



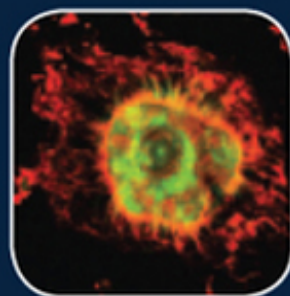
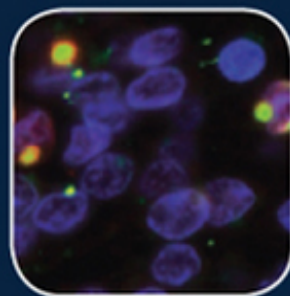
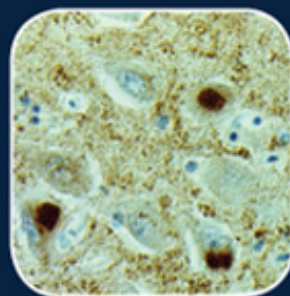
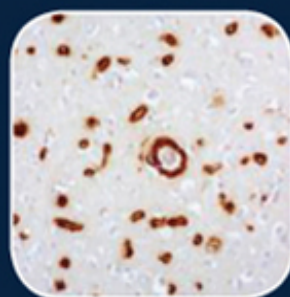
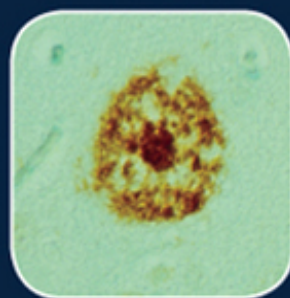
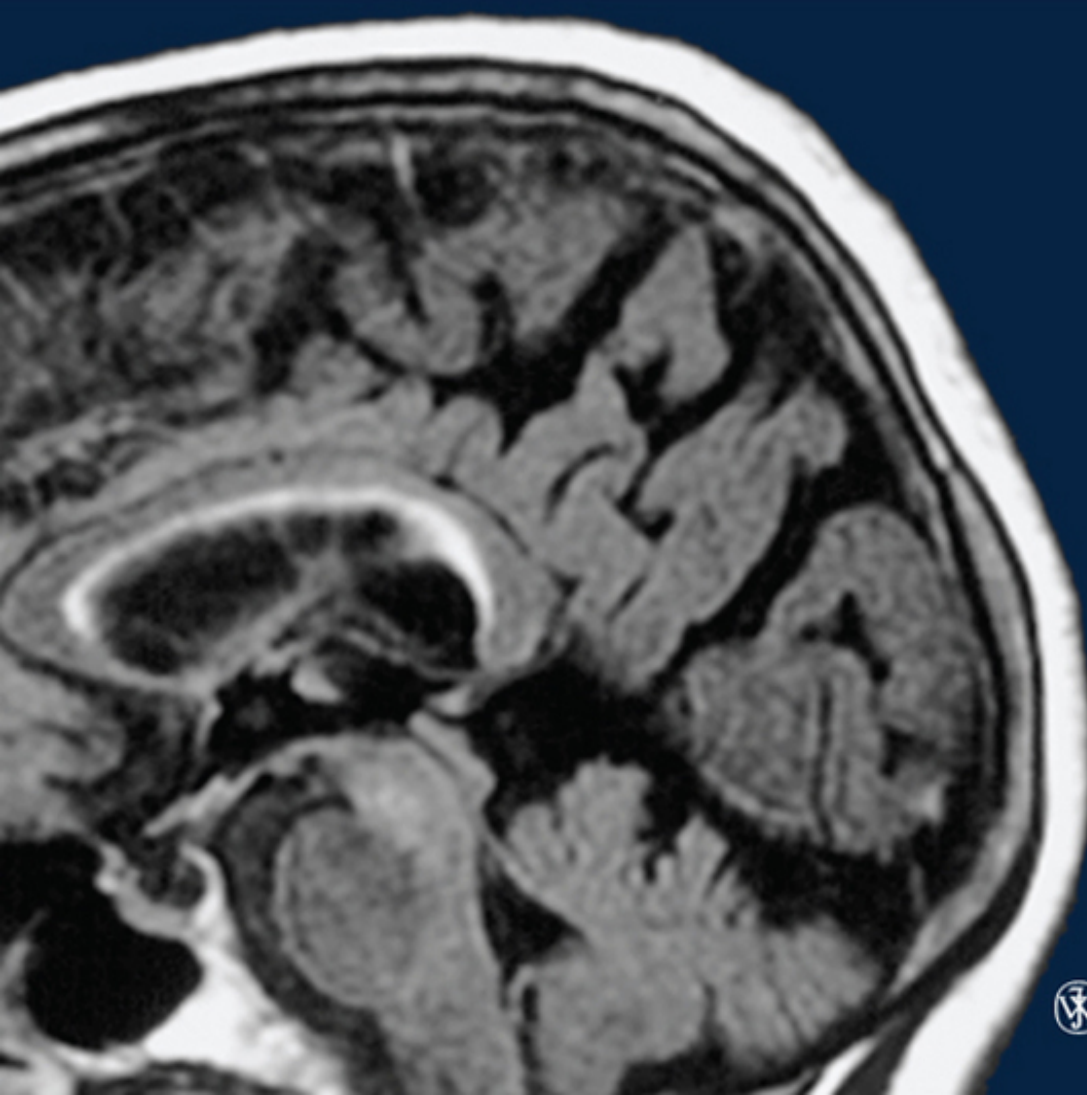
NEURODEGENERATION

