

**Editors' Note:** In WriteClick this week, in reference to “CAG repeat expansion in Huntington disease determines age at onset in a fully dominant fashion” by Lee et al., Drs. Aziz and Roos question the study’s use of motor onset as the only marker for disease onset. The authors clarify the rationale behind their methodology. Drs. Meng, Zhang, and Kao ask authors Klein et al. about the differences between the neuronal connectivity networks of the STN and VIM in reference to their recent study on deep brain stimulation. Authors Klein et al. summarize recent studies into the circuitry.

*Megan Alcauskas, MD, and Robert C. Griggs, MD*

#### CAG REPEAT EXPANSION IN HUNTINGTON DISEASE DETERMINES AGE AT ONSET IN A FULLY DOMINANT FASHION

**N. Ahmad Aziz, Raymund A.C. Roos, Leiden, the Netherlands:** We read with interest the article by Lee et al.<sup>1</sup> concerning the potential effect of the CAG repeat size in the normal *HTT* allele on age at motor onset in Huntington disease (HD). Although the authors have done an excellent job in analyzing data on an impressively large number of patients with HD, we feel that the following points should be considered before dismissing a potential disease-modifying role of the normal *HTT* allele. First, the authors’ findings concern age at motor onset only yet cognitive and behavioral disturbances often precede motor onset and should be treated equally in defining age at onset as in our study.<sup>2</sup> Second, the authors equate age at motor onset to rate of disease progression,<sup>1</sup> and do not formally assess serial clinical measurements on the same individuals as we previously reported.<sup>2</sup> However, the observation that, despite a similar age at onset, homozygote patients display a faster rate of clinical deterioration suggests that mechanisms contributing to age at onset and disease progression might not entirely overlap.<sup>3</sup> Third, although excluding outliers generally yields more robust statistical models, this comes at the cost of missing potentially interesting genetic modifiers at the allelic extremes.<sup>4</sup>

**Author Response: James F. Gusella, Jong-Min Lee, Marcy E. MacDonald, Boston:** We thank Aziz et al. for their interest in our study<sup>1</sup> but feel that some clarification is required. They are correct that our study was aimed exclusively at determining whether the shorter CAG repeat allele in HD has a significant impact, either alone or in interaction with the longer, expanded allele, on the age at which motor disturbance—the phenotype considered diagnostic of the disorder—is manifest.

This phenotype represents one point in a long pathogenic process triggered by the expanded CAG repeat. There are other, less HD-specific phenotypes that may be displayed by HD individuals including cognitive and behavioral disturbances. It is possible that for these other phenotypes, the shorter CAG repeat allele may be a modifying factor. However, such a modifying effect would have to act on a step in pathogenesis that is not important in the pathogenic pathway that leads to motor onset. Consequently, this question should be examined by studying age at onset of the given phenotype on its own, rather than studying a single population in which ages at onset of motor, cognitive, or behavioral symptoms are not distinguished from each other.

It is inaccurate to state that we “equate age at motor onset with rate of disease progression.” In our study, the age at which HD motor symptoms are manifest offers a direct measure of the rate of the pathogenic process up to that point. That the length of the expanded CAG repeat is tightly correlated with age at onset indicates that the mutation’s effects are the primary determinant of this particular rate. Conversely, “progression,” as referred to by Aziz et al., represents an examination of serial clinical measurements on the same individuals and therefore typically refers to phenotypes that occur after onset. It has been shown that many measures of progression show little if any correlation with the length of the expanded CAG repeat, indicating that other factors are the primary determinants of the rate of progression of any particular clinical measurement or of severity scores based upon them. We previously reported the absence of any significant correlation of the expanded CAG repeat length on duration of dis-

ease, as measured by the time from motor onset to death (and therefore not biased by studying primarily living subjects).<sup>5</sup> We have not examined the shorter HD CAG repeat for any specific measures of progression and therefore cannot exclude it as a factor in this process, which is clearly distinct from the process that leads to motor onset.

Finally, we showed that using genotypic extremes in an inappropriate statistical paradigm can lead to false-positive results. This can negatively influence the time, energy, and funds expended on false leads. It does not deny the potential value of extreme individuals, but simply indicates that another mode of analysis is required to reach definitive conclusions from such individuals.

Copyright © 2012 by AAN Enterprises, Inc.

1. Lee JM, Ramos EM, Lee JH, et al. CAG repeat expansion in Huntington disease determines age at onset in a fully dominant fashion. *Neurology* 2012;78:690–695.
2. Aziz NA, Jurgens CK, Landwehrmeyer GB, et al. Normal and mutant HTT interact to affect clinical severity and progression in Huntington disease. *Neurology* 2009;73:1280–1285.
3. Squitieri F, Gellera C, Cannella M, et al. Homozygosity for CAG mutation in Huntington disease is associated with a more severe clinical course. *Brain* 2003;126:946–955.
4. Ross OA, Singleton AB. Does trans size matter in Huntington disease? *Neurology* 2012;78:686–687.
5. Gusella JF, Persichetti F, MacDonald ME. The genetic defect causing Huntington's disease: repeated in other contexts? *Mol Med* 1997;3:238–246.

