

Edited by
David J. Kwiatkowski, Vicky Holets Whittemore, and
Elizabeth A. Thiele



Tuberous Sclerosis Complex

Genes, Clinical Features, and Therapeutics

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Tuberous Sclerosis Complex

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Contents

Preface XVII

List of Contributors XIX

Part I **Basics** 1

1 **The History of Tuberous Sclerosis Complex** 3

Vicky H. Whittemore

- 1.1 Definition 3
- 1.2 The History of Tuberous Sclerosis Complex 4
- 1.3 Hereditary Nature of TSC 6
- 1.4 Molecular Mechanisms in TSC 7
- 1.5 The Future of TSC 7
- References 8

2 **Natural History of Tuberous Sclerosis Complex and Overview of Manifestations** 11

Elizabeth A. Thiele and Sergiusz Jóźwiak

- 2.1 TSC: Multisystem Involvement 13
 - 2.1.1 TSC and the Brain 13
 - 2.1.2 TSC and the Skin 15
 - 2.1.3 TSC and the Heart 16
 - 2.1.4 TSC and the Kidney 16
 - 2.1.5 TSC and the Lung 17
 - 2.1.6 TSC and the Eye 17
 - 2.1.7 TSC and the Other Organ Systems 18
- 2.2 TSC: A Spectrum Across the Life Span 18
- 2.3 TSC: A “Model” System 19
- References 20

3	Diagnostic Criteria for Tuberous Sclerosis Complex	21
	<i>E. Steve Roach and Steven P. Sparagana</i>	
	Introduction	21
	References	24
Part II	Genetics	27
4	Genetics of Tuberous Sclerosis Complex	29
	<i>David J. Kwiatkowski</i>	
4.1	Introduction	29
4.2	Historical Review of Linkage Analysis and Positional Cloning of the <i>TSC1</i> and <i>TSC2</i> Genes	29
4.2.1	Initial Linkage Studies	29
4.2.2	Positional Cloning of <i>TSC2</i> (1993)	30
4.2.3	Positional Cloning of <i>TSC1</i> (1997)	31
4.3	The <i>TSC1</i> and <i>TSC2</i> Genes: Genomic Structure, Splicing, Predicted Sequences, and Domains	31
4.3.1	Genomic Structure and Location of <i>TSC1</i> and <i>TSC2</i>	31
4.3.2	Alternative Splicing of <i>TSC1</i> and <i>TSC2</i>	32
4.3.3	Interspecies Comparisons of <i>TSC1</i> and <i>TSC2</i>	33
4.3.4	Predicted Amino Acid Sequences of <i>TSC1</i> (Hamartin) and <i>TSC2</i> (Tuberin) and Their Functional Domains	34
4.4	Mutational Spectrum of <i>TSC1</i> and <i>TSC2</i>	34
4.4.1	Introduction	34
4.4.2	Overview of Types of Mutation and Mutation Frequencies for <i>TSC1</i> and <i>TSC2</i>	37
4.4.3	Distribution of Mutations Along the Length of <i>TSC1</i> and <i>TSC2</i>	37
4.4.4	Single-Base Substitutions in <i>TSC1</i> and <i>TSC2</i>	40
4.4.5	Insertions and Deletions in <i>TSC1</i> and <i>TSC2</i>	42
4.4.6	Large Genomic Deletions/Rearrangements in <i>TSC1</i> and <i>TSC2</i>	42
4.4.7	Polymorphisms	43
4.4.8	Perspectives on Mutational Variation at the TSC Loci	43
4.5	Frequency and Significance of Mosaicism in TSC	45
4.6	Considerations in Patients in Whom No Mutation Can Be Identified	46
4.7	The Role of <i>TSC1</i> and <i>TSC2</i> in Tumor Development	47
4.7.1	The Role of <i>TSC1</i> and <i>TSC2</i> in Hamartoma Development in TSC Patients	47
4.7.2	The Role of <i>TSC1</i> and <i>TSC2</i> Genes in Cancer Development in Non-TSC Patients	48
4.8	The Future of Molecular Diagnostics in TSC	50
	References	53

5 Genotype–Phenotype Studies in TSC and Molecular Diagnostics 61

Kit S. Au and Hope Northrup

- 5.1 Introduction 61
- 5.2 Comprehensive Genotype–Phenotype Reports 62
- 5.3 Genotype–Phenotype Correlation 67
 - 5.3.1 *TSC2* Versus *TSC1* Gene Mutations 67
 - 5.3.1.1 NMI Patients 68
 - 5.3.1.2 Familial Versus Sporadic Cases 69
 - 5.3.2 Protein Truncation Versus Missense Mutations 70
 - 5.3.3 Whole Gene/Large Deletion Versus Small Mutation 71
 - 5.3.3.1 *TSC1* Large Deletions 71
 - 5.3.3.2 *TSC2* Large Deletions 72
 - 5.3.4 Mutations in *TSC2* GAP Domain 72
 - 5.3.4.1 *TSC2* GAP Domain Mutations 72
 - 5.3.4.2 *TSC2* Gene Amino-Termini Mutants Versus Carboxy-Termini Mutants 73
 - 5.3.5 Mosaicism 74
 - 5.3.6 Male Versus Female Sex 74
- 5.4 Molecular Diagnostic Methods 75
- 5.5 Conclusion 77
 - References 79