the molecular pathology of dementia
and movement disorders

SECOND EDITION

Edited by

Dennis W. Dickson and Roy O. Weller



 **WILEY-BLACKWELL**

Table of Contents

Cover

Title page

Copyright page

List of Contributors

Preface

List of Abbreviations

Part 1: Introduction: Basic Mechanisms of Neurodegeneration

**1 Introduction to Neurodegeneration:
The Molecular Pathology of Dementia
and Movement Disorders**

Introduction

**Molecular classification of
neurodegenerative disorders**

**Shared mechanisms in neurodegenerative
disorders**

2 Cell Death and Neurodegeneration

Introduction

Definition

Future directions

3 Oxidative Stress and Balance in Neurodegenerative Diseases

Definition

Detection of cellular oxidative damage

Consequences and mechanisms of cellular oxidative damage

Future directions

4 Protein Aggregation in Neurodegeneration

Introduction

Protein misfolding can lead to protein aggregation

How do protein aggregates damage cells?

Lessons from prion diseases: prionoids

Are all protein aggregates evil?

5 Protein Degradation in Neurodegeneration: The Ubiquitin Pathway

Definition

The nervous system

The ubiquitin system in chronic neurodegenerative disease

Autophagy, ubiquitin and neurodegeneration

A unifying hypothesis? Can malfunction or overwhelming of the UPS and autophagy explain chronic neurodegenerative disease?

6 Genetics of Neurodegeneration

Introduction

Molecular genetics, positional cloning and genetic analysis of mendelian disease

Genetic approaches to complex disease

How will genetic analysis change over the next few years?

How should a clinician or pathologist approach a familial disorder?

Molecular genetics complements and subverts the notions of clinicopathological entities

How genetics guides treatments aimed at pathogenesis

The present situation and our tasks

7 Transgenic Animal Models of Proteinopathies

Introduction

Amyloid precursor protein mouse models of amyloidosis

Tau transgenic mouse models of tauopathies

Combined tau and amyloid precursor protein transgenic models of Alzheimer's disease

Mouse models of synucleinopathies

Mouse models of TDP-43 proteinopathies

Part 2: Alzheimer's Disease and Aging

8 Clinical Aspects of Alzheimer's Disease

Definitions of dementia and Alzheimer's disease

Epidemiology of dementia and Alzheimer's disease

Proposed risk factors and protective factors for Alzheimer's disease

Clinical features of Alzheimer's disease

Clinical Stages of Alzheimer's disease

Laboratory evaluations in suspected Alzheimer's disease

Treatment

Future directions

9 Genetics of Alzheimer's Disease

Introduction

Early-onset Alzheimer's disease genetics

Late-onset Alzheimer's disease genetics

Systematic field synopsis and meta-analyses: the AlzGene database
Genome-wide association studies in Alzheimer's disease
Potential functional implications of top-ranking putative late-onset Alzheimer's disease genes
Conclusion

