

Contents

Part I Molecular Bases of Nucleotide Expansions

Mechanisms of DNA Repeat Expansion

R. R. SINDEN, M. J. PYTLOS, V. N. POTAMAN	3
1 Introduction: Repeat Expansion and Deletion Associated with Human Neurodegenerative Disease	3
2 DNA Structures Formed by Disease-Associated DNA Repeats	5
2.1 Inverted Repeats, Hairpins	5
2.2 Slipped-Strand DNA Structures and Slipped Intermediate DNA Molecules	8
2.3 Triplex DNA	9
2.4 Quadruplex DNA	10
2.5 Unwound DNA	10
2.6 Parallel-Strand DNA	11
3 Effects of Alternative DNA Conformations on Biology	12
3.1 Replication Blockage by Hairpins, Triplex, Quadruplex, and Triplet Repeats	12
3.2 Aberrant Polymerization Associated with DNA Repeats: Slippage During Primer Template Misalignment and Strand Switching	13
3.3 Helicase Activity at Hairpins, Triplex DNA, Quadruplex DNA, and Triplet Repeats	14
3.4 Recombination Associated with DNA Repeats	15
3.5 Interaction of DNA Replication, Repair, and Recombination Proteins with DNA Repeats	16
4 Pathways for Repeat Expansion	18
4.1 Primer-Template Misalignment During Replication Can Account for Repeat Length Changes Less Than Twofold in Length in Disease-Associated DNA Repeats	18
4.2 Strand Switching During Synthesis of d(ATTCT) · d(AGAAT) DNA Repeats Can Result in Complex Expansion Mutations	20

4.3	DNA Mismatch Repair May, or May Not, Participate in Small Repeat Length Changes During Replication in Dividing Cells or During Gap Repair in Nondividing Cells	23
4.4	DNA Repair of Slipped-Strand Intermediates Containing (CTG) _n Hairpins or (CAG) _n Loopouts	25
4.5	Recombination at Disease-Associated DNA Repeats Can Lead to Deletions and Expansions	26
4.6	Double-Strand Break Repair, Replication Restart, and Checkpoint Control Associated with Repeat Replication	27
4.7	DNA Amplification Provides a Facile Means for Repeat Expansion for SCA10 d(ATTCT) · d(AGAAT) Repeats	31
4.8	Influence of the Direction of Replication, Origin Proximity, Origin Activity, and Transcription on Repeat Instability . . .	33
5	Concluding Remarks: Mutation Mechanisms, DNA Repeats, and Human Disease— Where Have We Come in 15 Years? . .	37
	References	39

Part II Disorders Associated with Non-coding Repeats

Molecular Correlates of Fragile X Syndrome and FXTAS

F. TASSONE, P. J. HAGERMAN	57
1 Overview	57
2 Introduction and Clinical Perspective	58
2.1 Fragile X Syndrome	58
2.2 Clinical Involvement Among Carriers of Premutation Alleles of the <i>FMR1</i> Gene	59
3 Expression of the <i>FMR1</i> Gene	60
3.1 Mechanisms of CGG Repeat Expansion	60
3.2 Regulation of Expression of the <i>FMR1</i> Gene in the Normal and Premutation Ranges	63
3.3 Regulation of Transcription Start Site Selection	64
3.4 Increased Transcription in the Premutation Range	65
3.5 Mechanisms of Silencing/Reactivation of the <i>FMR1</i> Gene . .	65
3.6 Regulation of Translation of the <i>FMR1</i> mRNA	68
4 Function of the <i>FMR1</i> Protein	69
4.1 FMRP Can Function as a Negative Regulator of Translation .	70
4.2 A Possible Role for FMRP in Regulating Actin Cytoskeletal Dynamics	71
4.3 The mGluR Hypothesis as a Specific Example of How FMRP Could Regulate Synaptic Function/Plasticity .	71
5 The Molecular Basis of FXTAS	72
References	74