### THE TREMOR NETWORK TARGETED BY SUCCESSFUL VIM DEEP BRAIN STIMULATION IN HUMANS

**Fan-gang Meng, Jian-guo Zhang, Beijing, China; C. Chris Kao, Nashville, TN:** Klein et al.<sup>1</sup> provide evidence that the network of structural connectivity can be reconstructed from stimulation contact sites to remote targets in deep brain stimulation (DBS) of the ventral intermediate nucleus of thalamus (VIM) in humans. Essential tremor (ET) is the most common tremor disorder and Parkinson disease (PD) is often accompanied by tremors. ET and PD can both be treated with DBS but the difference is that STN was used as a target in PD and VIM in ET. There is evidence that STN stimulation-induced motor improvement was sustained at 10 years in PD,<sup>2</sup> and habituation of tremor suppression can be developed in VIM-DBS in ET.<sup>3</sup> As the stimulation effect of the 2 targets is different, the mechanisms must be investigated. In addition, the differences

in the reproducible networks of structural connectivity must be determined. Subthalamic nucleus (STN) and VIM stimulation activate different remote targets, and this might relate to the tolerance of VIM-DBS in ET but long-term effect of STN-DBS in PD. Further studies are needed to explore the reproducible network reconstruction of STN and VIM and to understand the mechanism of stimulation.

**Author Response: Johannes C. Klein, Rudiger Hilker, Frankfurt, Germany:** We thank Meng et al. for their interest in our work. Stimulation of VIM and STN produces significantly different clinical results, along with a different spectrum of side effects.

It is likely that these observations are due to differences of the neuronal circuitry, including remote connections of these regions. Optogenetic studies in parkinsonian rodents have found that stimulation of axons projecting to the STN, in contrast to stimulation of its cell bodies, mediates suppression of motor symptoms.<sup>4</sup> This study underlines the importance of modulating the STN's connective network for clinical efficacy in the treatment of PD.

A diffusion tractography study analyzed remote connections of the STN in a set of normal volunteers.<sup>5</sup> The authors reconstructed a remote network of connectivity that is very different from the VIM network, and comparable to previous studies of STN connectivity in nonhuman animals. These differences between VIM and STN networks may explain the disparate clinical effects of DBS of these targets. However, data regarding the connectivity of the target point in STN patients are not yet available.

Copyright © 2012 by AAN Enterprises, Inc.

1. Klein JC, Barbe MT, Seifried C, et al. The tremor network targeted by successful VIM deep brain stimulation in humans. *Neurology* 2012;78:787–795.
2. Castrioto A, Lozano AM, Poon YY, Lang AE, Fallis M, Moro E. Ten-year outcome of subthalamic stimulation in Parkinson disease: a blinded evaluation. *Arch Neurol* 2011; 68:1550–1556.
3. Barbe MT, Liebhart L, Runge M, et al. Deep brain stimulation in the nucleus ventralis intermedialis in patients with essential tremor: habituation of tremor suppression. *J Neurol* 2011;258:434–439.
4. Gradinaru V, Mogri M, Thompson KR, Henderson JM, Deisseroth K. Optical deconstruction of parkinsonian neural circuitry. *Science* 2009;17:324:354–359.
5. Aravamuthan BR, Muthusamy KA, Stein JF, Aziz TZ, Johansen-Berg H. Topography of cortical and subcortical connections of the human pedunculo-pontine and subthalamic nuclei. *Neuroimage* 2007;37:694–705.

Author disclosures are available upon request ([journal@neurology.org](mailto:journal@neurology.org)).

# Neurology<sup>®</sup>

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

N. Ahmad Aziz, James F. Gusella, Raymund A.C. Roos, et al.

*Neurology* 2012;79:952-953

DOI 10.1212/WNL.0b013e3182697986

**This information is current as of August 27, 2012**

### **Updated Information & Services**

including high resolution figures, can be found at:  
<http://n.neurology.org/content/79/9/952.full>

### **References**

This article cites 5 articles, 3 of which you can access for free at:  
<http://n.neurology.org/content/79/9/952.full#ref-list-1>

### **Permissions & Licensing**

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:  
[http://www.neurology.org/about/about\\_the\\_journal#permissions](http://www.neurology.org/about/about_the_journal#permissions)

### **Reprints**

Information about ordering reprints can be found online:  
<http://n.neurology.org/subscribers/advertise>

*Neurology*® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2012 by AAN Enterprises, Inc.. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.

