Neuropathological investigations of three murine models of Huntington's disease

A thesis presented for the degree of
Doctor of Philosophy,
University of London

Aysha S. Raza Bsc. (Hons)
2009
This thesis is dedicated to the memory of S.M. Jamil-ur Rahman, who was the greatest advocate of a ‘good English education.’

I Aysha S Raza, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm this has been indicated in this thesis.
“I am just beginning to discover the difficulty of expressing one’s ideas on paper. As long as it consists solely of descriptions it’s pretty easy; but when reasoning comes into play, to make a proper connection, a clearness and a moderate fluency, is to me as I have said, a difficulty of which I had no idea.”

Charles Darwin near the end of the voyage of HMS Beagle
Abstract

Huntington’s disease (HD) is a purely genetic neurodegenerative disorder affecting approximately 1 in 10,000 people. It is most commonly associated with excessive involuntary movement, or chorea, combined with varying degrees of other motor, psychiatric and cognitive disturbances. Identification of the mutation in the HD gene prompted the generation of several transgenic mouse models. HD is but one of a family of at least 9 triplet repeat disorders, all of which exhibit protein aggregation by a similar mechanism. The understanding of one disease is therefore of importance to the understanding of them all. This thesis aims to be a comprehensive comparative study of three very different mouse models of HD elucidating the pathological changes that precede and accompany the disease process.

The work described in this thesis presents a detailed account of a longitudinal study of the pathological changes that occur within the brains of founder generations of mice transgenic for exon 1 of the HD gene, containing a highly expanded CAG repeat, the R6 lines. I have determined the intracellular sites for deposition and accumulation of the mutant protein huntingtin (htt), within both the neurons and glia of the central nervous system. The progressive accumulation of additional proteins within these aggregates has been described. The temporal evolution and spatial distribution of the neuronal intranuclear inclusion (NII) was determined using both immunohistochemical and morphometric analyses. The cellular consequences resulting from the aggregation of mutant htt were also investigated. I have conducted a detailed morphometric analysis of neurones within the cerebral cortex, striatum and cerebellum throughout the period of protein deposition, until the eventual degeneration of these cells. The dendritic and somal changes resulting from the cellular disruption associated with these NII are also described.

In a further series of experiments I have investigated the changes that occur in a novel model of HD, namely the conditional, doxycycline inducible double transgenic mouse, HD94 model. It was interesting to find that the same construct when differently manipulated in two mouse lines can produce such contrasting symptoms and pathology. This was highlighted by the comparison of immunohistochemical and morphometric analyses between the HD94 and the R6 lines, where the pattern of mutant protein deposition was found to vary significantly.

Lastly I have studied a more genetically accurate murine model of HD, the HD80 ‘knock-in model’. These mice develop a pathology broadly similar to that of the R6 lines but markedly different to that of the HD94, and over a much longer time frame.

This detailed comparative analysis of the molecular and cellular pathology of three transgenic mouse models of HD provides new insights identifying novel and unique neuropathology and suggests new approaches for therapeutic treatments for this disease.
Acknowledgements

I must thank a lot of people whose roles have been vital in the long gestation of this thesis, and who are far too many to name individually. However I am enormously indebted to my supervisor Stephen Davies who has seen me through the pain barrier and I am grateful for his advice and friendship and it has been a real honour to know and work with such a gifted scientist. Grateful thanks go also to Jon Clarke for agreeing to be my second supervisor. Very special thanks to Mark Turmaine for advice on all things EM and for his friendship. And thanks are also due to Elizabeth Slavik-Smith\textsuperscript{2} for advice on all things nuclear and shoes.

This PhD would not have been possible without the mouse models for which I am obliged to; Gillian Bates, Laura Mangiarini and Ben Woodman for the endless supply of the R6 mice, Peggy Shelbourne for her knock-in mice and Ai Yamamoto for her conditional mouse model and great times in New York. I would like also to thank the Huntington’s Disease Society of America for funding this PhD, as well as the Hereditary Disease Foundation, The Wellcome Trust and The Bogue Fellowship for small sums of money over a very long time.

