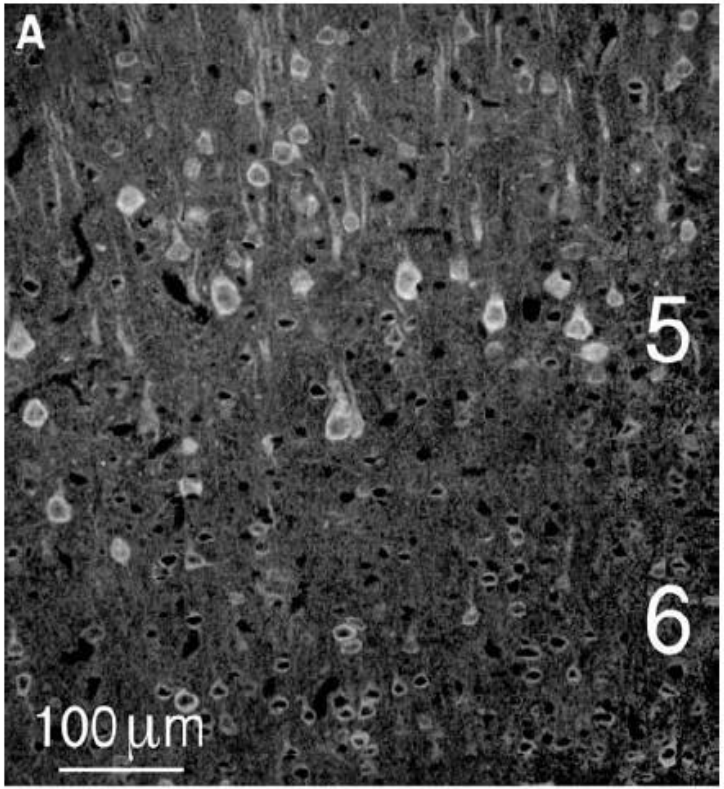
Unidad de Trastornos del Movimiento

Servicio de Neurología

Fundación Jiménez Díaz



III REUNIÓN ANUAL DEL ÁREA DE NEUROCIENCIAS DEL IIS-FJD
8 de junio del 2021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Clinical Neuropharmacology
Vol. 18, No. 1, pp. 58–63

Cerebrospinal Fluid Homovanillic Acid Is Reduced in Untreated Huntington's Disease

P. J. García Ruiz, †M. A. Mena, V. Sanchez Bernardos, W. Díaz Neira, ‡S. Gimenez Roldan, *J. Benitez, and J. García de Yebenes

*Departments of Neurology and *Genetics, Fundación Jimenez Díaz; †Research Laboratory, Centro Ramón y Cajal; and ‡Department of Neurology, Hospital Gregorio Marañon, Madrid, Spain*

Summary: We measured homovanillic acid (HVA), 5-hydroxy indole acetic acid (5-HIAA), and tryptophan (TP) in cerebrospinal fluid (CSF) of 20 neuroleptic-free patients with Huntington's disease (HD), and compared mean values with those from four control groups including 15 normal individuals, 38 patients with dystonia, 23 untreated patients with Parkinson's disease, and 61 patients with other neurological diseases (ONDs). The mean levels of HVA in the CSF of patients with HD were reduced compared with those from normal controls ($p < 0.001$), dystonic patients ($p < 0.005$), individuals with ONDs ($p < 0.0001$), and even from untreated parkinsonian patients ($p < 0.05$). 5-HIAA and TP levels in the CSF of patients with HD were not significantly different from those in the CSF of control patients. Our data suggest a reduced dopamine neurotransmission in HD and may account for the bradykinesia observed in our patients. **Key Words:** Huntington's disease—Cerebrospinal fluid—Homovanillic acid—5-Hydroxy indole acetic acid—Tryptophan.

Journal of the Neurological Sciences 362 (2016) 115–117

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Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Reaction time and rhythm of movement in Huntington's disease

A. Martínez Pueyo *, P.J. García-Ruiz, C.E. Feliz, J. Garcia Caldentey, J. Del Val, A. Herranz

Department of Neurology, Fundación Jiménez Díaz, Madrid, Spain

ARTICLE INFO

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Self pace timing precision
Hand tapping
Cognitive tests
Stroop test

ABSTRACT

Huntington disease (HD) is characterized by several hyperkinesias though motor slowness is also another cardinal in this disease. In addition, self-paced timing movements are also disturbed in HD, which may also affect several rhythmic voluntary movements such as gait. Motor slowness can be measured with clinical scales such as the Unified Huntington's Disease Rating Scale (UHDRS) and timed tests, but also with the reaction time (RT) paradigm.

We evaluated RT as a measure of motor slowness in 30 patients with genetically confirmed Huntington's disease and 24 control subjects. We also evaluated self-paced timing precision (SPTP) by applying a simple software program devised by our group. Clinical assessment was performed according to the UHDRS, including motor section, total functional capacity (TFC) and cognitive section (verbal fluency test, symbol digit, and Stroop test)

The mean values obtained for RT and SPTP were statistically different in HD as compared with those from controls ($p < 0.0005$). We observed a statistically significant correlation between RT and TFC scores ($rs = -0.57$, $p < 0.005$ Spearman's correlation) and also between SPTP values and TFC scores ($rs = -0.40$, $p < 005$ Spearman's correlation). In addition, RT and SPTP significantly correlated with cognitive scores (including digit symbol, verbal fluency and Stroop tests).

Simple tests such as RT and SPTP provide an objective evaluation of motor impairment in HD yielding measures that correlate with clinical assessment and functional disability.

Nervenarzt 2001 · 72:437–440 © Springer-Verlag 2001

Originalien

P. Garcia Ruiz[1] · A. Fontán[1] · C. Cenjor[2] · E. Ulmer[3] · E. Gomez Tortosa[1] · R. Sanchez Pernaute[1] · A. Rojo[1] · J. García de Yébenes[1]

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Störung der Blicksakkaden bei der Huntington-Krankheit

Klinische Korrelationen

Zusammenfassung

Störungen der Okulomotorik sind bei der Huntington-Krankheit (HK) seit langem beschrieben worden. Über die genauere Korrelation zwischen okulomotorischen Störungen und klinischen Verlaufsformen ist jedoch wenig bekannt. Wir haben die Blicksakkaden bei 32 Huntington-Patienten mit molekulargenetisch gesicherter HK untersucht. Sie gliederten sich in 3 Gruppen: 6 Patienten mit juveniler HK (YOHD), 19 mit adulter HK (ADHD) und 7 mit spät beginnender HK (LOHD). Im Vergleich zur Kontrollgruppe zeigten die Sakkaden der HK-Patienten eine Zunahme der Latenz ($p<0,05$), eine Abnahme der Geschwindigkeit ($p<0,0005$) und eine verminderte Zielsicherheit ($p<0,01$). Dabei konnte zwischen den verschiedenen Gruppen der Erkrankten eine statistisch signifikante Differenz der Parameter festgestellt werden: YOHD war charakterisiert durch eine normale Latenz und verminderte Geschwindigkeit, während bei LOHD die Latenz verlängert war bei normaler Geschwindigkeit. Ferner wurden bei der HK eine signifikante Korrelation zwischen Sakkadenparametern und genetischen Daten (Expansion des CAG-repeats) gefunden.

Schlüsselwörter

Huntington-Krankheit · Blicksakkaden · Videonystagmographie

Okulomotorische Störungen sind bei der Huntington-Krankheit (HK) schon seit langem bekannt. Speziell die Blicksakkaden wurden oft mit verschiedenen Methoden [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11] untersucht. Es ist bekannt, dass die Latenz bzw. Reaktionszeit für Zielsakkaden verlängert ist, die Geschwindigkeit verlangsamt und die Sakkade hypometrisch [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11]. Noch nicht untersucht wurde eine allfällige Korrelation zwischen okulomotorischen Störungen und klinischer Verlaufsform der Erkrankung. Zur Erforschung einer derartigen Korrelation haben wir bei 32 Patienten mit HK verschiedene Sakkadenparameter untersucht.

Patienten

Untersucht wurden 32 Patienten mit molekulargenetisch gesicherter HK (9 Frauen, 23 Männer). Dabei handelte es sich um 6 Patienten mit juveniler HK („young onset Huntington's disease" *YOHD*), 19 Patienten mit adulter HK („adult onset Huntington's disease" *AOHD*) und 7 mit später Erkrankungsbeginn („late Onset Huntington's disease" *LOHD*). Die klinische Daten sind aus der Tabelle 1 ersichtlich. Die Patienten wurden nach dem CAPIT-HD-Protokoll [12] klinisch untersucht; die Stadieneinteilung erfolgte gemäß Capit-HD und Shoulhslon-Skala [13]. 16 gesunde Freiwillige ähnlichen Alters bildeten die Kontrollgruppe.