The Neglected Fragile X Mutations: *FRAXE* and *FRAXF*

D. L. NELSON, Y. GU	87
1 History of the Xq27-q28 Fragile Sites	87
2 Clinical Features of <i>FRAXE</i> Disease	89
3 Repeat Dynamics in Patients and Families	90
4 The <i>FMR2</i> Locus	91
5 Mouse Model of <i>Fmr2</i> Deficiency and <i>Drosophila Lilli</i>	93
6 The <i>FMR3</i> Transcript	95
7 <i>FRAXF</i> and <i>FAM11A</i>	95
8 Future Prospects	98
References	99

Friedreich Ataxia

M. PANDOLFO	103
1 Clinical Features and Pathology	103
2 Gene Structure and Expression	104
3 The d(GAA) Triplet Repeat Mutation	105
3.1 Instability of Expanded Repeats	105
3.2 Origin and Mechanisms of Expansion of the Repeat	106
4 Pathogenic Mechanisms: Triplexes and Sticky DNA	108
5 Genotype-Phenotype Correlation	110
5.1 d(GAA) Triplet Repeat Expansion	110
5.2 Point Mutations	110
6 Frataxin Structure and Function	111
7 Animal Models	112
8 Pathogenic Mechanisms in Friedreich Ataxia	113
9 Perspectives for Treatment	113
References	115

Dodecamer Repeat Expansion in Progressive Myoclonus Epilepsy 1

M. D. LALIOU, S. E. ANTONARAKIS, H. S. SCOTT	121
1 Introduction and Disease Features	121
2 Linkage Analysis and Positional Cloning of the EPM1 Gene	122
3 Cystatin B	123
4 Point Mutations and Polymorphisms of the Cystatin B Gene	126
5 Effect of Point Mutations on Cystatin B Expression	126
6 A Dodecamer Repeat Expansion is the Most Common Mutation in EPM1	128
7 Instability of the Dodecamer Repeat	129
8 Size of the Repeat and Age of Onset of the Epilepsy	131
9 Effect of Expansion on Cystatin B Expression	131
10 Mechanism of Transcriptional Repression	132
11 Loss of Cystatin B Function and Disease Pathophysiology	134
References	136

Myotonic Dystrophies Types 1 and 2

P. TENG-UMNUAY, M. S. SWANSON	143
1 The Myotonic Dystrophies: an Overview	143
2 Genetics and Clinical Presentation of the Myotonic Dystrophies: DM1 Versus DM2 Disease: Many Similarities but Significant Differences	144
3 RNA Gain-of-Function Model for Myotonic Dystrophy	146
3.1 Myotonic Dystrophy Associated Microsatellite Expansions Are Toxic at the RNA Level	146
3.2 Toxic RNAs Molecules Sequester Muscleblind-like Proteins	148
3.3 Poly r(CUG) Toxicity Requires Expression of Specific Muscleblind-like Isoforms	150
3.4 The Splicing Connection: DM is Associated with Fetal Exon Retention in Adults	151
3.5 MBNL and CELF Proteins are Splicing Antagonists Which Regulate Fetal Exon Splicing	154
3.6 Is Myotonic Dystrophy Caused by MBNL Loss, CUGBP1 Overexpression or Both?	154
4 Congenital Myotonic Dystrophy: a Distinct Disease with a Different Molecular Etiology?	155
4.1 The DMPK (CTG) _n Expansion Alters the Chromatin Structure and Expression of the DM1 Locus	156
4.2 Cell Culture Models for Congenital Myotonic Dystrophy	157
4.3 Mouse Transgenic and Knockout Models for Congenital Myotonic Dystrophy	158
References	159

Spinocerebellar Ataxia Type 8

K. A. DICK, J. W. DAY, L. P. W. RANUM	167
1 Introduction: Repeat Expansions and SCA8	167
2 Rapid Cloning of the SCA8 Repeat Expansion	168
3 The d(CTG) Repeat Cosegregates with a Novel Form of Ataxia	168
4 Organization of the SCA8 Gene	169
5 Clinical Features of SCA8	170
6 Disease Penetrance Affected by d(CTG) Repeat Length: the MN-A Family	171
7 Reduced Penetrance of SCA8 in Other Families	172
8 SCA8 Expansions on Control Chromosomes	173
9 SCA8 Expansions Cosegregate with Ataxia in Small Families	174
10 Haplotype Analysis of SCA8 Expansion Chromosomes	174
11 Factors that May Influence SCA8 Disease Penetrance	175
11.1 The d(CTA) Repeat Tract	175
11.2 Interruptions Within the d(CTG) Expansion	176