Heartfelt thanks to Susan Evans for taking a chance and putting me on the road to science and for keeping me rooted in the big picture. Yvonne DeVille for being the best listener and helping me to maintain some semblance of sanity towards the end. Wendy Birch for being the best distraction from work ever, and whose friendship means a lot to me.

Thanks also to my family who have supported me through my education and helped make this a far more challenging experience than it needed to be!

I must also thank my Openlab elves Adil Raza and Jenny Parker who spent weeks measuring things instead of getting up to no good in their summer holidays! I am indebted to the late great Brian Ruth and ‘Mac’ Mike Corder for bailing me out of every misbehaving computer episode of which there have been many!

Finally I would like to thank the members of the lab, past, present and future, the good, bad and ugly all of whom have made the lab a colourful place to work in and who made it a character-building experience, hopefully one that has left me a better more patient person! I wish them all well in their own research projects and thank them for helping the evolution of mine.

And thanks inevitably to the fluffy people without whom there would be no thesis to quote Walt Disney: ‘I only hope that we never lose sight of one thing—that it was all started by a mouse’. ☁️
# Contents

Dedication.................................................................................................................................................i

Quote from Darwin...........................................................................................................................................ii

Abstract.....................................................................................................................................................iii

Acknowledgements...................................................................................................................................iv

Contents....................................................................................................................................................v

Figures.....................................................................................................................................................viii

Abbreviations..........................................................................................................................................xiii

I. Introduction:

**Chapter 1: Introduction**.........................................................................................................................1
  1.1. Historical background............................................................................................................................3
  1.2. Epidemiology.......................................................................................................................................4
  1.3. Aetiology.............................................................................................................................................4
  1.4. Disease symptoms...............................................................................................................................5
  1.5. Current therapies...............................................................................................................................7
  1.6. Pathology..........................................................................................................................................8
  1.7. The HD gene mutation.......................................................................................................................12
  1.8. Consequences of (CAG)n in HD.......................................................................................................14
  1.9. Huntington......................................................................................................................................16
    1.9.1. Normal huntingtin.........................................................................................................................17
    1.9.2. Abnormal huntingtin....................................................................................................................17
  1.10. Trinucleotide repeat diseases...........................................................................................................18
  1.11. Disease model systems....................................................................................................................19
  1.12. Current theories of HD pathogenesis...............................................................................................22
    1.12.1. Protein aggregation.....................................................................................................................22
    1.12.2. Seeding aggregation theory.........................................................................................................23
    1.12.3. Polar zipper theory.......................................................................................................................23
    1.12.4. The NII......................................................................................................................................24
    1.12.5. The DNI..................................................................................................................................28
    1.12.6. Cell damage control: The UPS system.......................................................................................29
    1.12.7. Cell death................................................................................................................................33
    1.12.8. Glial response to the presence of NII s.....................................................................................35
  1.13. Aims of this study.............................................................................................................................36

II. Materials and methods:

**Chapter 2: Materials and methods**...................................................................................................37
  2.1. Transgenic mouse models...................................................................................................................38
    2.1.1. Mangiarini/Bates Transgenic R6 Models....................................................................................40
    2.1.2. Yamamoto HD94 Conditional Model.........................................................................................44
    2.1.3. Shelbourne Knock-in Model.........................................................................................................47
  2.2. Tissue processing for light microscopy.............................................................................................49
  2.3. Tissue processing for electron microscopy.....................................................................................49

---

"Neuropathological Investigations of Three Murine Models of Huntington's Disease"
Chapter 3: The nature of the Inclusion ................................................................. 59
  3.1. Mangiarini/Bates Transgenic R6 Models ....................................................... 59
  3.2. Yamamoto HD94 Conditional Model .......................................................... 68
  3.3. Shelbourne Knock-in Model .......................................................... 74
  3.4. Summary of results .................................................................................... 78