10 Neuropathology of Alzheimer's Disease and its Variants

Definition
Synonyms and historical aspects
Macroscopy
Histopathology
Clinicopathological correlations
Associated pathology
Staging and neuropathological diagnostic criteria
Differential diagnosis
Experimental models

11 Amyloid- β Production

Introduction
Normal structure and function of the amyloid precursor protein
Secretase enzymes that process the juxtamembranous domains of the amyloid precursor protein

Factors modulating β - and γ -secretase function

A β Aggregation and accumulation in the extracellular space

Downstream events in the evolution of Alzheimer's disease

12 Elimination of Amyloid β from the Brain, its Failure in Alzheimer's Disease and Implications for Therapy

Introduction

Mechanisms and pathways for the elimination of amyloid β from the normal brain

Genetics

Therapies for the reduction of amyloid β in the brain in Alzheimer's disease

Future directions

Part 3: Tauopathies

13 Introduction to the Tauopathies

Historical aspects

Tau isoforms

Assembly of tau

Hyperphosphorylation of tau

Isoform composition of tau filaments

Genetics

Future directions

14 Frontotemporal Dementia and Parkinsonism Linked to Chromosome 17

Definition

Historical aspects

Epidemiology

Genetics

Clinical features

Neuropathology

Hyperphosphorylation of tau

Tau filaments

Soluble and insoluble tau

Pathogenesis

Mechanisms of neurodegeneration

Therapies and future directions

15 Progressive Supranuclear Palsy and Corticobasal Degeneration

Definition

Synonyms and historical aspects

Epidemiology

Genetics

Clinical features

Macroscopy

Histopathology

Combined pathologies

Ultrastructural findings

Biochemistry

Differential diagnosis

Animal and experimental models
Pathogenesis
Future directions and therapy

16 Pick's Disease

Introduction
Definition
Synonyms and historical aspects
Epidemiology
Genetics
Clinical features
Macroscopy
Histopathology
Immunohistochemistry and ultrastructural findings
Biochemistry
Differential diagnosis of Pick's disease
Clinicopathological correlations
Experimental models
Pathogenesis
Future directions and therapy
Acknowledgment

17 Argyrophilic Grain Disease

Definition
Synonyms and historical aspects
Epidemiology
Genetics
Clinical features

Macroscopy

Histopathology

Immunohistochemistry and ultrastructural findings

Biochemistry

Differential diagnosis

Experimental models

Future directions

18 Parkinsonism-Dementia Complex of Guam

Definition

Synonyms and historical aspects

Epidemiology

Genetics

Clinical features

Macroscopy

Histopathology and distribution of lesions

Biochemistry

Parkinsonism-dementia complex and 43 kDa trans-activation-responsive region

DNA-binding protein

Parkinsonism-dementia complex and amyotrophic lateral sclerosis of Guam

Parkinsonism-dementia complex and amyotrophic lateral sclerosis of Guam and Kii parkinsonism-dementia complex and amyotrophic lateral sclerosis