Methode

Zielsakkaden (rasche, in Richtung, Amplitude und Geschwindigkeitverlauf vorprogrammierte konjugierte Augenbewegungen, die dem Erfassen neuer Sehobjekte dienen) wurden mittels Videonystagmographie [14, 15, 16] mit dem von Ulmer entwickelten Instrument gemessen. Eines der beiden Augen („Sklave") wurde mit einer CDD-Infrarotkamera (mit einer Sensitivität von <1 lux und einer Auflösung von >300.000 pixel) aufgenommen, während das andere Auge („Master") einen Zielpunkt fixieren musste. Grundsätzlich war das rechte Auge der „Master", das linke der „Sklave". Der visuelle Stimulus war ein weißer Punkt auf einem Monitor (36 cm Kantenlänge) in einer Entfernung von 128 cm vom Probanden. Die Untersuchungen wurden im Halbdunkeln durchgeführt. Die Probanden wurden informiert, dass der Zielpunkt springen wird und dass sie diesem so genau wie möglich folgen sollen. Wir untersuchten insgesamt 20 horizontale Sakkaden bei jedem Patient, hervorgerufen durch einen erwarteten Wechsel des Zielpunktes (20°-Sprung in bestimmten zeitlichen Intervall) und einen unerwarteten Zielwechsel (Sprung in unregelmäßiger

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Clinical Neuropharmacology
Vol. 23, No. 1, pp. 50–52

Bradykinesia in Huntington's Disease

Pedro J. Garcia Ruiz, Estrella Gomez Tortosa, Vicenta Sanchez Bernados, Ana Rojo, Aurora Fontán, and Justo Garcia de Yebenes

Department of Neurology, Fundacion Jimenez Diaz, Madrid, Spain

Huntington's disease (HD) is characterized by the presence of hyperkinesias, but bradykinesia is also present in most patients. We studied the motor performance of 18 patients with genetically proven HD (age, 38.5 ± 10 y; clinical stage, 1.7 ± 1.7; (CAG) triplet length, 49.2 ± 6.8 triplets; all but three patients were free from neuroleptics) and compared with a control group (n = 18) and with a typical Parkinson's disease (PD) group (n = 20). Motor study included the four timed tests commonly used for PD : Pronation-supination (PS), finger dexterity (FD), movement between two points (MTP) and walking test (WT). Tests were done at 9 AM. The PD group was studied in "off" condition, with no medication given for 12 hours. The HD group was slower than the controls on all tasks (all tests significant, $p < 0.01$, Mann-Whitney U test) and even slower than PD group (for FD, $p < 0.05$). A significant correlation was found between each test and clinical stage (for PS, r = 0.84; for FD, r = 0.75; for MTP, r = 087, and for WT, r = 0.77, Pearson). Severe bradykinesia was present in HD, and motor impairment is related to clinical stage. **Key Words:** Huntington's disease—Bradykinesia—Motor performance

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ORIGINAL COMMUNICATION

Pedro J. García Ruiz
Jaime Hernández
Susana Cantarero
Manuel Bartolomé
Vicenta Sánchez Bernardos
Justo García de Yébenes

Bradykinesia in Huntington's disease. A prospective, follow-up study

Abstract Bradykinesia is a frequent finding in Huntington's disease (HD), but some aspects are presently unknown; including the natural evolution of bradykinesia over time and the correlation between bradykinesia and functional capacity.

We studied the motor performance of 20 genetically confirmed patients with HD (age: 40±10.8 years; age at onset 33.6±11 years; total functional capacity (TFC): 9.57±3; UHDRS total motor scale: 31.4±13, triplet length (CAG)n: 46.7±4 triplets).These patients were studied in baseline conditions and after 18.7±6 months of follow-up. In addition, HD patients were compared with 20 age-matched normal controls. Motor study included the four CAPIT timed tests commonly used for Parkinson's disease:

occurred over time in three of the four motor tasks (especially FD and WT). A significant correlation between timed tests and TFC score was found (for MTP, r: –0.845; p < 0,0001). In addition a significant correlation between timed tests and the UHDRDS total motor scale was also found (for MTP, r: 0.864; p < 0.0001)

In conclusion, simple timed motor tests can detect a deterioration of motor activity over time in HD. Timed tests might be useful to follow the natural evolution of HD

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Received in revised form: 7 August 2001
Accepted: 20 August 2001

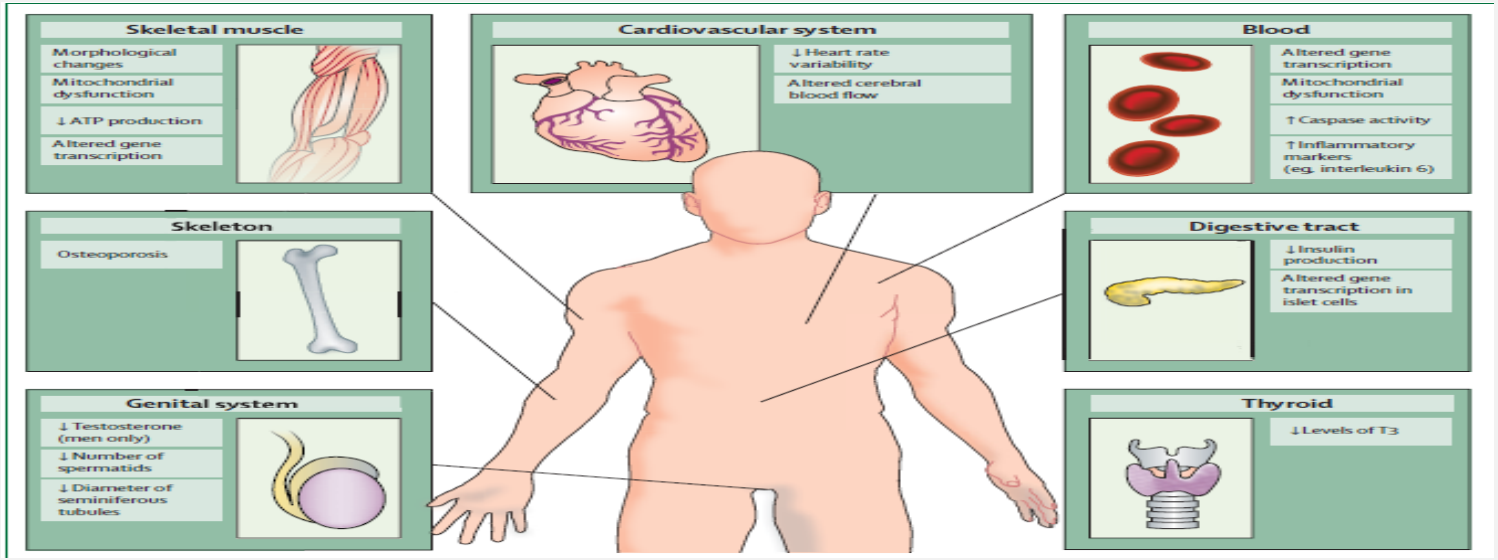
Dr. P. J. García Ruiz (✉) · J. Hernández ·

Beyond the brain: widespread pathology in Huntington's disease

Jorien MM van der Burg, Maria Björkqvist, Patrik Brundin

Lancet Neurol 2009; 8: 765–74

Huntington's disease (HD) is an inherited neurodegenerative disorder caused huntingtin protein. Today, more than 15 years after the genetic defect underlying is still not well understood and there is no adequate treatment. Research into this disorder has conventionally focused on neurological symptoms and brain pathology, particularly neurodegeneration in the basal ganglia and cerebral cortex. Mutant huntingtin is, however, ubiquitously expressed throughout the body. Indeed, contrary to earlier thinking, HD is associated with abnormalities in peripheral tissues. These abnormal changes are not all secondary to brain dysfunction, but most seem to be directly caused by expression of mutant huntingtin in peripheral tissues. In this article, we highlight this emerging field of research and how it might affect our understanding of the pathogenesis of this disease, the development of novel biomarkers of disease progression, and the identification of new potential treatments.



Desde hace años se sabe que la Huntingtina posee multiples funciones y parece importante en la fisiologia general porque la EH es una enfermedad multisistémica

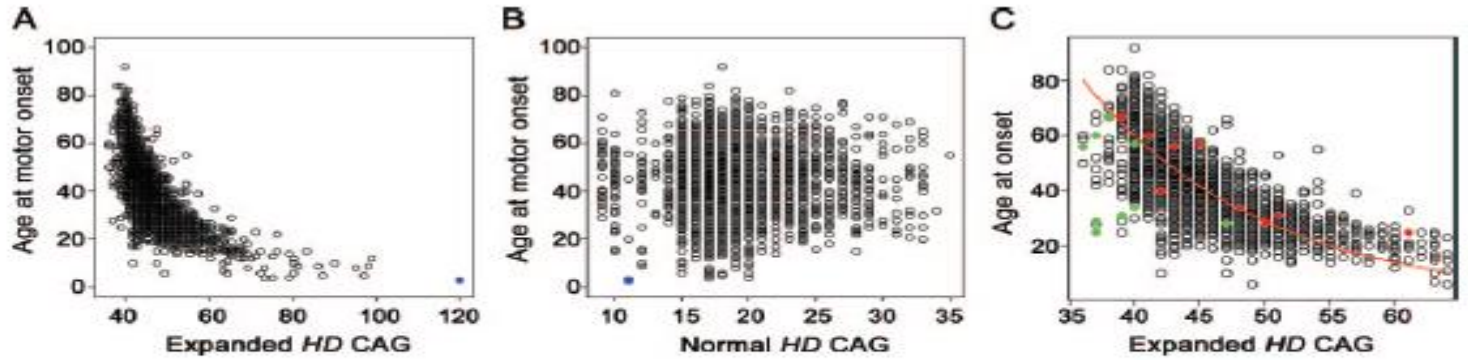
ARTICLES

CAG repeat expansion in Huntington disease determines age at onset in a fully dominant fashion

J.-M. Lee, PhD
E.M. Ramos, BSc
J.-H. Lee, PhD
T. Gillis, BS
J.S. Mysore, BSc
M.R. Hayden, MD, PhD
S.C. Warby, PhD
P. Morrison, MD
M. Nance, MD
C.A. Ross, MD, PhD
R.L. Margolis, MD
E. Squitieri, MD, PhD

ABSTRACT

Objective: Age at onset of diagnostic motor manifestations in Huntington disease (HD) is strongly correlated with an expanded CAG trinucleotide repeat. The length of the normal CAG repeat allele has been reported also to influence age at onset, in interaction with the expanded allele. Due to profound implications for disease mechanism and modification, we tested whether the normal allele, interaction between the expanded and normal alleles, or presence of a second expanded allele affects age at onset of HD motor signs.



An initial regression model was generated using all 4,068 subjects with Huntington disease (HD), each heterozygous for 1 expanded allele (>35 CAG) and 1 allele in the normal range (<36 CAG). (A) The relationship between expanded allele CAG repeat length and age at onset of motor signs. (B) The relationship between normal allele CAG repeat length and age at onset of motor signs. Filled blue circle: a subject with 120 CAGs with a disproportionate influence on the model. (C) Subjects with 2 expanded alleles (>35 CAGs) were plotted (filled red circle: longer expanded allele; green: shorter expanded allele) over the heterozygote subsample conforming to statistical assumptions underlying regression analysis (3,674 HD subjects based upon expanded CAGs from 40–53 and statistical exclusion of outliers; see figures e-3, e-4, and e-5). One homozygous subject has 2 equal alleles of 42 CAGs. The minimal adequate model for this heterozygote data set is shown as a red line.