Chapter 4: Immunocytochemical investigations ............................................... 83
  4.1. Mangiarini/Bates Transgenic R6 Model ....................................................... 83
     4.1.1. Molecular components ....................................................................... 83
     4.1.2. Regional sequential patterns ............................................................... 86
     4.1.3. Temporal sequential patterns .............................................................. 96
  4.2. Yamamoto HD94 Conditional Model .......................................................... 101
     4.1.1. Regional sequential patterns ............................................................... 101
     4.2.2. Temporal sequential patterns .............................................................. 103
  4.3. Shelbourne Knock-in Model ...................................................................... 105
     4.3.1. Regional sequential patterns ............................................................... 106
     4.3.2. Temporal sequential patterns .............................................................. 110
  4.4. Summary of results .................................................................................... 113

Chapter 5: Morphometric Studies .................................................................... 115
  5.1. Mangiarini/Bates Transgenic R6 Models ....................................................... 116
  5.2. Yamamoto HD94 Conditional Model .......................................................... 123
  5.3. Shelbourne Knock-in Model ...................................................................... 126
  5.4. Summary of results .................................................................................... 129

Chapter 6: Golgi Studies ..................................................................................... 133
  6.1. Mangiarini/Bates Transgenic R6 Models ....................................................... 135
     6.1.1. Striatal pathology ................................................................................ 136
         6.1.1.1. Dendritic arbors ........................................................................... 136
         6.1.1.2. Diameters of dendritic shafts ......................................................... 139
         6.1.1.3. Spine density ............................................................................... 142
         6.1.1.4. Spine morphology & abnormal dendritic growths ..................... 143
     6.1.2. Giant cholinergic neurones ................................................................. 145
     6.1.3. Cortical pathology ............................................................................. 146
     6.1.4. Hippocampal cell pathology ............................................................... 147
     6.1.5. Purkinje cell pathology ..................................................................... 148
     6.1.6. Glia .................................................................................................. 149
     6.1.7. Olfactory bulbs ................................................................................. 150
  6.2. Yamamoto HD94 Conditional Model .......................................................... 151
     6.2.1. Striatal pathology ............................................................................. 151
         6.2.1.1. Dendritic arbors ........................................................................... 151
         6.2.1.2. Diameters of dendritic shafts ......................................................... 152
         6.2.1.3. Spine density ............................................................................... 154
  6.3. Shelbourne Knock-in Model ..................................................................... 156
     6.3.1. Striatal pathology ............................................................................. 156

Neuropathological Investigations of Three Murine Models of Huntington's Disease

6.3.1.1. Dendritic arbors.......................................................... 157
6.3.1.2. Diameters of dendritic shafts........................................ 158
6.3.1.3. Spine density.............................................................. 160
6.4. Summary of results...................................................... 161

Chapter 7: Neuronal Death Processes................................................. 168
7.1. Mangiarini/Bates Transgenic R6 Models................................. 171
7.2. Yamamoto HD94 Conditional Model.................................... 180
7.3. Shelbourne Knock-in Model............................................... 184
7.4. Summary of results.......................................................... 190

Chapter 8: Glial Observations.......................................................... 193
8.1. Mangiarini/Bates Transgenic R6 Models................................. 193
8.2. Yamamoto HD94 Conditional Model.................................... 201
8.3. Shelbourne Knock-in Model............................................... 205
8.4. Summary of results.......................................................... 209

IV. Discussion:

Chapter 9: Discussion........................................................................ 213
9.1. Huntingtin aggregation in the nucleus and the formation of an NII........................................ 214
9.2. Continued accumulation of Huntingtin protein............................ 218
9.3. Cachexia, Sarcopaenia & Neuronal shrinkage............................ 224
9.4. Neuronal Atrophy and dendritic remodelling............................ 230
9.5. Dark cell degeneration....................................................... 241
9.6. Apoptosis in HD.............................................................. 242
9.7. Autophagy & autophagic cell death....................................... 245

V Conclusion:

Chapter 10: Conclusions.............................................................. 249
10.1. Conclusions drawn from this study........................................ 250
10.2. Further Studies.............................................................. 252

Appendices:.................................................................................... 253
Appendix 1: Legend for brain sections used in this thesis.................... 254
Appendix 2: Summary timeline of the R6/2 model.............................. 257
Appendix 3: Summary timeline of the R6/1 model.............................. 258
Appendix 4: Summary timeline of the HD94 model........................... 259
Appendix : Summary timeline of the HD80 model............................ 260

References:...................................................................................... 261
List of references.............................................................................. 262
List of Figures & Tables

Chapter 1: Introduction

Figure 1: George Huntington aged 24 when he wrote his landmark paper..........................2
Figure 1.1: HD brain pathology from Harper.................................................................8
Figure 1.2: Grades of HD brain from Bird.......................................................................9
Figure 1.3: The HD gene from Gusella et al. 1996..........................................................13
Figure 1.4: Phenotype in relation to CAG repeat size....................................................14
Figure 1.5: Variability in age of onset in relation to CAG repeat size...............................16
Figure 1.6: Variability in the age of onset in relation to CAG repeat sizes in poly Q diseases..16
Table 1.1: Trinucleotide repeat diseases.........................................................................18
Figure 1.7: Max Perutz and the structural model of the polar zipper..............................24
Figure 1.8: Electron micrographs showing the nature of the NII.....................................25
Figure 1.9: The NII as seen at light microscopy level.......................................................26
Figure 1.10: Electron micrographs and light microscopy photos of the DNI....................29
Figure 1.11: Schematic diagram of the proteasome.......................................................30
Figure 1.12: Schematic diagram of the ubiquitin proteasome system............................31
Figure 1.13: Schematic diagram of protein management systems in the cell..................32

Chapter 2: Materials and methods

Figure 2.1: Diagram of the constructs of all the R6 lines of murine model........................40
Figure 2.2: Simplified construct of the R6/2 model.........................................................40
Figure 2.3: Photographs of R6/2 and control mice............................................................43
Figure 2.4: Photographs of R6/2 and control mice in tail suspension/clasping test...........43
Figure 2.5: Simplified construct of the HD94 model.........................................................45
Figure 2.6: Diagram explaining the DOX system used in the HD94 model.......................48
Figure 2.7: Photographs of HD94 mice in tail suspension/clasping test...........................46
Figure 2.8: Schematic diagram of how the HD80 mice were constructed........................47
Table 2.1: Table of all the primary anti htt antibodies used.............................................51
Table 2.2: Table of all the primary antibodies used in this study.....................................51
Figure 2.9: Diagram explaining the Sholl analysis............................................................57
Figure 2.10: Diagram explaining how branch orders were determined............................57

Chapter 3: The Nature of the Inclusion

Figure 3.1: Drawing of the evolution of the inclusion in the neurone...............................59
Figure 3.2: Characterisation scale for inclusion evolution.................................................60
Figure 3.3: Comparative immunostaining of htt in the R6/2 and R6/1 models..................61
Figure 3.4: Graphs of cortical and striatal NII and somal areas in R6/2 brains..................63
Figure 3.5: Graphs of cortical and striatal NII and somal areas in R6/1 brains..................65
Figure 3.6: Graphs of volumes and surface areas in R6/2 model.....................................66
Figure 3.7: Graphs of volumes and surface areas in R6/1 model......................................66
Figure 3.8: EM48 stained NII and DNI in the striatum of the R6/2 model at EM............67
Figure 3.9: Inclusions in the HD94 model at LM............................................................68
Figure 3.10: EM48 stained DNIs in the striatum of the HD94 model...............................69
Chapter 4: Immunocytochemical Investigations

