

Contents

Preface	xiii	Transgenerational Disease Etiology	14
Contributors	xv	Impact and Future Studies	15
		Glossary	15
		References	15
1. Transgenerational Epigenetics	1	3. Historical Perspective of Transgenerational Epigenetics	17
<i>Trygve O. Tollefsbol</i>		<i>Dao H. Ho</i>	
Introduction	1	Introduction	17
Definition and History of Generational Epigenetic Inheritance	2	Shifting Paradigms of Heredity and Evolution	17
Germline Epigenetics	3	Early Evidence of Non-Mendelian Inheritance	19
Epidemiology of Epigenetic Inheritance	3	The Origins of Epigenetics	20
Basic Mechanisms/Processes of Epigenetic Inheritance	3	Intersection of Phenomena and Mechanisms	20
Model Organisms	5	Transgenerational Epigenetics in Ecology and Physiology	21
Evolution of Transgenerational Epigenetics	5	Conclusion	22
Parental Epigenetic Inheritance	6	References	22
Environmental Epigenetic Effects on the Offspring	6		
Impact of Transgenerational Epigenetics on Disease	7	Section II	
Clinical Significance of Transgenerational Epigenetics	7	Germline Epigenetics	25
Controversies and Debate of Generational Epigenetic Inheritance	8	4. Epigenetics and the Maternal Germline	27
Conclusion	8	<i>Amy J. Osborne, Elizabeth J. Duncan, Andrew G. Cridge and Peter K. Dearden</i>	
References	8	Introduction	27
		Transgenerational Inheritance in the Maternal Germline	28
Section I		Defining Transgenerational Inheritance	28
Definitions and History of Generational Epigenetic Inheritance	9	Difficulties in Detecting Epigenetic Inheritance in the Maternal Germline	29
2. Definition of Epigenetic Transgenerational Inheritance and Biological Impacts	11	Periods of Sensitivity in the Female Germline	29
<i>Eric Nilsson and Michael K. Skinner</i>		Mechanisms for Transmission of Epigenetic Information in the Female Germline	31
Introduction and Historical Context	11	Methylation Reprogramming During Meiosis	31
Epigenetic Transgenerational Inheritance	11	Frequency of Transgenerational Inheritance	32
Germline Epimutations	13	Identifying Epigenetic Inheritance in the Female Germline	32
Transgenerational Inheritance of Disease and Phenotypic Variation	14	Examples of Transgenerational Inheritance in the Maternal Germline	32

Transgenerational Maternal Epigenetic Inheritance in Mice	33	The Evidence for Transgenerational Epigenetics in Humans	60
Evidence for Maternal Germline Epigenetic Inheritance in Humans	34	Transgenerational Cycles of Low Birth Weight	60
Factors that Complicate the Assessment of Maternal Germline Epigenetic Inheritance	34	Developmental Origins of Health and Disease	60
Discussion	34	Transgenerational Studies in Humans: Variations in Food Supply in Overkalix	61
Evolution and Epigenetics	35	Long-Term Consequence of Prenatal Exposure to the Dutch Famine	61
Genetic Assimilation	35	Long-Term Consequence of Exposure to the Chinese Famine in Early Life	62
Implications of Transgenerational Inheritance for Evolution	35	Intergenerational Effects of Maternal Birth Season on Offspring in Rural Gambia	63
Transgenerational Inheritance in the Female Germline	36	Programming Through Lifestyle Changes Associated with Ramadan	63
Future Directions	36	Programming Through Food Supplementation	64
Epigenetic Variation in Natural Populations	37	Potential Mechanisms of Transgenerational Transmission: Transgenerational Epigenetic Inheritance	64
Identification of Species and Times that Might be More Sensitive to Transgenerational Epigenetic Inheritance	37	Summary	64
Identification of Model Systems for Studying Maternal Transmission of Epigenetic Information	37	References	64
Molecular Mechanisms	38		
Evolution	38		
Acknowledgments	38		
References	38		
5. Epigenetic Changes in the Paternal Germline	43	Section IV	
<i>Kristin E. Murphy, Patrick J. Murphy and Douglas T. Carrell</i>		Basic Mechanisms/Processes of Epigenetic Inheritance	67
Introduction	43	7. Metastable Epialleles	69
PGC Epigenetic Reprogramming	44	<i>Richard Kellermayer</i>	
Epigenetics of Meiotic Prophase I	46	Definitions	69
Histone-to-Protamine Transition During Spermiogenesis	47	Murine MEs	70
Zygotic Epigenetic Reprogramming	48	Human ME Candidates	71
Transgenerational Epigenetic Inheritance, Aging, and Environmental Effects	49	Potential for the Transgenerational Inheritance of MEs	72
Epigenetics in Male-Factor Infertility	50	References	72
Conclusions	51		
References	52	8. Towards the Molecular Mechanisms of Transgenerational Epigenetic Inheritance: Insights from Transgenic Mice	75
		<i>Ravinder Kaundal, Yan Yang, Timothy Nottoli and Tian Chi</i>	
Section III		Introduction	75
Epidemiology of Epigenetic Inheritance	57	TEI In Classical Transgenes: Heritable Transcription Silencing	76
6. Epidemiology of Transgenerational Epigenetics	59	Potential Mechanisms of TEI at the Classical Transgenes	78
<i>Tessa Roseboom and Rebecca Painter</i>		General Features of Heritable Silencing: Lessons from the CD4 Gene	78
Introduction	59		
Transgenerational Effects	60		

