A Comparison of Huntington Disease and Huntington Disease-Like 2 Neuropathology

Dobrila D. Rudnicki, PhD, Olga Pletnikova, MD, Jean-Paul G. Vonsattel, MD, Christopher A. Ross, MD, PhD, and Russell L. Margolis, MD

Abstract

Huntington disease-like 2 (HDL2) is an autosomal dominant disorder characterized by adult-onset, progressive motor abnormalities, psychiatric disturbances, and dementia ending in premature death. Clinically, it most closely resembles Huntington disease (HD), although a subset of affected individuals have parkinsonian features. Here, we systematically compare 5 HDL2 and 5 HD brains with the hypothesis that, reflecting the clinical presentation, the neuropathology of the 2 diseases would be similar. Gross and microscopic examination revealed prominent striatal neuron loss and astrocytic gliosis in a dorsal to ventral gradient in each disorder and cortical atrophy. Nuclear protein aggregates were as common in HDL2 as in HD, and the ultrastructural features of HDL2 and HD aggregates were similar. Electron microscopy also revealed degenerating neurons, some with evidence of autophagy, in both HDL2 and HD. Small ribonuclear foci, previously associated with potentially neurotoxic RNA transcripts in HDL2 brain, although the protein aggregates stained by anti-TATA-box binding protein antibodies, were similar. Overall, the neuropathologic features of HDL2 and HD are very similar but not identical, suggesting that the pathogenetic mechanisms of the 2 diseases may partially overlap.

Key Words: Myotonic dystrophy, Neurodegeneration, Trinucleotide.

INTRODUCTION

Huntington disease-like 2 (HDL2) is an adult-onset neurodegenerative disorder that is clinically and pathologically very similar to Huntington disease (HD). One form of the disorder, typified by the index family and subsequently reported in other families, begins with weight loss and diminished coordination before age 40 and progresses to include rigidity, dysarthria, hyperreflexia, bradykinesia, and tremor, with no clear cerebellar signs (1–3). Psychiatric symptoms, dystonia, and mild chorea are frequently present, and the disorder culminates in a bedridden nonverbal state with profound dementia approximately 10 to 15 years after onset, with death 5 to 10 years thereafter. An alternative presentation is characterized by somewhat later-onset, more pronounced chorea and less prominent dystonia, bradykinesia, and rigidity. More than 30 pedigrees have been identified, most of which have definite or probable African ancestry (4). Huntington disease-like 2 accounts for approximately 1% of all cases referred for HD testing in the United States that test negative for HD. The frequency is substantially more common among black South Africans with an HD phenotype.

The causative mutation of HDL2 is a CAG/CTG repeat expansion on chromosome 16q24.3 (2). On the sense strand in the CTG orientation, the repeat falls within a variably spliced exon of junctophilin-3 (JPH3), a brain-specific member of the junctophilin gene family. The protein products of these genes are thought to play a role in anchoring endoplasmic reticulum to the plasma membrane, thereby facilitating the interaction of plasma membrane voltage-gated channels with endoplasmic reticulum calcium flux (5–7).

Expanded repeats in HDL2 range from 40 to 59 triplets in length, similar to the range observed in HD; the normal range is 6 to 28, with rare alleles in an intermediate zone. Like the HD repeat length, the HDL2 repeat length is inversely correlated with age of disease onset (4).

Magnetic resonance imaging scans of HDL2 patients show pronounced striatal and cortical atrophy with little or no atrophy of the cerebellum or brainstem. The scans are indistinguishable from those of HD patients with a similar disease duration (4). Thus far, preliminary reports of the neuropathology of 3 HDL2 cases (1, 8) and more detailed reports of 2 other cases (9) have been published. All cases show relatively selective striatal and cortical atrophy.

All reported HDL2 cases contain intranuclear protein aggregates detectable with antibodies that are thought to be partly specific for proteins with polyglutamine expansions (10). The aggregates also stain with anti-ubiquitin antibodies. Although transcripts antisense to JPH3 containing a CAG...
repeat may be transcribed, probably at low levels, there is so far no clear evidence that these transcripts are translated into a protein with expanded polyglutamine tracts in HDL2 patient brains (D. Rudnicki, unpublished data).