Figure 4.1: Regional sequential maps of the R6/2 and R6/1 longitudinal studies
Figure 4.2: Regional inclusion staining of R6/2 model at 1 week of age
Figure 4.3: Regional inclusion staining of R6/2 model at 2 weeks of age
Figure 4.4: Regional inclusion staining of R6/2 model at 3 weeks of age
Figure 4.5: Regional inclusion staining of R6/2 model at 4 weeks of age
Figure 4.6: Regional inclusion staining of R6/1 model at 1 month of age
Figure 4.7: Regional inclusion staining of R6/1 model at 2 months of age
Figure 4.8: Regional inclusion staining of R6/1 model at 3 months of age
Figure 4.9: Regional inclusion staining of R6/1 model at 4 months of age
Figure 4.10: Temporal sequential tables and photos in cortex of the R6/2 model
Figure 4.11: Temporal sequential tables and photos in cortex of the R6/1 model
Figure 4.12: Temporal sequential tables and photos in striatum of the R6/2 model
Figure 4.13: Temporal sequential tables and photos in striatum of the R6/1 model
Figure 4.14: Temporal sequential tables and photos in cerebellum of the R6/2 model
Figure 4.15: Temporal sequential tables and photos in cerebellum of the R6/1 model
Figure 4.16: Regional sequential maps of the HD94
Figure 4.17: Regional inclusion staining of HD94 model at 36 weeks of age
Figure 4.18: Temporal sequential tables and photos of the HD94 model
Figure 4.19: Regional sequential maps of the HD80 model
Figure 4.20: Regional inclusion staining of HD80 full length (FL) model
Figure 4.21: Regional inclusion staining of HD80 fragment (Fr) model
Figure 4.22: Temporal sequential tables and photos of the HD80 FL at 24 months
Figure 4.23: Temporal sequential tables and photos of the HD80 Fr at 24 months
Figure 4.24: Temporal sequential tables and photos of the HD80 FL at 36 months
Figure 4.25: Temporal sequential tables and photos of the HD80 Fr at 36 months

Chapter 5: Morphometric Studies

Figure 5.1: Graph showing the loss of body and brain weight
Figure 5.2: Photographs of R6/2 and control brains
Figure 5.3: Graphs showing somal areas for neuronal populations in R6/2 model
Chapter 6: Golgi Studies

Figure 6.1: Drawings of medium spiny neurones from HD and control brain..........................133
Figure 6.2: Drawings of medium spiny neurones from R6/2 and LMC brain..........................136
Figure 6.3: Graphs of Sholl analyses of the R6/2 model at 4, 8 and 12 weeks of age...............137
Figure 6.4: Graphs of Sholl analyses of the R6/1 model at 36 weeks/9 months of age...........138
Figure 6.5: Graphs of dendritic shaft diameters in the R6/2 and R6/1 models.........................139
Figure 6.6: Drawings of dendritic branch segments in the R6/2 model................................140
Figure 6.7: Drawings of dendritic branch segments in the R6/1 model................................141
Figure 6.8: Graphs of dendritic spine density in the R6/2 and R6/1 models...........................142
Figure 6.9: Diagram showing different spine morphologies..............................................143
Figure 6.10: Drawings showing different dendritic morphologies in the R6/2 model..............144
Figure 6.11: Drawings showing giant cholinergic neurones in the R6/2 model.........................145
Figure 6.12: Drawings showing cortical pyramidal neurones in the R6/2 model......................146
Figure 6.13: Drawings showing hippocampal pyramidal neurones in the R6/2 model..............147
Figure 6.14: Drawings showing Purkinje cells of the cerebellum in the R6/2 model................148
Figure 6.15: Drawings showing glial cells in the R6/2 model.............................................149
Figure 6.16: Drawings showing mitral cells of the olfactory bulb in the R6/2 model..............150
Figure 6.17: Graphs of Sholl analyses of the HD94 and R6/1 models at 36 weeks of age........151
Figure 6.18: Graphs of dendritic shaft diameters in the HD94 and R6/1 models......................152
Figure 6.19: Drawings of dendritic branch segments in the HD94 model...............................153
Figure 6.20: Graphs of dendritic spine density in the HD94 and R6/1 models.........................154
Figure 6.21: Graphs of Sholl analysis of the HD80 model..................................................157
Figure 6.22: Graphs of dendritic shaft diameters in the HD80 model....................................158
Figure 6.23: Drawings of dendritic branch segments in the HD80 model..............................159
Figure 6.24: Graphs of dendritic spine density in the HD80 model......................................160
Figure 6.25: Summary of Sholl analyses of all models and and drawings of R6/2 arbours......163
Figure 6.26: Drawings of dendritic arbours of R6/1 & HD94 models.................................164
Figure 6.27: Drawings of dendritic arbours of the HD80 model.........................................164
Figure 6.28: Summary graphs of all parameters in R6/2....................................................165
Figure 6.29: Summary graph of shaft diameters of all models studied.................................166
Figure 6.30: Summary graph of spine density analyses of all models studied.......................166
Chapter 7: Neuronal Death Processes