Desde 1993 ya se conocía la expansión anormal en el gen de la EH

Human Molecular Genetics, 2003, Vol. 12, No. 24 **3359–3367**
DOI: 10.1093/hmg/ddg352

Dramatic tissue-specific mutation length increases are an early molecular event in Huntington disease pathogenesis

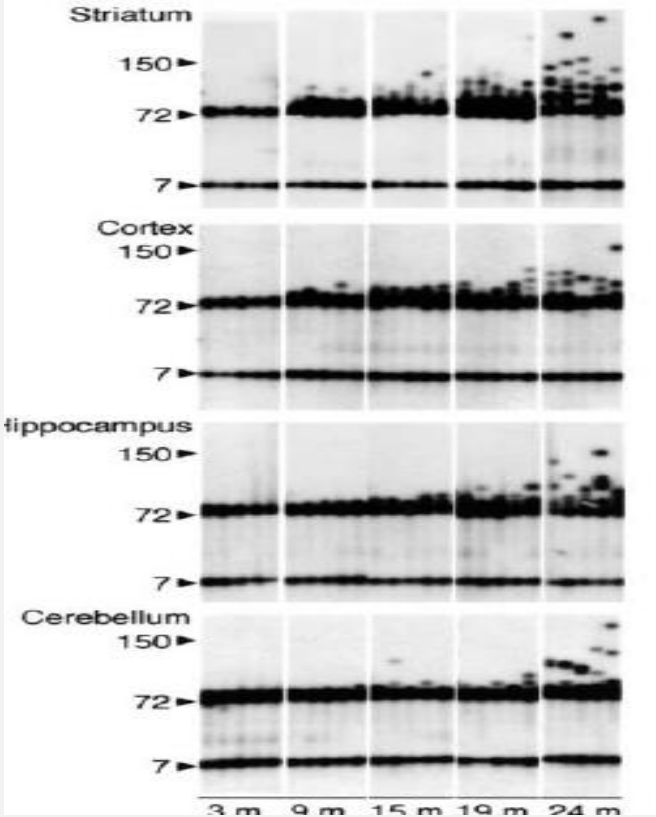
Laura Kennedy[1], Elizabeth Evans[1], Chiung-Mei Chen[1], Lyndsey Craven[1], Peter J. Detloff[2], Margaret Ennis[1] and Peggy F. Shelbourne[1,*]

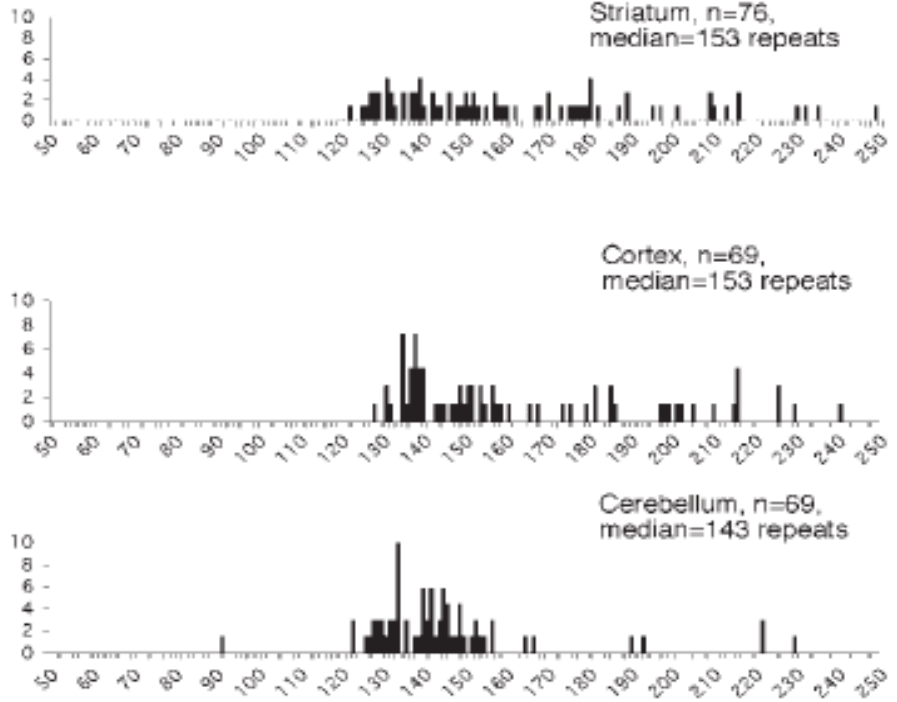
[1]Division of Molecular Genetics, Faculty of Biomedical and Life Sciences, University of Glasgow, Glasgow G11 6NU, UK and [2]Department of Biochemistry and Molecular Genetics, University of Alabama at Birmingham, 720 20th Street South, Birmingham, Alabama, USA

Received August 26, 2003; Revised September 29, 2003; Accepted October 13, 2003

Huntington disease is caused by the expansion of a CAG repeat encoding an extended glutamine tract in a protein called huntingtin. Although the mutant protein is widely expressed, the earliest and most striking neuropathological changes are observed in the striatum. Here we show dramatic mutation length increases (gains of up to 1000 CAG repeats) in human striatal cells early in the disease course, most likely before the onset of pathological cell loss. Studies of knock-in HD mouse models indicate that the size of the initial CAG repeat mutation may influence both onset and tissue-specific patterns of age-dependent, expansion-biased mutation length variability. Given that CAG repeat length strongly correlates with clinical severity, we suggest that somatic increases of mutation length may play a major role in the progressive nature and cell-selective aspects of both adult-onset and juvenile-onset HD pathogenesis and we discuss the implications of this interpretation of the data presented.

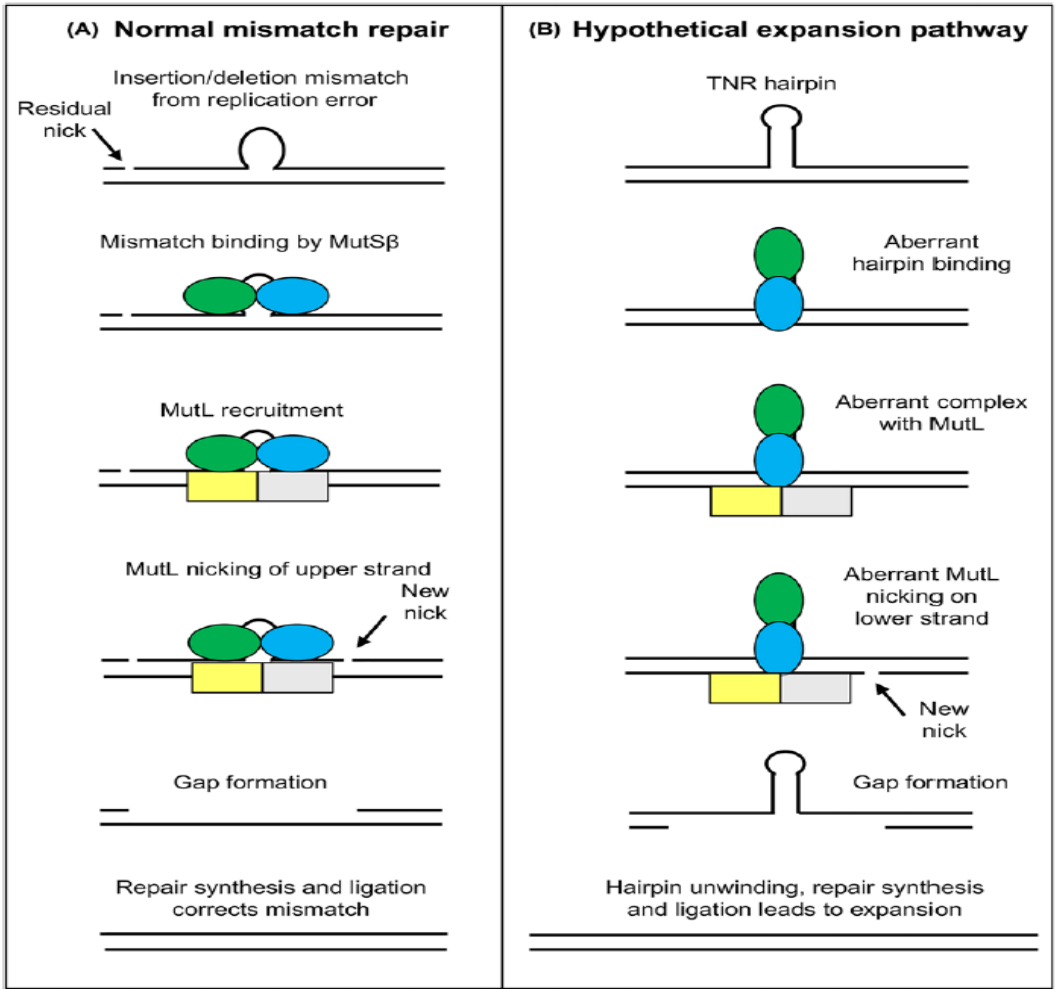
Dramatic tissue-specific mutation length increases are an early molecular event in Huntington disease pathogenesis





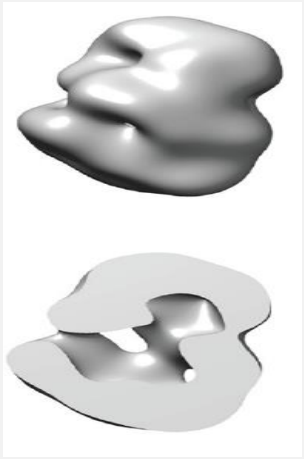
Neuronal Signaling (2020) **4** NS20200010
https://doi.org/10.1042/NS20200010