Pathogenesis

Experimental models

Future directions and therapy
Acknowledgments

19 Postencephalitic Parkinsonism

Definition

Synonyms and historical aspects

Epidemiology

Genetics

Clinical features

Macroscopy

Histopathology

Immunohistochemistry and ultrastructural findings

Biochemistry

Differential diagnosis

Experimental models

Pathogenesis

Future directions and therapy

Part 4: Synucleinopathies

20 Introduction to α -Synucleinopathies

Introduction

21 Parkinson's Disease

Definition

Synonyms and historical aspects

Epidemiology

Genetics

Clinical features

Neuroimaging

Laboratory findings and biomarkers

Neuropathology

Neuronal vulnerability

α -Synuclein (Lewy) pathology

Lewy bodies and neuronal cell death

Evolution of Lewy body-related pathology

Pathophysiology of Parkinson's disease

Symptom-related lesion patterns in

Parkinson's disease

Involvement of extranigral systems

Biochemistry

Proteins in substantia nigra

Differential diagnosis

Etiology and pathogenesis of Parkinson's disease

Therapy

22 Dementia with Lewy Bodies and Parkinson's Disease Dementia

Definition

Synonyms and historical aspects

Epidemiology

Genetics

Clinical features

Macroscopy

Histopathology

Immunocytochemistry and ultrastructural findings

Biochemistry

Differential diagnosis

Experimental models

Pathogenesis

Future directions and therapy

23 Lewy Bodies in Conditions other than Disorders of α -Synuclein

Introduction

Niemann-Pick type C disease

Acid β -glucosidase-associated Parkinson's disease

PLA2G6-associated disorders

Pathogenesis

24 Multiple System Atrophy

Definition

Synonyms and historical aspects

Epidemiology

Genetics

Clinical features

Macroscopy

Histopathology

Immunohistochemistry and ultrastructural findings

Biochemistry

Differential diagnosis

Experimental models
Pathogenesis
Future directions and therapy

Part 5: Trinucleotide Repeat Disorders

25 Introduction to Trinucleotide Repeat Diseases

Introduction

26 Huntington's Disease

Definition

Synonyms and historical aspects

Epidemiology

Genetics

Clinical features

Macroscopy

Histopathology

Immunohistochemistry and ultrastructural findings

Biochemistry

Differential diagnosis

Experimental models

Pathogenesis

Future directions and therapy

27 Spinocerebellar Ataxias

Definition

Synonyms and historical aspects

Epidemiology

Genetics

Clinical features

Neuropathology of spinocerebellar ataxias

Macroscopic pathology

Histopathology

Immunohistochemistry

Experimental models

Pathogenesis

28 Friedreich's Ataxia

Definition

Synonyms and historical aspects

Epidemiology

Genetics

Clinical features

Macroscopy

Histopathology and immunocytochemistry

Ultrastructural findings

Biochemistry

Differential diagnosis

Pathogenesis

Future directions and therapy

29 Dentatorubral-pallidoluysian Atrophy

Definition

Synonyms and historical aspects
Epidemiology
Genetics
Clinical features
Macroscopy
Histopathology
Immunohistochemistry and ultrastructural findings
Biochemistry
Differential diagnosis
Experimental models
Pathogenesis
Future directions and therapy

30 Spinal and Bulbar Muscular Atrophy

Definition and historical aspects
Clinical features
Genetics
Histopathology
Experimental models
Pathogenesis
Treatment

Part 6: Prion Disorders

31 Introduction to Prion Disorders

Molecular biology of prions

Physiological role of the cellular prion protein

Anatomy and pathophysiology of prion diseases

Prophylaxis and therapy: the big challenge

Open questions in prion diseases

32 Sporadic Creutzfeldt-Jakob Disease

Definition

Synonyms and historical aspects

Epidemiology

Genetics

Clinical features

Macroscopy

Histopathology

Immunohistochemistry and ultrastructure

Biochemistry

Subtypes of sporadic Creutzfeldt-Jakob disease: clinicopathological profile and molecular basis of heterogeneity