Figure 7.1: SEM of healthy and apoptosing HeLa cells .................................................................168
Figure 7.2: Schematic diagram of apoptosis and necrosis ........................................................ ....169
Figure 7.3: Drawing of distribution of DCD profiles in anterior cingulate cortex in R6/2 .........171
Figure 7.4: TEM of DCD in anterior cingulate cortex in 17 week old R6/2 .........................172
Figure 7.5: TEM of DCD in anterior cingulate cortex of R6/1 brain..............................................174
Figure 7.6: Map & photos showing DCD profiles in R6/2 & R6/1 brain........................................176
Figure 7.7: Schematic maps showing distribution of DCD profiles in R6/2 & R6/1 model ......177
Table 7.1: Table of the incidence of DCD and NIIs in R6/2 model..............................................178
Table 7.2: Table of the incidence of DCD and NIIs in R6/1 model..............................................179
Figure 7.8: TEM of DCD in cortex of HD94 model........................................................................181
Figure 7.9: Map & photos showing DCD profiles in HD94 brain..............................................182
Figure 7.10: Schematic maps showing distribution of DCD profiles in HD94 model ..............182
Table 7.3: Table of the incidence of DCD and NIIs in HD94 model..............................................183
Figure 7.11: TEM showing aspects of DCD in the HD80 model.................................................185
Figure 7.12: Map & photos showing DCD profiles in FL HD80 brain........................................187
Figure 7.13: Map & photos showing DCD profiles in Fr HD80 brain........................................188
Figure 7.14: Schematic maps showing distribution of DCD profiles in FL & Fr HD80...........189
Table 7.4: Table of the incidence of DCD and NIIs in FL & Fr HD80 model.........................189

Chapter 8: Glial Observations

Figure 8.1: Photographs of immunostaining of R6/2 brain for various glial markers............196
Figure 8.2: TEM of dying neurones being engulfed by glia in R6/2 model..............................197
Figure 8.3: LM photograph of inclusions in glial cells of R6/2 corpus callosum....................198
Figure 8.4: TEM of glia in the corpus callosum of R6/2............................................................198
Figure 8.5: TEM of NIIs in R6/2 neuroglia...............................................................................199
Figure 8.6: LM photograph of GFAP stained glial cell in HD94 model....................................201
Figure 8.7: Photographs of immunostaining of HD94 brain for various glial markers.........202
Figure 8.8: LM photograph of htt staining of glia in corpus callosum of HD94 brain...........203
Figure 8.9: TEM of dying neurones being engulfed by glia in HD94 cortex............................204
Figure 8.10: Photographs of immunostaining of HD80 brain for various glial markers........206
Figure 8.11: Photographs of immunostaining of LMC brain for various glial markers.........207
Figure 8.12: TEM of dying neurones & glia in HD80 brain.....................................................208