PORTLAND PRESS

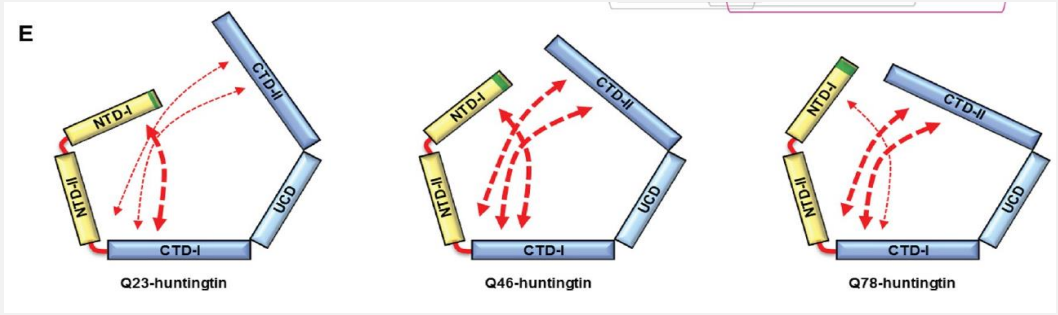


Huntingtin's spherical solenoid structure enables polyglutamine tract-dependent modulation of its structure and function

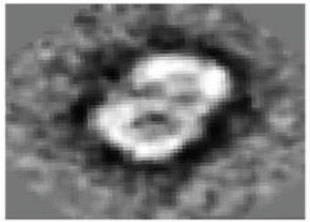
Ravi Vijayvargia[1,2†], Raquel Epand[3], Alexander Leitner[4], Tae-Yang Jung[5,6,7], Baehyun Shin[1,2], Roy Jung[1,2], Alejandro Lloret[1,2‡], Randy Singh Atwal[1,2], Hyeongseok Lee[5], Jong-Min Lee[1,2], Ruedi Aebersold[4,8], Hans Hebert[6,7], Ji-Joon Song[5]*, Ihn Sik Seong[1,2]*



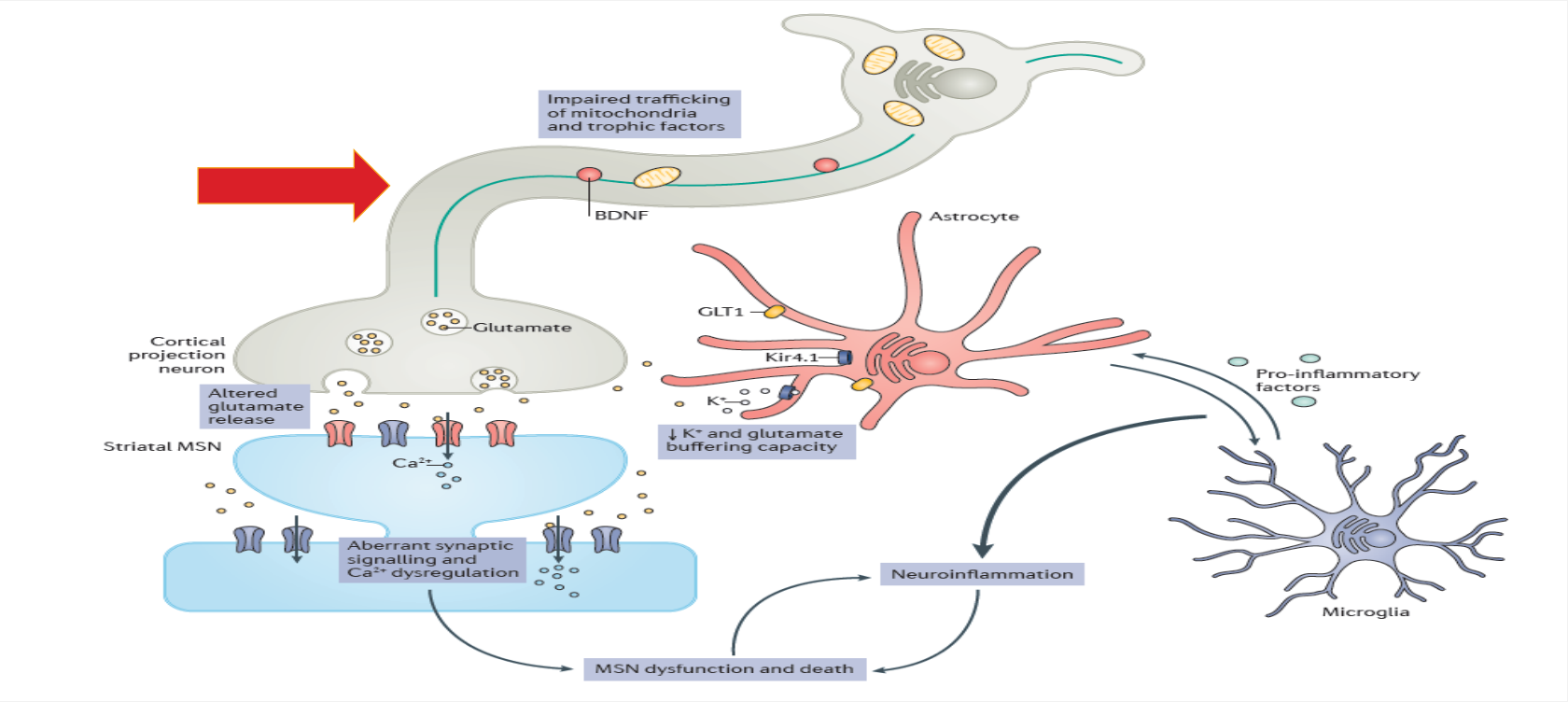
Vijayvargia *et al*. eLife 2016;5:e11184. DOI: 10.7554/eLife.11184



Q23-huntingtin



La Huntingtina (HTW) es una proteina de >3100 aminoacidos plegada en forma de ovillo con hueco central. La expansion CAG es filogeneticamente nueva y ocupa la cola de proteina…



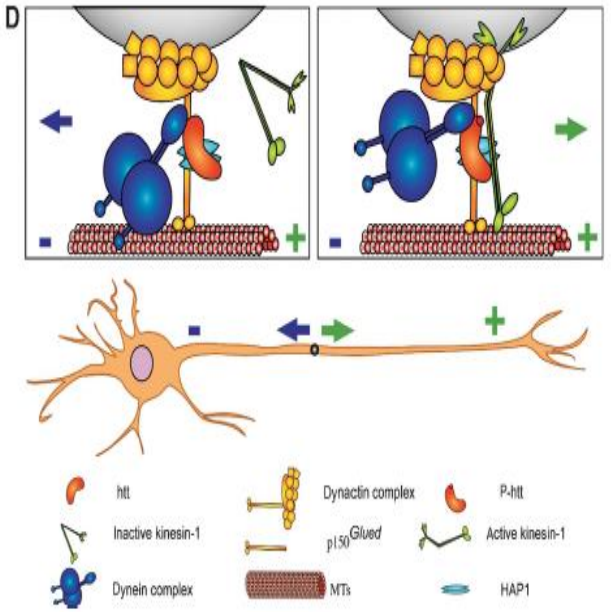
La WHT actúa en embriogénesis y en el desarrollo cerebral…y posteriormente en labores de mantenimiento neuronal…y no neuronal a múltiples niveles…

Huntingtin phosphorylation acts as a molecular switch for anterograde/retrograde transport in neurons

Emilie Colin[1,2,4], Diana Zala[1,2,4], Géraldine Liot[1,2], Hélène Rangone[1,2,5], Maria Borrell-Pagès[1,2,6], Xiao-Jiang Li[3], Frédéric Saudou[1,2,*] and Sandrine Humbert[1,2,*]

The EMBO Journal (2008) 27, 2124–2134

The transport of vesicles in neurons is a highly regulated process, with vesicles moving either anterogradely or retrogradely depending on the nature of the molecular motors, kinesins and dynein, respectively, which propel vesicles along microtubules (MTs). However, the mechanisms that determine the directionality of transport remain unclear. Huntingtin, the protein mutated in Huntington's disease, is a positive regulatory factor for vesicular transport. Huntingtin is phosphorylated at serine 421 by the kinase Akt but the role of this modification is unknown. Here, we demonstrate that phosphorylation of wild-type huntingtin at S421 is crucial to control the direction of vesicles in neurons. When phosphorylated, huntingtin recruits kinesin-1 to the dynactin complex on vesicles and MTs. Using brain-derived neurotrophic factor as a marker of vesicular transport, we demonstrate that huntingtin phosphorylation promotes anterograde transport. Conversely, when huntingtin is not phosphorylated, kinesin-1 detaches and vesicles are more likely to undergo retrograde transport. This also applies to other vesicles suggesting an essential role for huntingtin in the control of vesicular directionality in neurons.



La HTW actúa en todos los aspectos de transporte general axónico

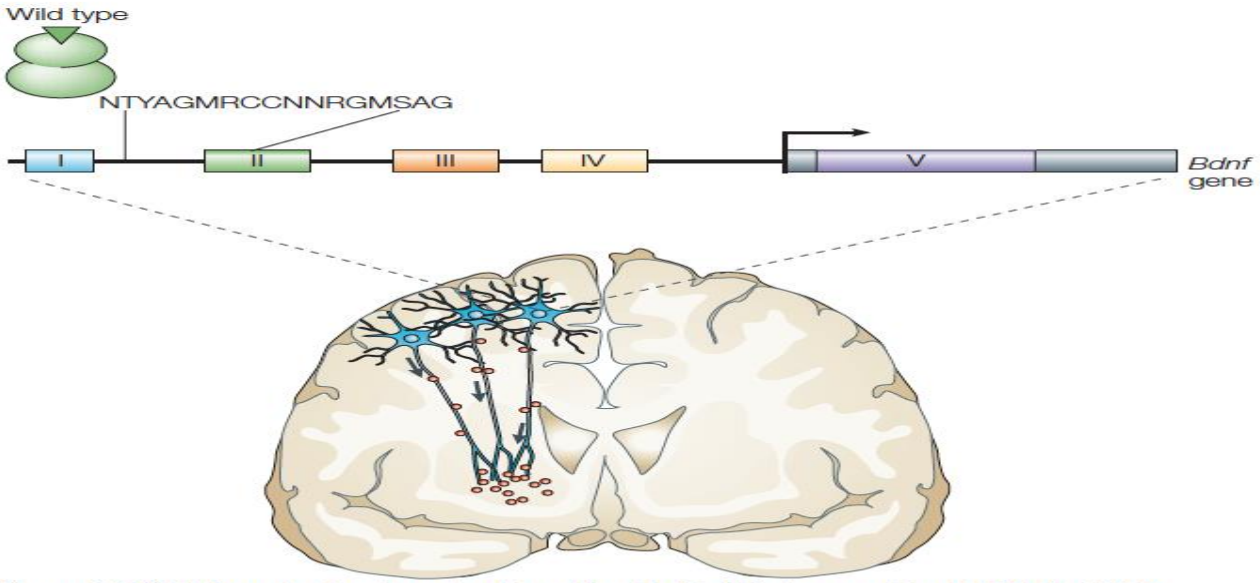


Figure 3 | **Wild-type but not mutant huntingtin facilitates cortical BDNF mRNA production.** Wild-type huntingtin contributes to brain-derived neurotrophic factor (*Bdnf*) transcription in the cortical neurons that project to the striatum by inhibiting the Repressor element 1/neuron-restrictive silencer element (RE1/NRSE) that is located in BDNF promoter exon II. I–IV indicate BDNF promoter exons in rodent *Bdnf*; V indicates the coding region. The RE1/NRSE consensus sequence is shown. Inactivation of the RE1/NRSE in *Bdnf* leads to increased mRNA transcription and protein production in the cortex. BDNF, which is also produced through translation from exons III and IV is then made available to the striatal targets via the cortico-striatal afferents. Wild-type huntingtin might also facilitate vesicular BDNF transport from the cortex to the striatum.