On the sense strand (in exon 2A of JPH3), the repeat alternatively encodes polyalanine, polyleucine, or resides in 3′ untranslated region (2). The presence of expanded polyalanine or polyleucine in HDL2 aggregates can also explain the staining of these aggregates with monoclonal antibody 1C2 because it has been reported to detect expanded polyalanine and polyleucine tracts in some cell models (11, 12). Antibodies raised against epitopes specific for the putative protein products of the polyalanine and polyleucine open reading frames of JPH3 exon 2A, or against an epitope encoded by exon 1 that is predicted to be present in all JPH3 protein products did not, however, detect proteins with expanded polyalanine or polyleucine in HDL2 patient brains and did not stain HDL2 inclusions (Rudnicki, unpublished data). Therefore, the nature and origin of HDL2 protein aggregates, and their relationship to RNA foci that are also detectable in HDL2 neurons (13), remain unknown.

Nonetheless, the clinical and genetic similarity between HD and HDL2 suggests the possibility of at least partially shared pathogenic mechanisms. To investigate the similarity between the 2 disorders further, we undertook a systematic comparative examination of HD and HDL2 neuropathology with a particular emphasis on protein aggregates.

MATERIALS AND METHODS

Brain Ascertainment

All tissue was collected at Johns Hopkins University under institutional review board-approved protocols. Five HDL2 brains from 3 kindreds were examined. The clinical description and preliminary pathology of Case 2205 (1) have been previously reported. Case 2232 presented at age 44; Case 2244 at 52, Case 2261 at age 29. The age of onset for Case 2267 is not known. Cases 2205, 2261, and 2267 were part of the index family; the other 2 cases, are unrelated to the index family or each other. Huntington disease-like 2 brains were matched with 6 HD brains, as listed in Table 1.

Neuropathology Protocol

Brains were removed, the left hemibrain was fixed in 10% buffered formalin for 2 weeks, and the right hemibrain was coronally sectioned and frozen for biochemical studies. Fixed tissue was processed, embedded in paraffin, and cut at 10 μm. Tissue sections were stained with hematoxylin and eosin or Hirano silver method (14), or were immunostained for ubiquitin, TATA-box binding protein (TBP), polyglutamine repeats, or by the huntingtin.

Immunohistochemistry

Brain tissue mounted on charged glass slides was deparaffinized, pretreated with 88% formic acid for 5 minutes, treated with H2O2, blocked with 3% normal goat serum in Tris-buffered saline, and incubated overnight at room temperature with antibodies raised against ubiquitin (Dako, Carpinteria, CA; 1:500), anti-polyglutamine tracts (1C2 antibody; Chemicon, Temecula, CA; 1:10000), or huntingtin (EM48; dilution 1:50; Chemicon). Subsequently, the tissue was incubated with biotinylated secondary antibodies (Vector Laboratories, Burlingame, CA) for 1 hour. Immunoreactions were visualized with the avidin-biotin-peroxidase complex and 3,3′ diaminobenzidine (both from Vector Laboratories). The density of intranuclear aggregates, detected by anti-ubiquitin and 1C2 immunostains, was determined in the amygdala and motor cortex of HDL2 and HD cases. Under 20× magnification, the number of aggregates in 10 random fields was counted in each region in each brain. For dopamine- and cyclic adenosine monophosphate-regulated phosphoprotein, M,32 kd (DARPP-32) staining (1:500; Chemicon), free-floating striatal tissue was incubated with antibodies raised against ubiquitin, TBP, polyglutamine repeats, or by the huntingtin.

TABLE 1. Summary of HD and HDL2 Clinical and Neuropathologic Data

<table>
<thead>
<tr>
<th>Case</th>
<th>Age, year</th>
<th>Sex</th>
<th>Duration of Disease, years</th>
<th>Postmortem Delay, hours</th>
<th>Brain Weight, g</th>
<th>Vonsattel Grading System</th>
<th>Repeat Length</th>
</tr>
</thead>
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<tr>
<td>HD-1231</td>
<td>81</td>
<td>F</td>
<td>29</td>
<td>100</td>
<td>850</td>
<td>4</td>
<td>44/17</td>
</tr>
<tr>
<td>HD-1246</td>
<td>74</td>
<td>F</td>
<td>42</td>
<td>13</td>
<td>1,100</td>
<td>2</td>
<td>47/23</td>
</tr>
<tr>
<td>HD-1256</td>
<td>51</td>
<td>F</td>
<td>20</td>
<td>4</td>
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<td>3</td>
<td>47/17</td>
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<td>47</td>
<td>F</td>
<td>31</td>
<td>3</td>
<td>600</td>
<td>4</td>
<td>63/17</td>
</tr>
<tr>
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<td>62</td>
<td>M</td>
<td>11</td>
<td>18</td>
<td>1,030</td>
<td>1</td>
<td>45/17</td>
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<td>72</td>
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<td>17</td>
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<td>26.3</td>
<td>25.8</td>
<td>25.8</td>
<td>900</td>
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<td>4</td>
<td>44/11</td>
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<td>HDL2-2261</td>
<td>41</td>
<td>F</td>
<td>12</td>
<td>3</td>
<td>840</td>
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<tr>
<td>HDL2-2267</td>
<td>52</td>
<td>F</td>
<td>N/A</td>
<td>28</td>
<td>870</td>
<td>4</td>
<td>54/13</td>
</tr>
<tr>
<td>Mean</td>
<td>51.6</td>
<td>11.8</td>
<td>34.0</td>
<td>1,020.8</td>
<td>3.8</td>
<td>50</td>
<td></td>
</tr>
</tbody>
</table>