Chapter 9: Discussion

Figure 9.1: Cartoon of possible foldings of htt protein..............................................................214
Figure 9.2: EMs of lewy body and fibrilar components in NII..................................................215
Figure 9.3: Hypothesised evolution of the inclusion.................................................................219
Figure 9.4: Diagram of all the nuclear bodies............................................................................220
Figure 9.5: Cartoon showing handling of misfolded proteins..................................................222
Figure 9.6: Diagram of the UPS.................................................................................................223
Figure 9.7: Graphs showing change in body and brain weights in R6/2 model......................226
Figure 9.8: Diagram of the influence of the mTOR pathway....................................................229
Figure 9.9: Graph showing neuronal atrophy in R6/2 model.....................................................230
Figure 9.10: Diagram explaining sholl and convex hull analyses..............................................232
Figure 9.11: Graphs showing dendritic changes in the R6/2 model............................................233
Figure 9.12: Diagram exploring mechanisms of atrophy in R6/2 model.....................................234
Figure 9.13: Drawings showing somal areas and spines in R6/2 model........................................235
Figure 9.14: Diagram explaining spine count discrepancy..........................................................235
Figure 9.15: Graph showing spread of spines over branch orders.............................................236
Table 9.1: Table of dendritic spine pathologies...........................................................................238
Figure 9.16: Diagram showing different modes of neuronal cell death.....................................241

Chapter 10: Conclusions

Figure 10.1: Graph showing correlation of atrophy and inclusion growth...............................250

Appendices

Appendix 2: Summary timeline of the R6/2 model.....................................................................257
Appendix 3: Summary timeline of the R6/1 model.....................................................................258
Appendix 4: Summary timeline of the HD94 model.................................................................259
Appendix 5: Summary timeline of the HD80 model.................................................................260

Neuropathological Investigations of Three Murine Models of Huntington's Disease
Abbreviations

A

ABC - Avidin-biotin complex
AD - Alzheimer's disease
ALS - Amyotrophic lateral sclerosis

B

BMI - Body mass index
β-Gal - Beta galactosidase, reporter protein from E.coli.

C

CAG - Codon coding for glutamine
CBP - Creb binding protein
CJD - Creutzfeld-Jakob disease
CNS - Central nervous system
C57 Black 6 - Background strain of mice

D

DAB - Diaminobenzidine
DCD - Dark cell degeneration
DNI - Dystrophic neurite inclusion
DRPLA - dentato-rubra-palado luisian atrophy

E

EM - Electron microscopy / micrograph
ER - Endoplasmic reticulum

F

FL - Full length Hdh gene integrated into the HD80 knock-in mouse model
Fr - Fragment of the Hdh gene integrated into the HD80 knock-in model
FVB - Background strain of mice sensitive to B strain of Friend Leukaemia virus
G
GABA-γ-Aminobutyric acid
GAD-Glutamic acid decarboxylase
GFAP-Glial fibrillary acidic protein, astrocyte marker.

H
HD-Huntington’s disease
HDCRG-Huntington’s Disease Collaborative Research Group
HDF-Hereditary Disease Foundation
Hdh-Huntington’s disease gene locus
HDSA-Huntington’s Disease Society of America
HSP-Heat shock proteins
Htt-Huntingtin protein

L
LM-Light microscopy
LMC-Litter-mate control
LTP-Long-term potentiation

M
MRI-Magnetic resonance imaging
mRNA-Messenger ribonucleic acid
mTOR-Mammalian Target of Rapamycin protein

N
NG2-Integral membrane proteoglycan, marker for immature glia.
NII-Neuronal intranuclear inclusion

P
PD-Parkinson’s disease
PDGF αR-Alpha receptor for platelet derived growth factor.
PML-Promyelocytic leukemia
R
RFLP-Restriction fragment linked polymorphism
S
SAHA-suberoylanilide hydroxamic acid
SBMA-Spinobulbar muscular atrophy
SCA-Spinocerebellar ataxia
SOD-Superoxide dismutase
T
TAU-Microtubule associated protein-Tau
TBP-TATA-binding protein
TEM-Transmission electron microscopy/micrograph
TUNEL-Terminal deoxynucleotidyl transferase (TdT)-mediated dUTP nick end labeling
U
Ubq-Ubiquitin
UPS-Ubiquitin proteasome system
Y
YAC-Yeast artificial chromosome