

ADVANCES IN  
EXPERIMENTAL  
MEDICINE  
AND BIOLOGY

---

Volume 685

# Diseases of DNA Repair

Edited by  
Shamim I. Ahmad

# CONTENTS

## **1. TRIPLE-A SYNDROME ..... 1**

Vijaya Sarathi and Nalini S. Shah

<b>Abstract.....</b>	<b>1</b>
<b>Introduction.....</b>	<b>1</b>
<b>Epidemiology.....</b>	<b>1</b>
<b>Etiology.....</b>	<b>2</b>
<b>Pathology.....</b>	<b>4</b>
<b>Diagnosis.....</b>	<b>5</b>
<b>Differential Diagnosis.....</b>	<b>5</b>
<b>Treatment.....</b>	<b>6</b>
<b>Conclusion.....</b>	<b>6</b>

## **2. AMYOTROPHIC LATERAL SCLEROSIS ..... 9**

J. Jefferson P. Perry, David S. Shin and John A. Tainer

<b>Abstract.....</b>	<b>9</b>
<b>Introduction.....</b>	<b>9</b>
<b>Clinical Features.....</b>	<b>9</b>
<b>Genetic Basis and the Molecular Mechanism of the Disease.....</b>	<b>10</b>
<b>Cu,ZnSOD.....</b>	<b>11</b>
<b>TDP-43.....</b>	<b>12</b>
<b>FUS/TLS.....</b>	<b>14</b>
<b>Conclusion.....</b>	<b>16</b>

## **3. EARLY-ONSET ATAXIA WITH OCULAR MOTOR APRAXIA AND HYPOALBUMINEMIA/ATAXIA WITH OCULOMOTOR APRAXIA 1 ..... 21**

Masayoshi Tada, Akio Yokoseki, Tatsuya Sato, Takao Makifuchi and Osamu Onodera

<b>Abstract.....</b>	<b>21</b>
<b>Introduction.....</b>	<b>21</b>
<b>Epidemiology.....</b>	<b>22</b>
<b>Genetics of EAOH/AOA1.....</b>	<b>23</b>

Clinical Features .....	24
Pathogenesis.....	28
Conclusion .....	30

#### **4. CLINICAL FEATURES AND PATHOGENESIS OF ALZHEIMER'S DISEASE: INVOLVEMENT OF MITOCHONDRIA AND MITOCHONDRIAL DNA .....**

Michelangelo Mancuso, Daniele Orsucci, Annalisa LoGerfo, Valeria Calsolaro  
and Gabriele Siciliano

Abstract.....	34
Alzheimer's Disease .....	34
Mitochondrial Structure and Function.....	36
Oxidative Stress and Mitochondrial Dysfunction in AD .....	37
The Role of Mitochondrial DNA.....	40
Conclusion .....	41

#### **5. HUNTINGTON'S DISEASE .....**

Emmanuel Roze, Cecilia Bonnet, Sandrine Betuing and Jocelyne Caboche

Abstract .....	45
History.....	45
Clinical Aspects .....	45
Genetic Aspects.....	47
Neuropathology .....	48
Molecular Mechanisms.....	48
Conclusion .....	53

#### **6. CLINICAL FEATURES AND MOLECULAR MECHANISMS OF SPINAL AND BULBAR MUSCULAR ATROPHY (SBMA).....**

Masahisa Katsuno, Haruhiko Banno, Keisuke Suzuki, Hiroaki Adachi,  
Fumiaki Tanaka and Gen Sobue

Abstract.....	64
Clinical Features .....	64
Genetic Basis.....	65
Histopathology.....	66
Molecular Mechanisms.....	66
Therapeutic Strategies.....	68
Conclusion .....	70

#### **7. SPINOCEREBELLAR ATAXIA WITH AXONAL NEUROPATHY .....**

Cheryl Walton, Heidrun Interthal, Ryuki Hirano, Mustafa A.M. Salih,  
Hiroshi Takashima and Cornelius F. Boerkoel

Abstract.....	75
Introduction .....	75

Symptoms of SCAN1 ..... 78  
 Genetic Basis of SCAN1 ..... 78  
 Tdp1 Function ..... 78  
 Molecular Basis of SCAN1 ..... 79  
 Current and Future Research..... 79  
 Conclusion ..... 81

**8. TUBEROUS SCLEROSIS COMPLEX AND DNA REPAIR..... 84**

Samy L. Habib

Abstract..... 84  
 Introduction: Clinical Manifestations of TSC Disease ..... 84  
 Renal Lesions in TSC-Deficient Mammals ..... 85  
 TSC1 and TSC2 Genes ..... 87  
 TSC Genes and Cell Signals..... 87  
 TSC and DNA Damage/Repair Pathway ..... 90  
 TSC2 Regulates DNA Damage/Repair Pathway ..... 90  
 Conclusion ..... 91

**9. HEREDITARY PHOTODERMATOSES ..... 95**

Dennis H. Oh and Graciela Spivak

Abstract..... 95  
 Introduction..... 95  
 Metabolic Photodermatoses ..... 96  
 Hereditary Photodermatoses of Unknown Etiology or Pathogenesis ..... 98  
 Defects in Cancer Suppressor Genes..... 99  
 Human Syndromes Defective in DNA Repair ..... 99  
 UV-Sensitive Syndrome (UV<sup>s</sup>S) ..... 101  
 Conclusion ..... 103

**10. TRICHOThIODYSTROPHY: PHOTOSENSITIVE, TTD-P,  
TTD, TAY SYNDROME ..... 106**

W. Clark Lambert, Claude E. Gagna and Muriel W. Lambert

Abstract..... 106  
 Clinical Manifestations ..... 106  
 Xeroderma Pigmentosum/Trichothiodystrophy Overlap Syndrome..... 107  
 Cockayne Syndrome/Trichothiodystrophy Overlap Syndrome ..... 107  
 Etiopathogenesis..... 107  
 Laboratory Diagnosis ..... 108  
 Animal Model ..... 109  
 Conclusion ..... 109