Forces Driving the Establishment of Silencing	78	The piRNA Pathway, Transposon Silencing, and Hybrid Dysgenesis in <i>Drosophila Melanogaster</i>	112
Forces Behind the Inheritance of the Silenced States	80	Transgenerational Epigenetic Inheritance in Mammals	113
Insights from Inducible Mouse Models: Timing is Everything for Mitotic Inheritance, but Location is also Crucial for TEI	81	piRNA Inheritance and Imprinting in Mouse	114
Conclusions and Future Perspectives	83	miRNA Inheritance and Paramutation in the Mouse	115
Acknowledgments	83	Transgenerational Epigenetic Inheritance in Humans	115
References	83	Conclusion	116
9. Histone-Mediated Transgenerational Epigenetics	87	Acknowledgements	116
<i>Jiong Li, Yingwen Ding and Ling Zheng</i>		References	116
Introduction	88	Section V	
Histones and Histone Modifications	88	Model Organisms	121
Histones	88	11. Animal Models of Transgenerational Epigenetic Effects	123
Histone Modifications	88	<i>Cheryl S. Rosenfeld</i>	
Variants of Core Histones	92	Introduction	124
Evidence that Histones are not Completely Erased During Gametogenesis	92	Considerations for Designing and Interpreting Transgenerational Animal Studies	125
Transgenerational Changes of Histone Modifications in Different Experimental Models	93	Which Generations Should be Examined?	125
<i>Arabidopsis</i>	93	Determination of Germline Transmission	125
<i>Caenorhabditis elegans</i>	93	Dose or Stressor Levels to Test	125
<i>Drosophila</i>	95	Consideration of Other Factors that Might Affect the Outcome Across Generations	126
Rodents	96	Statistical Methods	126
Altered Histone Modifications in Human Genetic Diseases	98	Naturally Occurring Epigenetic/Transgenerational Animal Models	127
Future Directions	99	Viable Yellow (<i>A^{vy}/a</i>) Mice	127
References	100	Kinky Tail (<i>Axin^{fu}</i>) Mice	128
10. Heritable Generational Epigenetic Effects through RNA	105	Extrinsic/Environmental Factor Induction of Transgenerational Effects in Animal Models	128
<i>Nicole C. Riddle</i>		Toxicants	128
Introduction	105	Nutrition/Obesity	130
Transgenerational Inheritance Via the Gametes	106	Environmental Stressors	131
Gametic RNA Populations	106	Mechanisms Leading to Transgenerational Inheritance	132
Small RNA Pathways	106	DNA Methylation	132
RNA-Guided Genome Rearrangements in Ciliates	108	Histone Protein Modifications	134
<i>Tetrahymena thermophila</i>	108	Non-Coding RNA (ncRNA)	134
<i>Oxytricha trifallax</i>	109	Germ Cell Nutrient Composition and Soluble Factor-Induced Germ Cell Epigenetic Changes	136
RNA Transport in Plant Systems	109	Parenting and Cultural Influences	136
Paramutation in Maize	110		
RNA Transfer Via the Gametes in <i>Arabidopsis Thaliana</i>	111		
Transgenerational Inheritance of RNAi in <i>Caenorhabditis Elegans</i>	111		