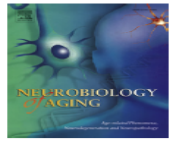
La HTW facilita la transcripción de **BDNF cortical y su traslado retrogrado a GB**

Neurobiology of Aging 84 (2019) 131–140

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging



Retrograde axonal transport of BDNF and proNGF diminishes with age in basal forebrain cholinergic neurons

Arman Shekari, Margaret Fahnestock*

Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, Ontario, Canada

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Neurotrophins
Neurodegeneration
Basal forebrain
Alzheimer's disease
Trk receptors

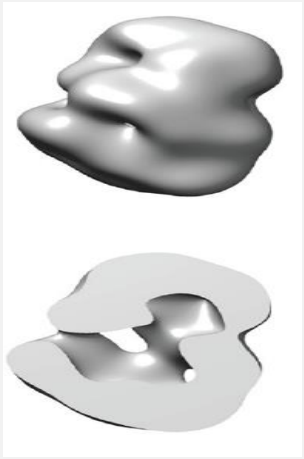
ABSTRACT

Basal forebrain cholinergic neurons (BFCNs) are critical for learning and memory and degenerate early in Alzheimer's disease (AD). BFCNs depend for their survival and function on nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), which are retrogradely transported from BFCN targets. Age is the greatest risk factor for developing AD, yet the influence of age on BFCN axonal transport is poorly understood. To model aging, embryonic rat basal forebrain or cortical neurons were cultured in microfluidic chambers. Senescence-associated beta-galactosidase staining indicated an aging phenotype only in BFCNs cultured for 18+ days in vitro. BDNF axonal transport impairments were observed exclusivley in aged BFCNs. BFCNs displayed robust proNGF transport, which also diminished with in vitro age. The expression of NGF receptor tropomyosin-related kinase-A and BDNF receptor tropomyosin-related kinase-B also decreased significantly with in vitro age in BFCNs only. These results suggest a unique vulnerability of BFCNs to age-induced transport deficits. These deficits, coupled with the reliance of BFCNs on neurotrophin transport, may explain their vulnerability to age-related neurodegenerative disorders like AD.

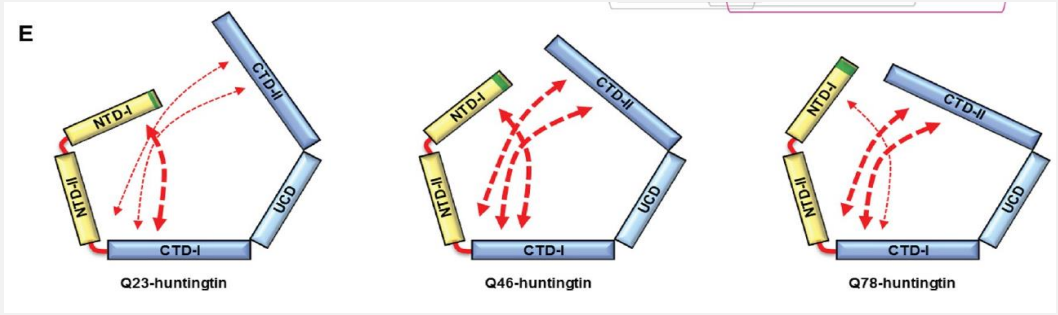
El transporte retrogrado de BDNF es crucial para la supervivencia neuronal…

Huntingtin's spherical solenoid structure enables polyglutamine tract-dependent modulation of its structure and function

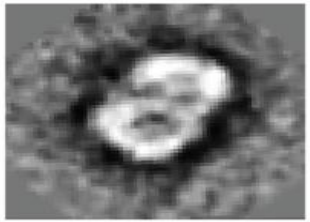
Ravi Vijayvargia[1,2†], Raquel Epand[3], Alexander Leitner[4], Tae-Yang Jung[5,6,7], Baehyun Shin[1,2], Roy Jung[1,2], Alejandro Lloret[1,2‡], Randy Singh Atwal[1,2], Hyeongseok Lee[5], Jong-Min Lee[1,2], Ruedi Aebersold[4,8], Hans Hebert[6,7], Ji-Joon Song[5]*, Ihn Sik Seong[1,2]*



Vijayvargia *et al*. eLife 2016;5:e11184. DOI: 10.7554/eLife.11184



Q23-huntingtin



La expansión de CAG en un terminal de la proteína altera su estructura, la proteína es mas rígida y se degrada de forma anómala….

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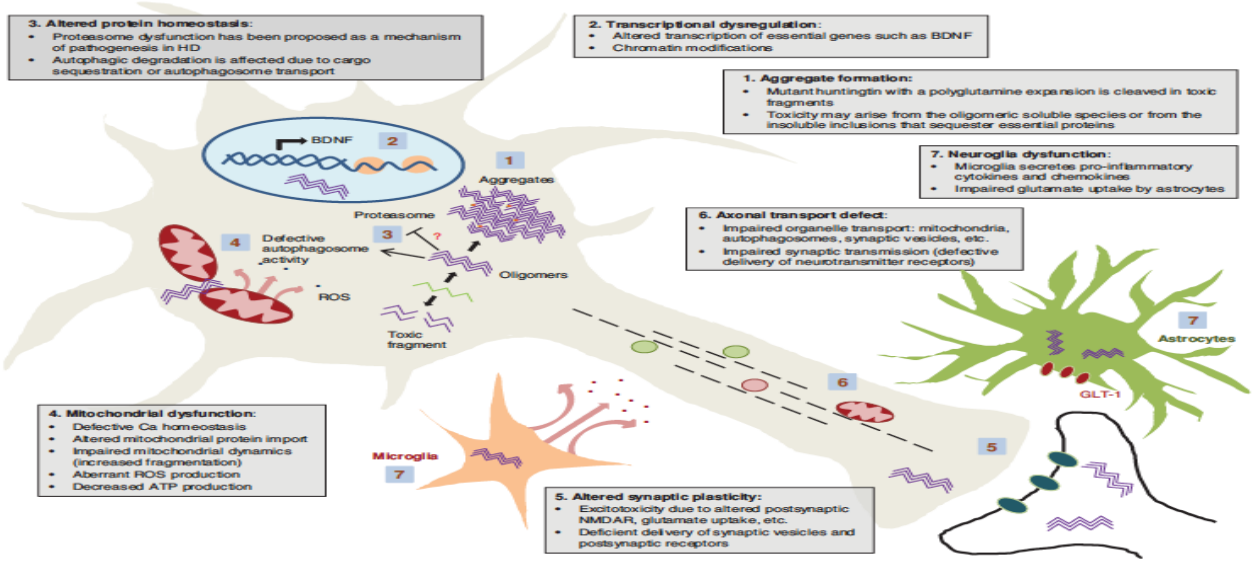

Figure 1. Schematic of selected mechanisms of pathogenesis in Huntington's disease (HD). BDNF, Brain-derived neurotrophic factor; ROS, reactive oxygen species; NMDAR, *N*-methyl-D-aspartate receptor.

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La Huntingtina mutada afecta muchos procesos conocidos

6298 • The Journal of Neuroscience, April 10, 2013 • 33(15):6298 – 6309

Neurobiology of Disease

Mutant Huntingtin Alters Retrograde Transport of TrkB Receptors in Striatal Dendrites

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Huntingtin (HTT), the protein mutated in Huntington's disease (HD), controls transport of the neurotrophin, brain-derived neurotrophic factor (BDNF), within corticostriatal neurons. Transport and delivery of BDNF to the striatum are reduced in disease, which contributes to striatal neuron degeneration. BDNF released by cortical neurons activates TrkB receptors at striatal dendrites to promote striatum survival. However, it remains to be determined whether transport of TrkB, the BDNF receptor, depends on HTT and whether such transport is altered in mutant situation. Here we show that TrkB binds to and colocalizes with HTT and dynein. Silencing HTT reduces vesicular transport of TrkB in striatal neurons. In HD, the polyQ expansion in HTT alters the binding of TrkB-containing vesicles to microtubules and reduces transport. Using a combination of microfluidic devices that isolate dendrites from cell bodies and BDNF coupled to quantum dots, we selectively analyzed TrkB retrograde transport in response to BDNF stimulation at dendrite terminals. We show that the retrograde transport of TrkB vesicles within striatal dendrites and the BDNF/TrkB-induced signaling through ERK phosphorylation and c-fos induction are decreased in neurons from an HD mouse model. Together, our findings demonstrate that HTT is a crucial regulator of TrkB trafficking. Transport defects in HD are not restricted to BDNF transport in cortical neurons but also affect trafficking of its ligand-bound receptor in the striatal neurons. This transport alteration may further impair BDNF-TrkB survival signaling within the corticostriatal connection that is most affected in HD.