**11. CORNELIA DE LANGE SYNDROME ..... 111**

Jinglan Liu and Gareth Baynam

Abstract..... 111  
 Clinical Characteristics ..... 111

Molecular Genetics of CdLS .....	113
Conclusion .....	119

## 12. RECTAL CANCER AND IMPORTANCE OF CHEMORADIATION IN THE TREATMENT .....

124

Sergio Huerta

Abstract.....	124
Introduction.....	124
Rectal Cancer: Metastasis and Survival Rates .....	125
Mechanisms of Cell Death By Ionizing Radiation .....	126
Mechanisms of Resistance to Radiation in Rectal Cancer .....	126
Proliferation Markers and Mitotic Index (Ki-67).....	127
p53, p21 and p27 and Apoptotic Index (AI) .....	127
Apoptosis.....	128
NFκB .....	130
Inhibitors of Apoptosis (IAPs: Survivin) .....	130
Conclusion .....	131

## 13. FAMILIAL CUTANEOUS MELANOMA .....

134

Johan Hansson

Abstract.....	134
Introduction.....	134
Risk Factors for Melanoma.....	134
Familial Melanoma—The Clinical Picture.....	134
Molecular Genetics of Familial Cutaneous Melanoma .....	136
High Risk Melanoma Genes.....	136
Candidate Loci for Novel Genes Predisposing to Familial CMM .....	139
Risk of Melanoma and Other Cancers in Melanoma Families with Germline <i>CDKN2A</i> Mutations .....	139
Genetic Testing in Familial Melanoma .....	140
Management of Familial Melanoma .....	140
Primary Prevention.....	141
Secondary Prevention of CMM .....	141
Pancreatic Carcinoma Surveillance .....	142
Conclusion .....	142

## 14. PRIMARY IMMUNODEFICIENCY SYNDROMES.....

146

Mary A. Slatter and Andrew R. Gennery

Abstract.....	146
Introduction.....	146
Role of DNA Repair Proteins in Adaptive Immunity .....	146
Genetic Defects Associated with Primary Immunodeficiency Syndromes .....	150
Treatment.....	159
Conclusion .....	160

## 15. INHERITED DEFECTS OF IMMUNOGLOBULIN CLASS SWITCH RECOMBINATION..... 166

Sven Kracker, Pauline Gardès and Anne Durandy

Abstract.....	166
Introduction.....	166
CSR Deficiency Caused by Activation-Induced Cytidine Deaminase (AID)-Defect .....	167
CSR Deficiency Caused by Uracil-N Glycosylase (UNG)-Defect .....	168
CSR Deficiency Caused by Post-Meiotic Segregation 2 (PMS2) Defect .....	169
CSR-Deficiency in Molecularly Defined Syndromes Affecting the DNA Repair Machinery .....	170
Conclusion .....	171

## 16. LIGASE IV SYNDROME..... 175

Dimitry A. Chistiakov

Abstract.....	175
Ligase IV Syndrome: Clinical Features .....	175
DNA Ligase IV Is a Component of Nonhomologous End-Joining Pathway of DNA Repair .....	175
DNA Ligase IV: Structure and Function .....	177
Animal Models with Genetic Defects in <i>Lig4</i> .....	179
Ligase IV Mutations Causing LIG4 Syndrome in Humans.....	179
<i>LIG4</i> Mutations Associated with Severe Combined Immunodeficiency.....	183
Conclusion .....	183

## 17. MUIR-TORRE SYNDROME..... 186

Pedro Mercader

Abstract .....	186
Introduction.....	186
Histopathology.....	187
Conclusion .....	192

## 18. WILMS' TUMOR..... 196

Carlos H. Martínez, Sumit Dave and Jonathan Izawa

Abstract.....	196
Introduction.....	196
Epidemiology .....	196
Genetic Basis and the Molecular Mechanism of the Disease .....	197
Wilms' Tumor Associated Syndromes.....	199
Histopathology.....	200
Clinical Features .....	201
Imaging Studies.....	202
Staging.....	202

Treatment.....	202
Bilateral Wilms' Tumor .....	205
Adult Wilms' Tumor .....	205
Conclusion .....	205

**19. CEREBRO-OCULO-FACIO-SKELETAL SYNDROME ..... 210**

Hiroshi Suzumura and Osamu Arisaka

Abstract.....	210
Introduction.....	210
Clinical Features .....	210
Prognosis.....	211
Differential Diagnosis .....	211
Conclusion .....	213

**20. DYSKERATOSIS CONGENITA ..... 215**

Vineeta Gupta and Akash Kumar

Abstract.....	215
Introduction.....	215
Clinical Features .....	216
Genetics of DC.....	216
Genetic Defects.....	216
Immunological Abnormalities.....	217
Treatment.....	217
Prognosis and Outcome.....	218
Conclusion .....	218

**21. RETINOBLASTOMA ..... 220**

Dietmar Lohmann

Abstract.....	220
Clinical Aspects .....	220
Second Cancers in Patients with Hereditary Rb.....	221
Molecular Genetics .....	222
Phenotypic Consequences of RB1 Gene Mutations.....	223
Conclusion .....	226

**22. VON HIPPEL LINDAU SYNDROME ..... 228**

Jenny J. Kim, Brian I. Rini and Donna E. Hansel

Abstract.....	228
Genetic Basis and Molecular Mechanism of VHL.....	228
Clinical Features .....	233
Conclusion .....	242

**INDEX..... 251**