Conclusions and Future Directions	137	Cell Functions Influenced by Hormonal	
Acknowledgements	137	Imprinting	166
References	137	Amino Acid-Type Hormones	166
		Peptide Hormones	167
		Other Molecules	167
12. Plant Models of Transgenerational Epigenetic Inheritance	147	The Receptor Nature of Binding Sites	
<i>Hidetaka Ito</i>		Induced by Imprinting	167
Introduction	148	Biology of the Hormonal Imprinting at a	
DNA Methylation in Plants	148	Unicellular Level	167
Establishment and Maintenance of DNA		References	169
Methylation in Plants	148		
Small RNAs and DNA Methylation	148		
Flexible DNA Methylation in Plants	149		
Histone Modification in Plants	149		
Histone Code	149		
Gene Regulation by Histone			
Modifications	150		
Transgenerational Inheritance of			
Epigenetic Marks	150		
Epialleles	150		
Epigenetic Regulation during Sexual			
Reproduction	150		
Inheritance of Epigenetic Variants	152		
Epigenetic Status and Effects in Plants	152		
Naturally Occurring Epialleles	153		
Stress-Induced Epigenetic Modifications	154		
Stress-Induced Epigenetic Variations	154		
Homologous Recombination			
Frequency	155		
Heat Stress Memory	155		
Transgenerational Defense	155		
Induced Defenses	155		
Priming	156		
Paramutation	156		
Conclusion and Perspective	157		
References	157		
13. Transgenerational Hormonal Imprinting in the Unicellular <i>Tetrahymena</i>	163		
<i>György Csaba</i>			
Introduction	163		
The Hormonal System of <i>Tetrahymena</i>	163		
Hormonal Imprinting	164		
Is Hormonal Imprinting Executed by			
Influencing DNA Methylation?	164		
Imprinting of the Nuclear Envelope	165		
Imprinter Molecules (Hormones)	165		
The Role of Signaling Pathways and			
Related Factors in the Provocation of			
Imprinting	166		
		Section VI	
		Evolution of Transgenerational Epigenetics	173
		14. Evolutionary Perspectives on Transgenerational Epigenetics	175
		<i>Tobias Uller</i>	
		Introduction	175
		Epigenetic Inheritance and Evolution	177
		Evolutionary Responses: Beyond the	
		Breeder's Equation	177
		Evolution of Epigenetic Inheritance: Stability	
		Versus Plasticity	181
		Conclusions	183
		Acknowledgements	183
		References	183
		15. Inheritance of Epigenome Variants Across Generations and its Implications on the Emergence of Phenotypic Novelties During Evolution	187
		<i>Jemma L. Geoghegan</i>	
		Introduction	187
		Transgenerational Epigenetics	188
		Gene-Environment Interactions	
		and Phenotypic Variation	188
		Epigenetic Modifications of Chromatin	189
		Re-Editing the Epigenome	189
		The Transgenerational Stability and Variability	
		of Epialleles	190
		Population Epigenetics	191
		Current Challenges and Future	
		Directions	192
		Conclusion	192
		Glossary	193
		Acknowledgements	193
		References	193

Section VII Parental Epigenetic Inheritance 195

16. Maternal Epigenetic Inheritance and Stress During Gestation: Focus on Brain and Behavioral Disorders 197

Therese A. Kosten and David A. Nielsen

Introduction	198
Epigenetic Inheritance	198
Chromatin Remodeling	198
DNA Methylation	199
Non-Coding RNA	199
Stress Effects	200
In the Adult Mammal	200
Types of Stressors and Effects on the Dam	200
Behavioral Effects in Offspring Exposed to	
Prenatal Stress	201
Social Behaviors	202
Addictive Behaviors	202
Emotional Behaviors	205
Cognitive Tasks and Sensory Processing	205
Summary of Prenatal Stress Effects on Behavior	208
HPA Axis Modifications in Offspring Exposed to Prenatal Stress	208
Neural Changes in Offspring Exposed to	
Prenatal Stress	210
Hippocampus and Amygdala	210
Striatum	211
Cortex	211
Epigenetic Effects of Gestational Stress	211
Future Directions	212
Factors that may Interact with Epigenetic Changes	212
Preventing or Reversing Consequences of Prenatal Stress Exposure	212
Transgenerational Effects of Gestational Stress Exposure	213
Summary	213
References	214

17. Paternal Epigenetic Inheritance 221

Rahia Mashoodh and Frances A. Champagne

Introduction	221
Paternal Transgenerational Effects	222
Nutritional Effects	222
Drugs and Toxins	222
Social Environments	222
Paternal Age	223
Mechanisms of Paternal Transgenerational Effects	223

Genetic Modifications	223
Epigenetic Modifications	224
Paternal Effects on Maternal Investment	228
Issues and Future Directions	231
References	232