11.3	Repeat Instability During Transmission	176
11.4	En Masse d(CTG) Repeat Contractions in Sperm	178
12	Molecular Parallels with Myotonic Dystrophy	179
13	Modeling SCA8 Pathogenesis in the Fly	179
14	Conclusion	180
	References	180

Recent Progress in Spinocerebellar Ataxia Type 10

X. LIN, T ASHIZAWA	185
1 Introduction	185
2 Clinical Presentations	186
2.1 Cerebellar Signs and Symptoms	186
2.2 Seizures	187
2.3 Other Extracerebellar Signs and Symptoms	187
3 Genetic Features	188
3.1 d(ATTCT) Pentanucleotide Repeat Expansion	188
3.2 Anticipation, Repeat Instability and Genotype–Phenotype Correlation	189
4 Molecular Studies	190
4.1 DNA Structure	190
4.2 Protein Function	191
4.3 RNA Gain of Function	192
5 Concluding Remarks	193
References	194

Part III Disorders Associated with Coding Repeats

Polyglutamine Diseases

M. J. FRIEDMAN, S. LI, X. LI	199
1 Introduction	199
2 Genetics of PolyQ Diseases	200
3 Neuropathology of PolyQ Diseases	203
4 PolyQ-Dependent Misfolding and Aggregation	205
5 Pathogenesis of the PolyQ Diseases	208
5.1 PolyQ Diseases as “Transcriptionopathies”	209
5.2 Disruption of Cytoplasmic Activities in PolyQ Disease	214
5.3 Other Contributors to Pathogenesis	216
6 Potential Therapeutic Strategies	217
7 Concluding Remarks	219
References	220

The Enigma of Spinocerebellar Ataxia Type 6

M. FRONTALI	233
1 Introduction	233
2 Genetics	233
3 The Cav2.1 α 1A Isoforms	234
4 Epidemiology	235
5 Clinical Features	236
6 Similar and Discrepant Clinical Features of SCA6 and EA2	239
7 Neuropathology	240
8 Toxic Gain of Function Versus Abnormal Channel Activity	241
9 Conclusions	243
References	243

Part IV Disorders Associated with Repeats in an Undetermined Location

Spinocerebellar Ataxia Type 12 and Huntington's Disease-Like 2: Clues to Pathogenesis

R. L. MARGOLIS, S. E. HOLMES, E. O'HEARN, D. D. RUDNICKI, J. HWANG, N. CORTEZ-APREZA, O. PLETNIKOVA, J. C. TRONCOSO	253
1 The Identification of Spinocerebellar Ataxia Type 12 and Huntington's Disease-Like 2	253
2 HDL2 and SCA12 Clinical Phenotype	254
3 HDL2 and SCA12 Pathological Phenotype	256
4 Epidemiology	258
5 Phenotype-Genotype Relationship	259
6 The HDL2 and the SCA12 Repeats Do Not Encode Polyglutamine	261
7 HDL2 and SCA12: Clues to Pathogenesis	265
7.1 HDL2 and Gain of Function	265
7.2 The Function of <i>JPH3</i> and <i>PPP2R2B</i>	266
7.3 Expression Level and Pathogenesis	268
8 Conclusion	269
References	271

Part V Postscript

Current Issues and Therapeutic Prospects

K. USDIN, M. FRY	279
1 Current Issues	279
1.1 Mechanisms of Nucleotide Repeat Expansion	279
1.2 Consequences of Repeat Expansion	280
2 Therapeutic Prospects	282

Contents	XVII
2.1	Gene Correction/Replacement 282
2.2	Targeting the Downstream Consequences of Expansion . . . 283
References	 285
Subject Index	 289