F, female; M, male; HD, Huntington disease; HDL2, Huntington disease-like 2.
reaction was performed using Vectastain avidin-biotin-peroxidase complex as previously described.

**Immunofluorescence and Immunofluorescence Combined With In Situ**

Immunofluorescence was performed on paraffin-embedded tissue using 1C2 (1:10000) and anti-TBP antibodies (N-12, dilution 1:2000, and Sl-1, 1:500; Santa Cruz Biotechnology, Santa Cruz, CA). After overnight incubations at 4°C, slides were incubated with Cy2- and Cy3-linked secondary antibodies (1:200; Jackson Immunoresearch Laboratories, West Grove, PA), stained with Hoechst (Molecular probes, Eugene, OR), and coverslipped. For immunofluorescence, in situ frozen frontal cortex tissue was used as previously described (13).

**Electron Microscopy**

Brain tissue was cut into 1-mm pieces and fixed in 2% glutaraldehyde/4% paraformaldehyde for at least 2 hours, washed in PBS, treated with 1% osmium tetroxide for 1 hour at 4°C, and washed in PBS. The tissue was then treated with 2% uranyl acetate for 1 to 2 hours, washed in PBS, dehydrated through a graded series of ethanol and propylene oxide solvents, embedded in a plastic resin, and cured at 68°C overnight. Sections of 1 to 3 μm were cut from the plastic resin blocks and stained with toluidine blue. Relevant areas of the thick sections were cut at 70 nm and placed on copper mesh grids, stained with uranyl acetate and lead citrate, washed in buffer, and viewed on a transmission electron microscope (TEM 7600; Hitachi, Tokyo, Japan).

**RESULTS**

**HDL2: Gross Pathology**

The critical parameters of the 5 HDL2 brains available for neuropathologic examination are listed in Table 1. The HDL2 brains showed atrophy that ranged from mild (brain weight, 1,210 g) to severe (brain weight, 840 g). The atrophy was predominantly cerebral, with sparing of the brainstem and cerebellum. There was no significant atherosclerosis of the circle of Willis. In coronal sections, cortical atrophy ranged from mild to severe, with up to 50% reduction in the thickness of the cortical mantle in the brains with extremely low weight (HDL2-2261 and HDL2-2267; Table 1). Most of the brains showed marked atrophy of the striatum comparable to HD Vonsattel Grades 3 to 4 (Table 1). The ventricular system revealed moderate hydrocephalus ex vacuo, and the white matter was reduced in volume but well myelinated. The thalamus, hypothalamus, amygdala, hippocampus, and entorhinal cortex were normal. The substantia nigra and locus ceruleus seemed normally pigmented. The pons, medulla, and the folia and deep cerebellar nuclei were normal. No vascular lesions were present. Overall, on gross examination (Fig. 1), the HDL2 brains were indistinguishable from HD brains of comparable Vonsattel stage.

**HDL2: Microscopic Pathology**

On microscopic examination, all of the HDL2 brains showed degeneration of the striatum characterized by marked loss of neurons detected by staining with DARPP-32, a specific marker of striatal projection neurons (Fig. 2). Astrocytic gliosis of the putamen and caudate, with a dorsal to ventral gradient, and relative sparing of the nucleus accumbens were observed in all HDL2 cases. The globus pallidus showed slightly milder degenerative changes compared with the striatum. In most cases, the cerebral cortex showed normal cytoarchitecture and preserved neuronal density. In some brains, changes of acute hypoxic ischemia were present. In Case 2267, there was marked loss of cortical neurons and gliosis, most severe in the visual cortex. This brain showed moderate numbers of neuritic senile plaques (CERAD B) (15) and abundant neurofibrillary tangles in the entorhinal cortex (Braak and Braak Neurofibrillary Tangle Score 1) (16). In the remainder of the cases, the hippocampus, entorhinal cortex, and amygdala were normal. No significant histologic changes were present in white matter, basal forebrain, thalamus, or subthalamic nucleus. Substantia nigra showed minimal pigment incontinence but was free of Lewy bodies and neurofibrillary tangles. The locus ceruleus, tegmentum and basis pontis, medulla, and cerebellum were