Pero singularmente el transporte de factores neurotroficos…

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Brain-derived Neurotrophic Factor Over-expression in the Forebrain Ameliorates Huntington's Disease Phenotypes in Mice

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Abstract

Huntington's disease (HD), a dominantly inherited neurodegenerative disorder characterized by relatively selective degeneration of striatal neurons, is caused by an expanded polyglutamine tract of the huntingtin protein. The huntingtin mutation reduces levels of brain-derived neurotrophic factor (BDNF) in the striatum, likely by inhibiting cortical BDNF gene expression and anterograde transport of BDNF from cortex to striatum. However, roles of the BDNF reduction in HD pathogenesis have not been established conclusively. We reasoned that increasing striatal BDNF through overexpression would slow progression of the disease if BDNF reduction plays a pivotal role in HD pathogenesis. We employed a *Bdnf* transgene driven by the promoter for the alpha subunit of Ca^{2+}/calmodulin-dependent kinase II to overexpress BDNF in the forebrain of R6/1 mice which express a fragment of mutant huntingtin with a 116-glutamine tract. The *Bdnf* transgene increased BDNF levels and TrkB signaling activity in the striatum, ameliorated motor dysfunction, and reversed brain weight loss in R6/1 mice. Furthermore, it normalized DARPP-32 expression, increased the number of enkephalin-containing boutons, and reduced formation of neuronal intranuclear inclusions in the striatum of R6/1 mice. These results demonstrate crucial roles of reduced striatal BDNF in HD pathogenesis and suggest potential therapeutic values of BDNF to HD.

…Y la super-expresión de BDNF podría ser un tratamiento potencial

Targeting Huntingtin Expression in Patients with Huntington's Disease

Sarah J. Tabrizi, M.B., Ch.B., Ph.D., Blair R. Leavitt, M.D., C.M., G. Bernhard Landwehrmeyer, M.D., Edward J. Wild, M.B., B.Chir., Ph.D., Carsten Saft, M.D., Roger A. Barker, M.R.C.P., Ph.D., Nick F. Blair, M.B., B.S.,* David Craufurd, M.B., B.S., Josef Priller, M.D., Hugh Rickards, M.D., Anne Rosser, M.B., B.Chir., Ph.D., Holly B. Kordasiewicz, Ph.D., Christian Czech, Ph.D., Eric E. Swayze, Ph.D., Daniel A. Norris, Ph.D., Tiffany Baumann, B.S., Irene Gerlach, Ph.D., Scott A. Schobel, M.D., Erika Paz, B.S., Anne V. Smith, Ph.D., C. Frank Bennett, Ph.D., and Roger M. Lane, M.D., for the Phase 1–2a IONIS-HTT_{Rx} Study Site Teams†

ABSTRACT

BACKGROUND

Huntington's disease is an autosomal-dominant neurodegenerative disease caused by CAG trinucleotide repeat expansion in *HTT*, resulting in a mutant huntingtin protein. IONIS-HTT_{Rx} (hereafter, HTT_{Rx}) is an antisense oligonucleotide designed to inhibit *HTT* messenger RNA and thereby reduce concentrations of mutant huntingtin.

METHODS

We conducted a randomized, double-blind, multiple-ascending-dose, phase 1–2a trial involving adults with early Huntington's disease. Patients were randomly assigned in a 3:1 ratio to receive HTT_{Rx} or placebo as a bolus intrathecal administration every 4 weeks for four doses. Dose selection was guided by a preclinical model in mice and nonhuman primates that related dose level to reduction in the concentration of huntingtin. The primary end point was safety. The secondary end point was HTT_{Rx} pharmacokinetics in cerebrospinal fluid (CSF). Prespecified exploratory end points included the concentration of mutant huntingtin in CSF.

RESULTS

Of the 46 patients who were enrolled in the trial, 34 were randomly assigned to receive HTT_{Rx} (at ascending dose levels of 10 to 120 mg) and 12 were randomly assigned to receive placebo. Each patient received all four doses and completed the trial. Adverse events, all of grade 1 or 2, were reported in 98% of the patients. No serious adverse events were seen in HTT_{Rx}-treated patients. There were no clinically relevant adverse changes in laboratory variables. Predose (trough) concentrations of HTT_{Rx} in CSF showed dose dependence up to doses of 60 mg. HTT_{Rx} treatment resulted in a dose-dependent reduction in the concentration of mutant huntingtin in CSF (mean percentage change from baseline, 10% in the placebo group and −20%, −25%, −28%, −42%, and −38% in the HTT_{Rx} 10-mg, 30-mg, 60-mg, 90-mg, and 120-mg dose groups, respectively).

CONCLUSIONS

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*Deceased.

†A full list of the members of the Phase 1–2a IONIS-HTT_{Rx} Study Site Teams is provided in the Supplementary Appendix, available at NEJM.org.

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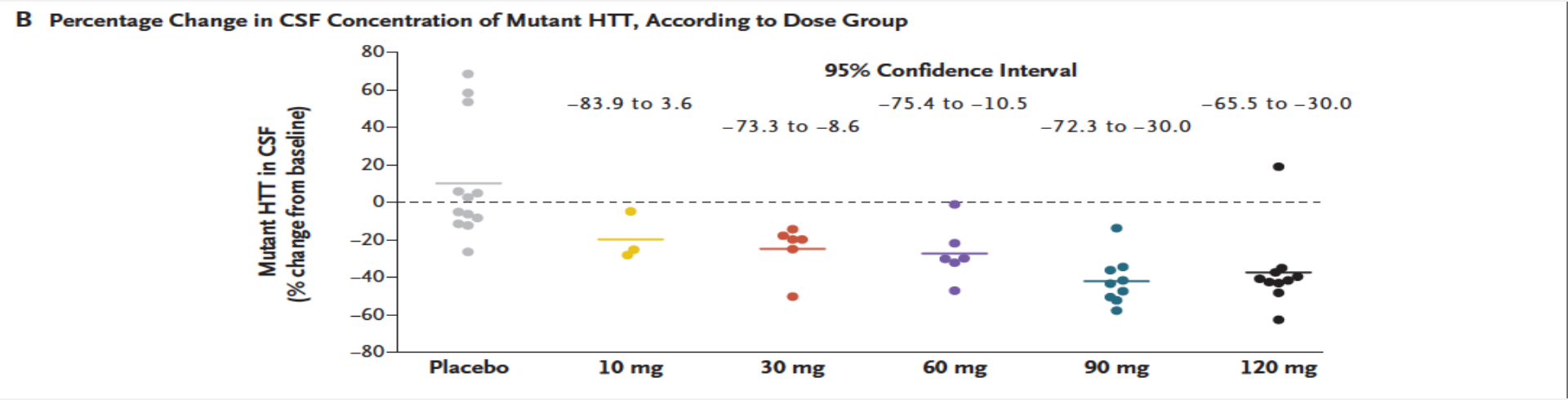
N Engl J Med 2019;380:2307-16.
DOI: 10.1056/NEJMoa1900907

La terapia génica ha llegado a enfermedades neurodegenerativas. Es complejo trabajar con el gen entero…la otra opción es actuar sobre la proteina con Oligon antisentido



Los oligonucleotidos antisentido disminuyen la HT GENERAL de forma evidente en modelos animales y humanos

doi:10.1093/brain/awr333 Brain 2012: 135; 1197–1209 | 1197

BRAIN
A JOURNAL OF NEUROLOGY

OCCASIONAL PAPER

Six-month partial suppression of Huntingtin is well tolerated in the adult rhesus striatum

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Huntington's disease is caused by expression of a mutant form of Huntingtin protein containing an expanded polyglutamine repeat. One possible treatment for Huntington's disease may be to reduce expression of mutant Huntingtin in the brain via RNA interference. Unless the therapeutic molecule is designed to be allele-specific, both wild-type and mutant protein will be suppressed by an RNA interference treatment. A key question is whether suppression of wild-type as well as mutant Huntingtin in targeted brain regions can be tolerated and result in a net benefit to patients with Huntington's disease. Whether Huntingtin performs essential functions in the adult brain is unclear. Here, we tested the hypothesis that the adult primate brain can tolerate moderately reduced levels of wild-type Huntingtin protein for an extended period of time. A serotype 2 adeno-associated viral vector encoding for a short hairpin RNA targeting rhesus *huntingtin* messenger RNA (active vector) was bilaterally injected into the striatum of four adult rhesus monkeys. Four additional animals received a comparable vector encoding a scrambled control short hairpin RNA (control vector). General health and motor behaviour were monitored for 6 months. Upon termination, brain tissues were sampled and assessed blindly for (i) *huntingtin* messenger RNA knockdown; (ii) Huntingtin protein expression; and (iii) neuropathological changes. Reduction in wild-type *huntingtin* messenger RNA levels averaging ~30% was measured in the striatum of active vector recipients 6 months post-injection. A widespread reduction in Huntingtin protein levels was also observed by immunohistochemistry in these animals, with an average protein reduction of ~45% relative to controls measured by western blot analysis in the putamen of active vector recipients. As with control vector recipients, no adverse effects were observed behaviourally, and no neurodegeneration was found on histological examination of active vector recipients. Our results suggest that long-term partial suppression of wild-type Huntingtin may be safe, and thus if a comparable level of suppression of mutant Huntingtin is beneficial, then partial suppression of both wild-type and mutant Huntingtin may result in a net benefit in patients with heterozygous Huntington's disease.

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Potent and sustained huntingtin lowering via AAV5 encoding miRNA preserves striatal volume and cognitive function in a humanized mouse model of Huntington disease

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ABSTRACT

Huntington disease (HD) is a fatal neurodegenerative disease caused by a pathogenic expansion of a CAG repeat in the huntingtin (*HTT*) gene. There are no disease-modifying therapies for HD. Artificial microRNAs targeting *HTT* transcripts for degradation have shown preclinical promise and will soon enter human clinical trials. Here, we examine the tolerability and efficacy of non-selective HTT lowering with an AAV5 encoded miRNA targeting human *HTT* (AAV5-miHTT) in the humanized Hu128/21 mouse model of HD. We show that intrastriatal administration of AAV5-miHTT results in potent and sustained HTT suppression for at least 7 months post-injection. Importantly, non-selective suppression of huntingtin was generally tolerated, however high dose AAV5-miHTT did induce astrogliosis. We observed an improvement of select behavioural and modest neuropathological HD-like phenotypes in Hu128/21 mice, suggesting a potential therapeutic benefit of miRNA-mediated non-selective HTT lowering. Finally, we also observed that potent reduction of wild type HTT (wtHTT) in Hu21 control mice was tolerated up to 7 months post-injection but may induce impairment of motor coordination and striatal atrophy. Taken together, our data suggests that in the context of HD, the therapeutic benefits of mHTT reduction may outweigh the potentially detrimental effects of wtHTT loss following non-selective HTT lowering.