Section VIII Environmental Epigenetic Effects on the Offspring 237

18. Transgenerational Epigenetics of Endocrine-Disrupting Chemicals 239

Rodney R. Dietert

Introduction	239
Endocrine-Disrupting Chemicals	240
Epigenetic Programming and the Developmental Origins of Health and Disease	241
Pathways to Epigenetic Alterations	243
Epigenetic Requirements to Produce Disease	244
A Potential Role for the Microbiome in Risk of Adverse Epigenetic Alterations	244
Multigenerational Versus Transgenerational Epigenetic Programming	245
The Genomic Reset Issue	246
Specific EDCs, EDC Mixtures, and Transgenerational Epigenetics	246
BPA	246
DES	247
DEHP	247
Dioxin	247
Flutamide	247
Jet Fuel (JP-8)	248
Methoxychlor	248
Pesticide Mixture	248
Plastics Mixture	248
Tributyltin	249
Vinclozolin	249
Conflicting Results	250
Implications and Conclusions	250
Acknowledgments	251
References	251

19. Transgenerational Effects of Perinatal Hormonal Imprinting 255

György Csaba

Introduction	255
Perinatal Hormonal Imprinting	255

Transgenerational Hormonal Imprinting	256	Non-Genomic Inheritance of Diabetes/Obesity	282
Perinatal Hormonal Mis-Imprinting by		The Epigenetic Turn	283
Endocrine Disruptors and its Inheritance	257	Transgenerational Effects	283
Aromatic Hydrocarbons	257	Ancestral Environments and Disease Risk in the Offspring	284
Other Endocrine Disruptors	259	Maternal versus Paternal Effects	285
Phytosteroids as False Imprinters	259	The Pedigree Structure	286
Late Imprinting	260	Transgenerational Epigenetic Inheritance in Mammals	288
The Importance of Hormonal Imprinting and its Heredity	260	Epigenetics and the Environment	289
References	265	The <i>Agouti</i> and the <i>Axin Fused</i> Mouse Models	289
		Exposure to Endocrine Disruptors	290
20. Phenotypic and Epigenetic Inheritance Across Multiple Generations in Mammals Through the Female Line	269	Transgenerational Inheritance of Diabetes in Humans	290
<i>Samuel P. Hoile, Karen A. Lillycrop, Leonie R. Grenfell, Mark A. Hanson and Graham C. Burdge</i>		The Dutch Hunger Winter Cohort	290
Introduction: Early Environment, Epigenetics and Induced Phenotypic Traits	269	The Överkalix Cohort	291
Models of Environmental Challenge and Implications for Transgenerational Inheritance	270	Other Human Cohorts	292
Passage of Induced Traits Between Generations: Evidence from Transient Environmental Challenge	270	Transgenerational Inheritance of Diabetes in Animal Models	293
Altered Nutrition	270	Transgenerational Inheritance of Diabetes after Maternal/Fetal Exposure	293
Synthetic Hormones and Endocrine Disruptors	271	Transgenerational Inheritance of Diabetes after Postnatal Environmental Exposure	295
Passage of Induced Traits Between Generations: Evidence from Persistent Environmental Challenge	272	The Debate: Transgenerational Epigenetic Inheritance of Diabetes?	297
Models of Transgenerational Phenotypic and Epigenetic Variation	273	Concluding Remarks	298
Conclusions	275	References	299
Acknowledgements	275		
References	275		
		22. Epigenetic Transgenerational Inheritance of Reproductive Disease	303
Section IX		<i>Ariane Paoloni-Giacobino</i>	
Impact of Transgenerational Epigenetics on Disease	279	Introduction	303
21. Transgenerational Epigenetic Inheritance of Type 2 Diabetes	281	The Epigenetic Control of Genes by DNA Methylation	304
<i>Josep C. Jiménez-Chillarón, Rubén Díaz, Marta Ramón-Krauel and Sílvia Ribó</i>		Gene Promoters	304
Introduction	281	Imprinted Genes	304
The Obesity and Diabetes Epidemics	282	Methylation Reprogramming	305
Developmental Origins of Health and Disease (DOHaD) Hypothesis	282	Epigenetic Effects on the Reproductive System	306
		Dysmethylation of Imprinted Genes and of Gene Promoters and Changes in mRNA Expression	306
		Interpretation of the Effects in Somatic Cells	313
		Questions and Perspectives	314
		How Can a Causal Relationship between a Methylation Defect and a Pathological Phenotype be Demonstrated?	314
		What is the Mechanism of the Resistance to Reprogramming?	315