![FIGURE 1. Gross comparison of Huntington disease-like 2 (HDL2), Huntington disease (HD), and control brain. Substantial reduction in the volume of the caudate and putamen and cortical thinning are present in both an HDL2 (Case 2261) and an HD case compared with a control.](http://jnen.oxfordjournals.org/)

![FIGURE 2. Striatal neuronal loss in Huntington disease (HD) and Huntington disease-like 2 (HDL2). DARPP-32 staining of striatum is markedly reduced in HD (Case 1247) and HDL2 (Case 2244) (both Vonsattel Grade IV) compared with a normal control.](http://jnen.oxfordjournals.org/)
normal. A blinded review (by J-P. V.) of 3 cases (stained slides and selected gross sections) concluded that the cases were consistent with HD.

Electron microscopy examination of HDL2 cortex (Case 2261) revealed neurons undergoing dark cell degeneration characterized by condensation of nucleus and cytoplasm, clumping of chromatin, and ruffled plasma membrane; not all degenerating neurons contained protein aggregates. Numerous neurons showed features of autophagy, that is, autophagic vacuoles (Fig. 3) (17). Nuclear membrane invagination was also frequently observed. Similar degenerating neurons have been described in HD transgenic mouse models and in HD (18–20).

**Distribution of HDL2 Protein Aggregates**

To compare HD and HDL2 protein aggregates, brains from a set of 5 HD cases with a repeat length similar to that of the HDL2 cases were studied (Table 1). Huntington disease-like 2 cases were younger and had shorter disease durations than the HD cases possibly because the disease process of HDL2 in these cases was more rapidly advancing. Postmortem delay was longer in the HDL2 cases than in the HD cases. Immunostaining with 1C2 and anti-ubiquitin of neurons in both HDL2 and HD revealed scattered single spherical or cigar-shaped perinucleolar aggregates approximately the same sizes (i.e., 1 to 2 μm) as the nucleoli (Fig. 4; Table 2). In HDL2, aggregates were stained by ubiquitin and 1C2 antibodies but not by anti-huntingtin antibodies (data not shown). 1C2 detected aggregates with more sensitivity than anti-ubiquitin in both HD and HDL2 cases (data not shown).

Aggregates were most consistently and conspicuously detected in the amygdala in both HDL2 and HD, and...
aggregates were also found in the motor cortex in all cases of HDL2 and HD (Table 2). A comparison of the frequency of aggregates in the amygdala and motor cortex suggests that aggregates are at least as frequent in HDL2 as in HD and, potentially, even more frequent in the amygdala (Fig. 5). The greater number of aggregates stained by 1C2 than by anti-ubiquitin in both diseases may merely reflect differences in antibody affinity but can also be interpreted to suggest inhomogeneity of aggregates.

In the motor cortex, aggregates were present in all neuronal layers. Aggregates were found in the entorhinal cortex in 3 HDL2 cases but in only 1 HD case. Of particular interest, aggregates were found in the striatum in only 3 of the 5 HDL2 cases and 3 of the 5 HD cases; the 2 HDL2 cases without striatal aggregates had the shortest repeat expansion. No aggregates were found in the subthalamic nucleus in any HD or HDL2 case, and no aggregates were found in pons or medulla of HDL2 cases. In contrast, aggregates were found in the pons and/or medulla in every HD case (Table 2). There was, however, no difference in the extent of gliosis in pons and medulla between HD and HDL2 cases.

### Ultrastructure of HD and HDL2 Inclusions

The ultrastructural features of aggregates in HDL2 and HD were similar. The aggregates appeared to be composed of loose fibrillary material approximately 10 to 20 nm in diameter, arranged in a 3-dimensional pattern, less electron dense than the nuclear chromatin, and displacing the normal nuclear structures. Aggregates in both HD and HDL2 had a perinucleolar arrangement. They were associated with minimal amounts of heterochromatin and did not seem to contact the nuclear envelope (Fig. 6).