Differential diagnosis

Pathogenesis

Future directions and therapy

33 Genetic Creutzfeldt-Jakob Disease

Definition

Historical aspects

*Phenotypes associated with genetic
Creutzfeldt-Jakob disease*

Differential diagnosis

Pathogenesis

Experimental models

Future directions and therapy

34 Fatal Familial and Sporadic Insomnia

Definition

Synonyms and historical aspects

Epidemiology

Genetics

Clinical features

Neuropathology

Immunohistochemistry

Biochemistry

Experimental models

Future directions and therapy

35 A New Prion Disease: Protease- Sensitive Prionopathy

Definition

Epidemiology

Genetics

Clinical features

Neuropathology

Biochemistry

Differential diagnosis

Pathogenesis

36 Variant Creutzfeldt-Jakob Disease

Definition

Synonyms and historical aspects

Epidemiology

Clinical features

Macroscopy

Histopathology

Immunohistochemistry and ultrastructural findings

Biochemistry

Differential diagnosis

Experimental models

Pathogenesis

Future directions and therapy

37 Gerstmann-Sträussler-Scheinker Disease

Definition

Historical aspects

Epidemiology

Genetics

Clinical features

Neuropathological features

Histopathology, immunohistochemistry and ultrastructural findings

Biochemical features

Differential diagnosis

Pathogenesis

38 Kuru

Definition

Synonyms and historical aspects

Genetics

Clinical features

Macroscopy

Histopathology

Immunohistochemistry and ultrastructural findings

Biochemistry

39 Iatrogenic Creutzfeldt-Jakob Disease

Definition

Synonyms and historical aspects

Epidemiology

Genetics

Clinical features

Macroscopy

Histopathology

Biochemistry

Differential diagnosis

Pathogenesis

Future directions and therapy

Part 7: Frontotemporal Lobar Degeneration and Amyotrophic Lateral Sclerosis/Motor Neuron Disease

40 Introduction

Classification and historical aspects

Frontotemporal lobar degeneration

Amyotrophic lateral sclerosis and motor neuron disease

Links between frontotemporal lobar degeneration and amyotrophic lateral sclerosis/motor neuron disease

Diagnostic evaluation in frontotemporal lobar degeneration

41 Frontotemporal Lobar Degeneration with TDP-43 Pathology

Definition

Synonyms and historical aspects

Epidemiology

Genetics

Clinical features

Macroscopy

Histopathology, immunohistochemistry and ultrastructural findings

Transactive response DNA-binding protein with M_r 43 kDa biochemistry in

frontotemporal lobar degeneration with TDP-43 pathology

Differential diagnosis

Normal function of transactive response

DNA-binding protein with M_r 43 kDa

Pathogenesis and experimental models

Future directions and therapy

Acknowledgments

42 Neuronal Intermediate Filament Inclusion Disease

Definition

Synonyms and historical aspects

Epidemiology

Genetics

Clinical features

Macroscopy

Histopathology

Immunohistochemistry and ultrastructural findings

Biochemistry

Differential diagnosis

Experimental models

Pathogenesis

Future directions and therapy

Acknowledgments

43 Frontotemporal Lobar Degeneration with FUS

Immunoreactive Inclusions

Definition

Synonyms and historical aspects

Epidemiology

Genetics

Clinical features

Macroscopy

Histopathology, immunohistochemistry and ultrastructural findings

Biochemistry

Differential diagnosis

Experimental models

Pathogenesis and future directions

44 Amyotrophic Lateral Sclerosis, Primary Lateral Sclerosis and Spinal Muscular Atrophy

Definition

Synonyms and historical aspects

Epidemiology

Genetics

Clinical features

Macroscopy

Histopathology

Immunohistochemistry and ultrastructural findings

Biochemistry

Differential diagnosis

Experimental models

Pathogenesis
Future directions and therapy

Part 8: Other Neurodegenerative Disorders

*45 Introduction: Genetic Analysis as a
Lumper and Splitter in
Neurodegenerative Disease*

*46 Inherited Amyloidoses and
Neurodegeneration: Familial British
Dementia and Familial Danish
Dementia*