Conclusions	315	Present Understanding of Transgenerational Epigenetic Inheritance	349
References	315	Genetic Significance of Transgenerational Epigenetic Inheritance	350
23. Cardiovascular Disease and Transgenerational Epigenetic Effects	321	Transgenerational Epigenetic Inheritance in Mental Disorders	351
<i>Alberto Zullo, Amelia Casamassimi, Francesco Paolo Mancini and Claudio Napoli</i>		Interruption of Negative Chain Reaction of Transgenerational Epigenetic Inheritance	351
Introduction	321	Acknowledgements	351
Transgenerational Effects in CVD	322	References	351
Transgenerational Epigenetic Changes in CVD: Single-Generation Transmission	323		
Epigenetic Changes and Atherosclerosis	327		
Epigenetic Changes and Lipid Metabolism	329		
Transgenerational Epigenetic Changes in CVD: Multiple-Generation Transmission	331		
Conclusions	332		
Acknowledgements	336		
References	336		
24. Mental Disorders and Transgenerational Epigenetics	343		
<i>Takeo Kubota, Takae Hirasawa and Kunio Miyake</i>			
Introduction	343		
Epigenetic Understanding of Congenital Mental Disorders	344		
Genomic Imprinting	344		
X Chromosome Inactivation	345		
DNA Methyltransferases	345		
Methyl CpG-Binding Domain Proteins	345		
Role of Epigenetics In Acquired Mental Disorders	345		
Epigenetic Bridge between Genetic Factors and Environmental Factors	345		
Environmental Factors that Affect Brain Function via Epigenetic Mechanisms	346		
Environmentally-Induced Epigenetic Changes in Humans	346		
Restoration of Epigenetic Status by Intrinsic and Extrinsic Factors	347		
Transgenerational Epigenetic Inheritance	348		
Importance of Transgenerational Epigenetic Inheritance	348		
Definition of Transgenerational Epigenetic Inheritance	348		
Transgenerational Epigenetic Inheritance in Plants	348		
Transgenerational Epigenetic Inheritance in Mammals	348		
Perspectives	349		
		Section X	
		Clinical Significance of Transgenerational Epigenetics	355
		25. Clinical Aspects of Transgenerational Epigenetics	357
		<i>Jorie Versmissen, Jeanine Roeters van Lennep and Eric J.G. Sijbrands</i>	
		Introduction	357
		How Can Epigenetics be Transgenerational?	358
		DNA Methylation	358
		Histone Modification	358
		Non-Coding RNA/RNA Interference	358
		Physiological Consequences of Transgenerational Epigenetics	358
		Behavior	358
		Fertility	359
		Pathophysiological Consequences of Transgenerational Epigenetics	359
		Obesity and Diabetes	359
		Cardiovascular Disease	359
		Kidney Disease	360
		Transgenerational Cancer Risk	360
		Autoimmune Disease	360
		Mental Disorders	361
		Assisted Reproduction	361
		Research and Diagnostics	361
		Therapy	362
		DNMT Inhibitors	362
		HDAC Inhibitors	362
		RNA Interference	362
		Drugs Already in Use with Epigenetic Effects	362
		Nutrition During Pregnancy	363
		Epigenetic Changes Caused by Radiation and Toxic Substances	363
		Conclusion	364
		References	364

Section XI Controversies and Debate of Generational Epigenetic Inheritance 369

26. Transgenerational Epigenetics: Current Controversies and Debates 371

David Crews and Andrea C. Gore

Introduction	371
Epigenetics and Behavioral Biology	374
Epigenotypes Versus Epiphenotypes (Molecular vs. Molar Epigenetics)	375
The Epigenotype or Molecular Epigenetics	375
The Epiphenotype or Molar Epigenetics	376
Context-Dependent vs. Germline- Dependent Epigenetic Modifications	376
Context-Dependent Epigenetic Modification	377
Germline-Dependent Epigenetic Modification	378
Transgenerational Inheritance	378

Body Burdens Include Our Personal Exposures, and Those Inherited From Our Ancestors	380
The Fallacy of Ecologically Relevant Dosages	381
Experimental Simulation of Exposures in the Real World (Mixtures and Synergy)	382
Thresholds	383
Species, Sex, and Individual Differences	384
Species Differences in Hormone Abundance, Metabolism, and Receptor–Ligand Interactions	384
Sex Differences in Responses	385
Individual Differences	386
Conclusion	386
Glossary	387
References	387

Glossary	391
Index	393