### Composition of Protein Aggregates

We have recently demonstrated that HDL2 brain contains nuclear RNA foci (13). These small foci contain JPH3 transcripts with expanded CUG repeats and the CUG-binding protein muscle blind-like 1. Other components of the

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**TABLE 2.** Distribution of Protein Aggregates Stained With the 1C2 Antibody in HD and HDL2 Cases

<table>
<thead>
<tr>
<th>Case</th>
<th>Motor Cortex</th>
<th>Amygdala</th>
<th>STN</th>
<th>Pons</th>
<th>Medulla</th>
<th>Cerebellum</th>
<th>Thalamus</th>
<th>Striatum</th>
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<tbody>
<tr>
<td>HD-1231</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
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<td>HD-1249</td>
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<td>HDL2-2205</td>
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<td>HDL2-2232</td>
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<td>HDL2-2267</td>
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</tbody>
</table>

HD, Huntington disease; HDL2, Huntington disease-like 2; STN, subthalamic nucleus.

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**FIGURE 5.** Quantitative comparison of inclusions in Huntington disease (HD) and Huntington disease-like 2 (HDL2) motor cortex and amygdala. Staining was performed with 1C2 and anti-ubiquitin antibody on paraffin sections from 5 HD and 5 HDL2 cases. Aggregates in HDL2 seem to be as numerous as in HD, with the exception that aggregates in amygdala stained with 1C2 seem to be more numerous in HDL2. Values represent mean of the 5 cases, ± SD. Amy, amygdala; Motor, motor cortex; ubi, ubiquitin.
foci remain unknown. One possibility is that these foci are a component of the much larger nuclear protein aggregates described here. To test this possibility, we examined the colocalization of riboprobe hybridization and 1C2 staining in the frontal cortex in 3 HDL2 brains. Our data show that foci and aggregates rarely, if ever, colocalize, and that cells tend to have 1 or the other structure, but not both (Fig. 7).

Both HD and HDL2 aggregates stain for 1C2, ubiquitin, and torsinA (21). Because there is no clear evidence of expanded polyglutamine tracts in HDL2 aggregates, staining with 1C2 has been difficult to explain. One possible explanation is that 1C2 stains TBP (22) within HDL2 aggregates. TATA-box binding protein, which contains the longest known normal polyglutamine tract in the human proteome, provided the epitope against which 1C2 was originally generated. Interestingly, expansion of the polyglutamine tract in TBP causes the neurodegenerative disease spinocerebellar ataxia 17 (23), which can present with an HD-like phenotype (24, 25). TATA-box binding protein was previously detected in HD aggregates (26). We found complete colocalization of 1C2 and anti-TBP staining in HDL2 aggregates (Fig. 8). The colocalization was confirmed with 2 different polyclonal anti-TBP antibodies, raised against amino acids 1 to 300 (S1-1) or against a peptide mapping to the N-terminus of human TBP (N-12). Although cross-reactivity with other proteins cannot be excluded, the location of the epitopes used to generate these anti-TBP antibodies and the identical results obtained with S1-1 and N-12 are consistent with the possibility that TBP accounts for at least some of the 1C2 staining of the HDL2 aggregates.

**DISCUSSION**

The central finding of this study is the remarkable similarity of HD and HDL2 on gross and microscopic examination, consistent with similar reports on HDL2 brains studied in isolation. The HDL2 cases available to us were indistinguishable from HD brains on gross examination, with prominent atrophy of the striatum and moderate atrophy of the cortex. Both diseases are characterized pathologically by degeneration of the striatum with a dorsal to ventral gradient and by the presence of intranuclear neuronal aggregates that appear structurally similar on examination by light microscopy and in their ultrastructure. Thus, the pathology of HD more closely resembles that of HDL2 than any other known disease; these observations are consistent with the clinical and genetic similarities of these disorders. Detection of cells with evidence of autophagic and nonautophagic cell death is also similar to the previous descriptions of these processes in HD (27, 28) and suggests additional similarities between HD and HDL2.