Definition

Synonyms and historical aspects

Epidemiology

Genetics

Clinical features

Macroscopy

Histopathology

*Immunohistochemistry and ultrastructural
findings*

Biochemistry

Differential diagnosis

Pathogenesis

*Animal models, future directions and
therapy*

47 Neurodegeneration with Brain Iron Accumulation

Definition

Synonyms and historical aspects

Epidemiology

Genetics

Clinical features

Macroscopy

Histopathology

Biochemistry

Differential diagnosis

Experimental models

Pathogenesis

Future directions and therapy

48 Familial Encephalopathy with Neuroserpin Inclusion Bodies

Definition

Synonyms and historical aspects

Epidemiology

Genetics

Clinical features

Macroscopy

Histopathology

Immunohistochemistry and ultrastructural findings

Biochemistry

Differential diagnosis

Experimental models

Pathogenesis

Future directions and therapy

49 Hereditary Ferritinopathies

Definition

Synonyms and historical aspects

Epidemiology

Genetics

Clinical features

Macroscopy

Histopathology, immunohistochemistry and ultrastructural findings

Biochemistry

Differential diagnosis

Experimental models

Pathogenesis

Future directions and therapy

Index

Neurodegeneration: The Molecular Pathology of Dementia and Movement Disorders

EDITED BY

DENNIS W. DICKSON MD

Professor of Pathology
Departments of Pathology (Neuropathology) and Neuroscience
Mayo Clinic, Jacksonville, FL, USA

ROY O. WELLER MD PhD FRCPath

Emeritus Professor of Neuropathology
Clinical Neurosciences
University of Southampton School of Medicine
Southampton General Hospital
Southampton, UK

SECOND EDITION

 **WILEY-BLACKWELL**
A John Wiley & Sons, Ltd., Publication



www.intsocneuropathol.com

This edition first published 2011, © 2003, 2011 by
International Society of Neuropathology

Wiley-Blackwell is an imprint of John Wiley & Sons, formed
by the merger of Wiley's global Scientific, Technical and
Medical business with Blackwell Publishing.

Registered office: John Wiley & Sons Ltd, The Atrium,
Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial offices: 9600 Garsington Road, Oxford, OX4 2DQ,
UK

The Atrium, Southern Gate, Chichester, West Sussex, PO19
8SQ, UK

111 River Street, Hoboken, NJ 07030-5774, USA"

For details of our global editorial offices, for customer
services and for information about how to apply for
permission to reuse the copyright material in this book
please see our website at www.wiley.com/wiley-blackwell.

The right of the author to be identified as the author of this
work has been asserted in accordance with the Copyright,
Designs and Patents Act 1988.

All rights reserved. No part of this publication may be
reproduced, stored in a retrieval system, or transmitted, in
any form or by any means, electronic, mechanical,
photocopying, recording or otherwise, except as permitted
by the UK Copyright, Designs and Patents Act 1988, without
the prior permission of the publisher.

Designations used by companies to distinguish their
products are often claimed as trademarks. All brand names
and product names used in this book are trade names,
service marks, trademarks or registered trademarks of their
respective owners. The publisher is not associated with any
product or vendor mentioned in this book. This publication is
designed to provide accurate and authoritative information

in regard to the subject matter covered. It is sold on the understanding that the publisher is not engaged in rendering professional services. If professional advice or other expert assistance is required, the services of a competent professional should be sought.

The contents of this work are intended to further general scientific research, understanding, and discussion only and are not intended and should not be relied upon as recommending or promoting a specific method, diagnosis, or treatment by physicians for any particular patient. The publisher and the author make no representations or warranties with respect to the accuracy or completeness of the contents of this work and specifically disclaim all warranties, including without limitation any implied warranties of fitness for a particular purpose. In view of ongoing research, equipment modifications, changes in governmental regulations, and the constant flow of information relating to the use of medicines, equipment, and devices, the reader is urged to review and evaluate the information provided in the package insert or instructions for each medicine, equipment, or device for, among other things, any changes in the instructions or indication of usage and for added warnings and precautions. Readers should consult with a specialist where appropriate. The fact that an organization or Website is referred to in this work as a citation and/or a potential source of further information does not mean that the author or the publisher endorses the information the organization or Website may provide or recommendations it may make. Further, readers should be aware that Internet Websites listed in this work may have changed or disappeared between when this work was written and when it is read. No warranty may be created or extended by any promotional statements for this work. Neither the publisher nor the author shall be liable for any damages arising herefrom.

ISBN: 9781405196932

A catalogue record for this book is available from the Library
of Congress and the British Library.

This book is published in the following electronic formats:

ePDF 9781444341225; Wiley Online Library
9781444341256; ePub 9781444341232; Mobi
9781444341249