INTRODUCTION

Huntington disease (HD) is a fatal neurodegenerative disease that affects ~13.7 per 100 000 individuals in the general population (1). HD is caused by a dominant CAG trinucleotide repeat expansion mutation in the huntingtin (*HTT*) gene beyond 35, which codes for an elongated polyglutamine (polyQ) tract in the HTT protein (2). HTT is a highly conserved protein that functions as a cellular scaffold, mediating interactions with many biomolecules and organelles, and as such is involved in a plethora of cellular pathways, including transcriptional regulation (3–5), mitochondrial function (6,7), axonal trafficking (8–10), endocytosis (11,12) and cellular stress responses (13–15). In HD, the expansion of the polyQ tract leads to perturbation of these normal functions and also induces the gain of toxic functions causing cellular dysfunction and ultimately neuron death. Notably, multiple preclinical studies have demonstrated that suppressing mutant HTT (mHTT) in the brain can improve and even reverse molecular, neu-

Ya se conoce que la reducción de la HT general es bien tolerada en modelos animales en etapa adulta

Dosing Stopped in Phase 3 Trial of Tominersen for Huntington's, Roche Says

by *Marta Figueiredo PhD* | March 30, 2021

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Journal of Huntington's Disease 6 (2017) 1–17
DOI 10.3233/JHD-170235
IOS Press

Review

Is Huntingtin Dispensable in the Adult Brain?

Jeh-Ping Liu and Scott O. Zeitlin*
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Abstract. Huntingtin (HTT) is an essential protein during early embryogenesis and the development of the central nervous system (CNS). Conditional knock-out of mouse *Huntingtin* (*Htt*) expression in the CNS beginning during neural development, as well as reducing *Htt* expression only during embryonic and early postnatal stages, results in neurodegeneration in the adult brain. These findings suggest that HTT is important for the development and/or maintenance of the CNS, but they do not address the question of whether HTT is required specifically in the adult CNS for its normal functions and/or homeostasis. Recently, it was reported that although removing *Htt* expression in young adult mice causes lethality due to acute pancreatitis, loss of *Htt* expression in the adult brain is well tolerated and does not result in either motor deficits or neurodegeneration for up to 7 months after *Htt* inactivation. However, recent studies have also demonstrated that HTT participates in several cellular functions that are important for neuronal homeostasis and survival including sensing reactive oxygen species (ROS), DNA damage repair, and stress responses, in addition to its role in selective macroautophagy. In this review, HTT's functions in development and in the adult CNS will be discussed in the context of these recent discoveries, together with a discussion of their potential impact on the design of therapeutic strategies for Huntington's disease (HD) aimed at lowering total *HTT* expression.

…Ciertamente la HTW tiene un papel fisiológico… fundamental en embriogénesis…y también… en edad adulta

Wild type huntingtin reduces the cellular toxicity of mutant huntingtin in mammalian cell models of Huntington's disease

Luk W Ho, Rosemary Brown, Michelle Maxwell, Andreas Wyttenbach, David C Rubinsztein

Abstract

***Objectives*—Recent data suggest that wild type huntingtin can protect against apoptosis in the testis of mice expressing full length huntingtin transgenes with expanded CAG repeats. It is not clear if this protective effect was confined to particular cell types, or if wild type huntingtin exerted its protective effect in this model by simply reducing the formation of toxic proteolytic fragments from mutant huntingtin.**

***Methods*—We cotransfected neuronal (SK-N-SH, human neuroblastoma) and non-neuronal (COS-7, monkey kidney) cell lines with *HD* exon 1 (containing either 21 or 72 CAG repeats) construct DNA and either full length wild type huntingtin or pFLAG (control vector).**

***Results*—Full length wild type huntingtin significantly reduced cell death resulting from the mutant *HD* exon 1 fragments containing 72 CAG repeats in both cell lines. Wild type huntingtin did not significantly modulate cell death caused by transfection of HD exon 1 fragments containing 21 CAG repeats in either cell line.**

***Conclusions*—Our results suggest that wild type huntingtin can significantly reduce the cellular toxicity of mutant HD exon 1 fragments in both neuronal and non-neuronal cell lines. This suggests that wild type huntingtin can be protective in different cell types and that it can act against the toxicity caused by a mutant huntingtin fragment as well as against a full length transgene.**

(*J Med Genet* 2001;38:450–452)

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L W Ho
R Brown

which is translated into an abnormally long polyglutamine tract in the huntingtin protein.[1 2]

HD is a member of a family of neurodegenerative diseases caused by CAG/polyglutamine expansions, which include spinobulbar muscular atrophy (SBMA), spinocerebellar ataxias (SCA) types 1, 2, 3, 6, and 7, and dentatorubral-pallidoluysian atrophy. All diseases are dominantly inherited (except for SBMA, which is X linked). In all cases, age at onset correlates inversely with repeat number.[2] The polyglutamine expansion mutation causes disease by conferring a novel deleterious function on the mutant protein and the severity correlates with increasing CAG repeat number and expression levels in transgenic mice and in cell culture models.[3 4]

While each of these diseases is associated with specific regions of neurodegeneration (which in some cases overlap), they are probably caused by similar pathological processes. A hallmark of many of these diseases, including HD, spinobulbar muscular atrophy (SBMA), dentatorubral-pallidoluysian atrophy (DRPLA), and spinocerebellar ataxias (SCA) types 1, 2, 3, 6, and 7, is the development of intracellular protein aggregates (inclusions) in the vulnerable neurones. However, the pathogenic role of these aggregates is the subject of vigorous debate.[5]

The function of wild type huntingtin is unclear. However, Rigamonti *et al*[6] recently showed that wild type huntingtin can protect CNS cells from a variety of apoptotic stimuli, including serum withdrawal, stimulation of death receptors, and pro-apoptotic Bcl-2 homologues. We were interested to test if wild type huntingtin protected against the toxicity of polyglutamine expansion mutations. While the

…De hecho sobre-expresar la HTW puede proteger de la toxicidad de la HTM…en modelos experimentales

JAMA Neurology | Clinical Implications of Basic Neuroscience Research

Huntingtin-Lowering Therapies for Huntington Disease
A Review of the Evidence of Potential Benefits and Risks

Blair R. Leavitt, MDCM; Holly B. Kordasiewicz, PhD; Scott A. Schobel, MD

Huntington disease (HD) is caused by a cytosine-adenine-guanine trinucleotide repeat expansion in the huntingtin gene, *HTT*, that results in expression of variant (mutant) huntingtin protein (HTT). Therapeutic strategies that reduce HTT levels are currently being pursued to slow or stop disease progression in people with HD. These approaches are supported by robust preclinical data indicating that reducing variant huntingtin protein is associated with decreased HD pathology. However, the risk-benefit profile of reducing either variant HTT or both variant and wild-type HTT is currently an open question that is being addressed in ongoing clinical trials. This review aims to examine the current data available regarding altered *HTT* in humans, normal animals, and animal models of HD. Studies indexed in PubMed were searched using the MeSH term *Huntington disease* or the text words *huntington* or *huntingtin* from August 31, 1999, to August 31, 2019, with no language restrictions. Additional studies were included from the reference lists of relevant studies and the authors' personal files. Articles describing at least 1 aspect of HTT reduction were included, prioritizing those published within the last 10 years. In vivo studies were also prioritized, with a focus on studies that examined the consequences of wild-type HTT reduction in adults. In a recently completed phase 1/2a study of RG6042 in 46 adults with early manifest HD, antisense oligonucleotide-mediated partial reduction of HTT was reported to be generally safe and well tolerated over the course of 4-monthly RG6042 doses. In case studies of people with rare genetic variations in huntingtin alleles, the loss of 1 wild-type allele was not associated with HD. People with homozygous cytosine-adenine-guanine expansions developed normally until the onset of HD, although they may have experienced a more aggressive disease course. In mouse models of HD, partial reduction of HTT was beneficial, with improvements in motor, cognitive, and behavioral phenotypes. The partial reduction of wild-type HTT in normal adult rodents and nonhuman primates was generally safe and well tolerated. The body of evidence reviewed in this article indicates a positive risk-benefit profile for the partial reduction of either variant HTT alone or both variant and wild-type HTT. These strategies target the underlying cause of HD and are currently being tested in several investigational clinical trials.