Protein aggregates in HD and HDL2 are also indistinguishable by immunohistochemistry with 1C2 and anti-ubiquitin antibodies and by electron microscopy. However, the distribution and composition of the aggregates in the 2 diseases are not identical. In HD brains, both nuclear and neuropil aggregates exist (29), whereas in HDL2 brains, only nuclear aggregates have been detected so far. Aggregates in HDL2 brains do not stain with anti-huntingtin antibodies, thereby permitting reliable postmortem distinction between HD and HDL2 even in the absence of genetic testing. The amygdala has the highest density and most conspicuous aggregates in both HDL2 and HD, followed by entorhinal and motor cortices. On the other hand, aggregates were less common in the striatum in both HDL2 and HDL2, the most severely degenerated region in both disorders. The presence of aggregates in the pons and/or medulla in every HD case, but not in HDL2 cases, is also striking. The apparent discrepancy between the presence of aggregates and the extent of neurodegeneration may be a result of selective loss of neurons containing aggregates earlier in the disease course. Alternatively, the aggregates may serve as a general marker of disease without marking degenerating neurons (30, 31). If so, the prominence of aggregates in the amygdala, particularly in HDL2, might have functional consequences that may be relevant to the psychiatric manifestations of these diseases. The relative prominence of brainstem aggregates in HD is more puzzling because brainstem pathology is not detectably different in HD compared with HDL2. Perhaps subtle clinical abnormalities attributable to brainstem dysfunction are more common in HD than in HDL2, although evidence for this difference is lacking.

Our examination of the composition of HDL2 protein aggregates demonstrated lack of colocalization of protein aggregates and RNA foci. One explanation for this is that the 2 structures reflect different and independent processes. Alternatively, RNA foci could form the nidus for larger protein aggregates such that secretion of protein would eventually block riboprobe hybridization to the JPH3 transcript. It is therefore possible that RNA toxicity is the primary pathogenic insult in HDL2, with protein aggregates a byproduct. However, given the lack of protein aggregates in DM1 and the markedly greater neurotoxicity in individuals
with HDL2 compared with DM1 patients with the same repeat length, it is unlikely that CUG repeat expansion alone can explain HDL2 neuropathology.

Based on the presence of an open reading frame antisense to JPH3 that includes the HDL2 CAG/CTG repeat, and the bidirectional transcription detected at the CAG/CTG repeat locus in SCA8 (32, 33), we and others have speculated that a cryptic transcript encoding polyglutamine can contribute to the pathogenesis of HDL2. The presence of 1C2-positive protein aggregates in HDL2 brain was taken as evidence of this possibility (33). However, although we have evidence that antisense transcripts on the HDL2 locus exist, we have so far been unable to detect a protein product from this putative transcript on Western blots using either antibodies thought to be specific to polyglutamine or an antibody raised against an epitope within the potential polyglutamine

![Figure 7](http://jnen.oxfordjournals.org/)

**FIGURE 7.** Protein aggregates in Huntington disease-like 2 (HDL2) are separate from RNA foci. Most nuclei in HDL2 frontal cortex contain either RNA foci or protein aggregates (first and second row, respectively). In neurons containing both RNA foci and protein aggregates, no strong colocalization was observed (third and fourth row). Colocalization was only detected in a single neuron in sections of frontal cortex from 3 different HDL2 brains (fifth row). Arrow, protein aggregates; arrowhead, RNA foci; asterisk, lipofuscin autofluorescence. Scale bar = 5 μm, applies to all panels.
reading frame on the strand opposite to JPH3 (unpublished data). This suggests to us that even if polyglutamine is expressed from the HDL2 locus, it may not be expressed at sufficiently high levels to explain the protein inclusions in HDL2 or HDL2 neurotoxicity. Our present finding that HDL2 protein aggregates contain TBP provides a potential alternative explanation for at least a portion of 1C2 staining of the aggregates. We speculate that TBP-containing nuclear aggregates, structurally resembling the nuclear aggregates observed in HD, form as part of the HDL2 neurotoxic process, potentially, but not necessarily, seeded by low levels of expanded polyglutamine expressed at the HDL2 locus. It is possible that sequestration of TBP in HDL2, and potentially in HD, may itself be of pathogenic relevance.

Overall, the pathologic alterations of HD and HDL2 are extremely similar. It is quite remarkable that the only consistent differences we were able to detect were in the content and distribution of protein aggregates, although the ultrastructure of the aggregates seems similar. These findings suggest that the pathogenic mechanisms of HD and HDL2 may partially converge, and that identifying the points of convergence may yield useful therapeutic targets for both diseases.

ACKNOWLEDGMENTS

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REFERENCES


FIGURE 8. Abundant presence of TATA-box binding protein in Huntington disease (HD) and Huntington disease-like 2 (HDL2) protein aggregates. Immunofluorescence was performed on HD and HDL2 cortex (medium frontal gyrus) sections. Scale bar = 5 μm.