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Supplemental content

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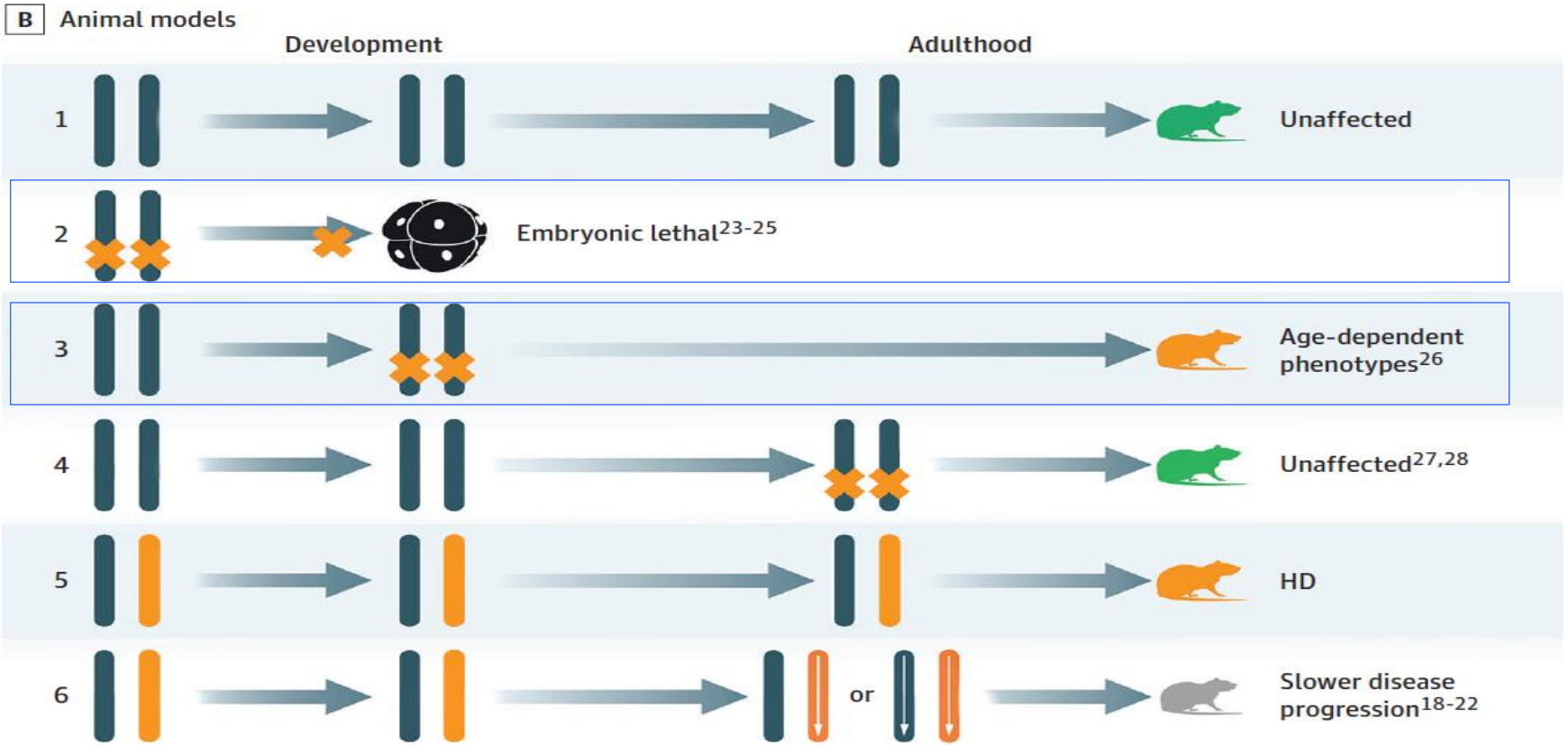
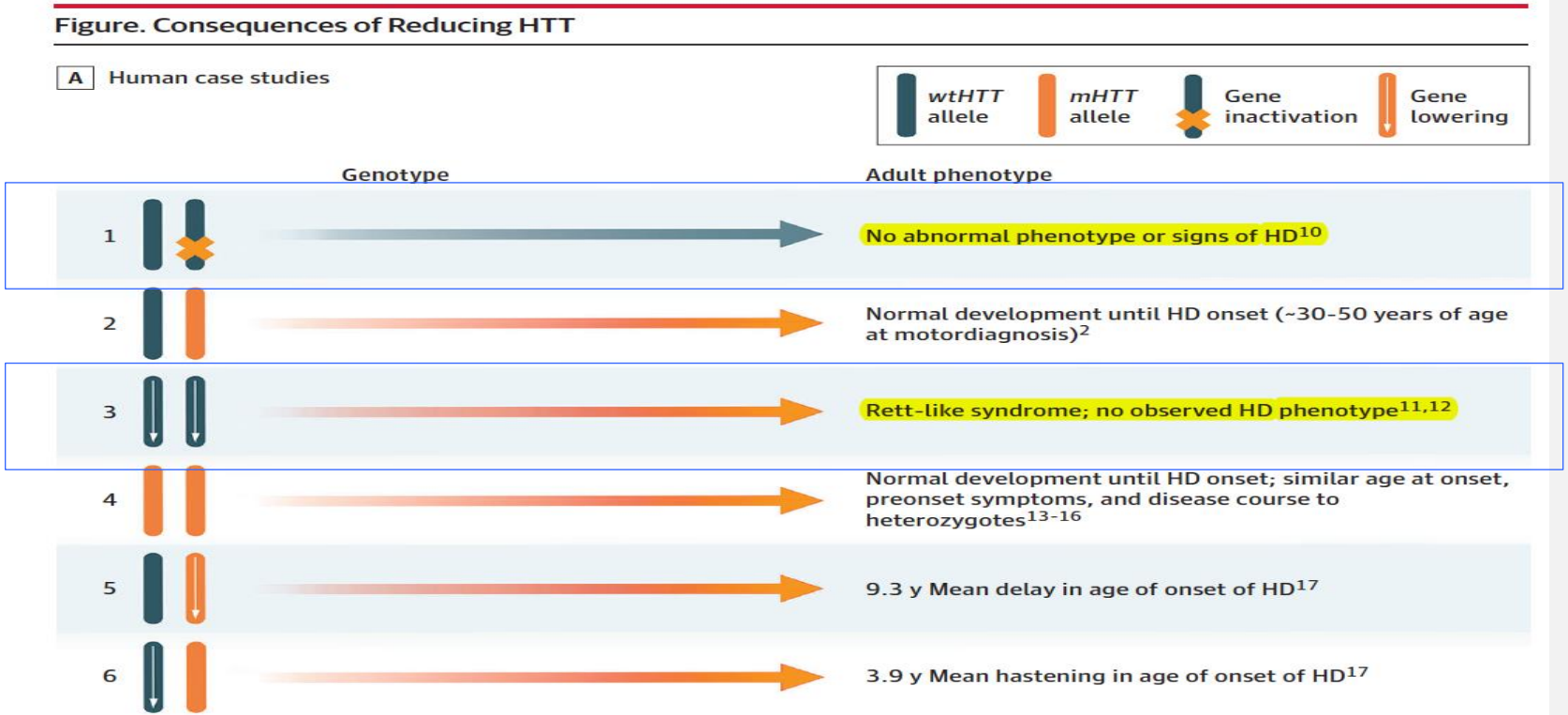
Que ocurre al disminuir los niveles de HTW ?



En modelos animales, la supresión de HTW es letal en periodo embrionario y edad dependiente después…

Figure. Consequences of Reducing HTT



En humanos hay experimentos ¨naturales¨. Se han detectado pacientes con supresión de un alelo y reducción del 50% del HTW..asintomático…Y se ha detectado supresión de ambos alelos con síndrome Rett-like

Molecular Neurobiology

ISSN0893-7648/03/28(3): 259–275/$25.00

Wild-Type Huntingtin Plays a Role in Brain Development and Neuronal Survival

***Anton Reiner,*[*,1] *Ioannis Dragatsis,*[2] *Scott Zeitlin,*[3] *and Daniel Goldowitz*[1]**

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Abstract

While the role of the mutated Huntington's disease (HD) protein in the pathogenesis of HD has been the focus of intensive investigation, the normal protein has received less attention. Nonetheless, the wild-type HD protein appears to be essential for embryogenesis, since deletion of the HD gene in mice results in early embryonic lethality. This early lethality is due to a critical role the HD protein, called huntingtin (Htt), plays in extraembryonic membrane function, presumably in vesicular transport of nutrients. Studies of mutant mice expressing low levels of Htt and of chimeric mice generated by blastocyst injection of *Hdh−/−* embryonic stem cells show that wild-type Htt plays an important role later in development as well, specifically in forebrain formation. Moreover, various lines of study suggest that normal Htt is also critical for survival of neurons in the adult forebrain.

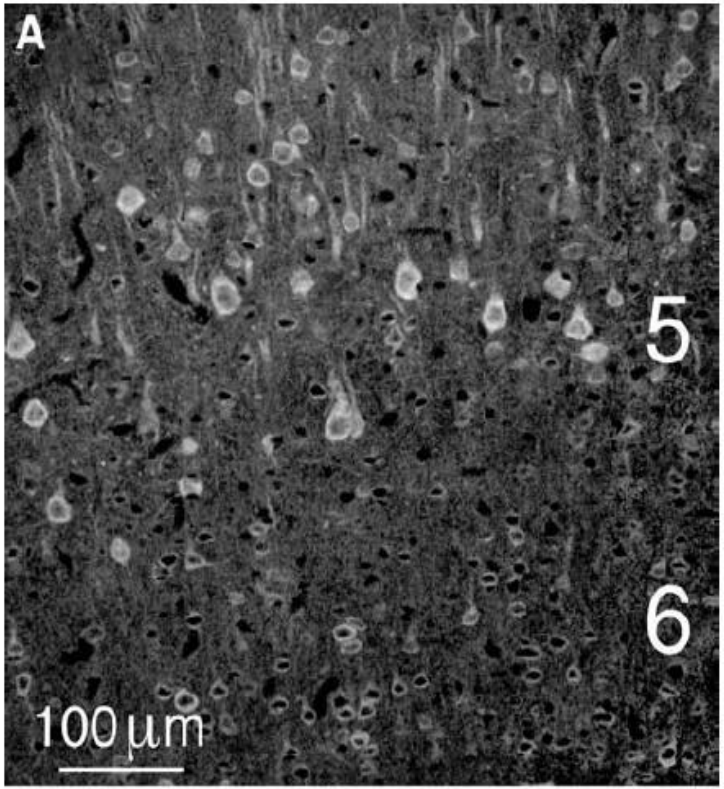
The observation that Htt plays its key developmental and survival roles in those brain areas most affected in HD raises the possibility that a subtle loss of function on the part of the mutant protein or a sequestering of wild-type Htt by mutant Htt may contribute to HD pathogenesis. Regardless of whether this is so, the prosurvival role of Htt suggests that HD therapies that block production of both wild-type and mutant Htt may themselves be harmful.

La HTW es fundamental en embriogénesis, …y la supresion de la HTT total no ha sido eficaz

PUNTOS CLAVE

1. La enfermedad de Huntington es una enfermedad multisistemica
2. La Huntingtina actua en multiples sistemas de neurodesarrollo y mantenimiento del transporte neuronal, especialmente GDNF
3. La HT mutada es incapaz de transportar eficientemente GDNF
4. La terapia génica actual permite reducir los niveles de Ht general un 40% y es bien tolerada, **pero no ha sido eficaz clinicamente**
5. Probablemente es necesario :

a) Reducir solo la Huntingtina mutada, no la salvaje
b) Actuar directamente sobre el BDNF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5
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