Part III Basic Science 85

6 The Role of Target of Rapamycin Signaling in Tuberous Sclerosis Complex 87

Brendan D. Manning

- 6.1 The Target of Rapamycin: An Evolutionarily Conserved Regulator of Cell Growth and Proliferation 87
 - 6.1.1 Rapamycin and the Discovery of TOR Proteins 87
 - 6.1.2 Molecular Characteristics of mTOR and Its Complexes 88
 - 6.1.3 Downstream of mTOR 89
 - 6.1.4 Upstream of mTOR 91
- 6.2 Genetic and Biochemical Studies Link the TSC1–TSC2 Complex to Cell Growth Control Through mTORC1 92
 - 6.2.1 *Drosophila* Genetics Lays the Groundwork 92
 - 6.2.2 Biochemical Studies Fill in the Gaps 92
 - 6.2.3 Rheb: A Direct Target of the TSC1–TSC2 Complex That Regulates mTORC1 93
 - 6.2.4 The TSC–Rheb–mTORC1 Circuit: Important Remaining Questions 94
- 6.3 The TSC1–TSC2 Complex as a Critical Sensor of Cellular Growth Conditions 95
 - 6.3.1 Growth Factors and Cytokines 96
 - 6.3.2 Energy and Nutrients 96

6.4	Primary mTOR-Related Signaling Defects Triggered by Disruption of the TSC1–TSC2 Complex	98
6.4.1	Constitutive and Elevated mTORC1 Signaling	98
6.4.2	mTORC1-Dependent Feedback Inhibition of PI3K Signaling	100
6.4.3	Loss of mTORC2 Activity	101
6.5	Pathological Consequences of mTOR Dysregulation in TSC	101
6.5.1	Neoplastic Lesions	102
6.5.2	Benign Tumors	102
6.5.3	Specific Clinical Features	103
6.6	Therapeutic Opportunities: Rapamycin and Beyond	104
	References	106
7	Rat and Mouse Models of Tuberous Sclerosis	117
	<i>David J. Kwiatkowski</i>	
7.1	Introduction	117
7.2	The Eker Rat	118
7.2.1	Historical Review: The Eker Rat: A Unique Spontaneous Mutation in Rat <i>Tsc2</i>	118
7.2.2	The Eker Rat <i>Tsc2</i> Model	118
7.2.3	Genetic Modifiers in the Eker Rat	121
7.2.4	Pathway Studies in the Eker Rat and Rapamycin Treatment	121
7.2.5	Brain and Neurologic Features of the Eker Rat	121
7.3	TSC Models in the Mouse	122
7.3.1	<i>Tsc2</i> Knockout Mice	122
7.3.2	Hypomorphic Alleles of <i>Tsc2</i>	125
7.3.3	<i>Tsc1</i> Knockout Mice	125
7.3.4	Mouse Studies: Interbreeding with Other Alleles	127
7.3.5	Mouse Models: Results from Tissue-Restricted Knockout of <i>Tsc1</i> or <i>Tsc2</i>	128
7.3.6	Mouse Models of TSC Brain Disease	130
7.3.7	Neurocognitive Studies in <i>Tsc1</i> ^{+/-} and <i>Tsc2</i> ^{+/-} Mice	133
7.3.8	Treatment Studies in the Mouse Models of TSC	137
7.4	Concluding Remarks	137
	References	139
8	Animal Models of TSC: Insights from <i>Drosophila</i>	145
	<i>Duoja Pan</i>	
8.1	Introduction	145
8.2	Connecting TSC1–TSC2 to the Insulin/PI3K Signaling Pathway	146
8.3	The <i>Tsc1</i> – <i>Tsc2</i> Complex as a Negative Regulator of TORC1	149
8.4	Identification of the Small GTPase Rheb as a Direct Target of the <i>Tsc1</i> – <i>Tsc2</i> Complex	149
8.5	Control of Autophagy by the <i>Tsc</i> – <i>Rheb</i> –TORC1 Pathway	150
8.6	Cross Talk Between the <i>Tsc</i> – <i>Rheb</i> –TORC1 Pathway and the Insulin Pathway	151

- 8.7 Relationship Between Tsc1–Tsc2 and Amino Acids-Mediated TORC1 Activation 152
- 8.8 Upstream of the Tsc1–Tsc2 Complex 152
- 8.9 Summary 154
References 154

Part IV Brain Involvement 159

- 9 Pathogenesis of TSC in the Brain 161**
Peter B. Crino, Rupal Mehta, and Harry V. Vinters
- 9.1 Introduction 161
- 9.2 Tubers 161
- 9.3 SENs and SEGAs 168
- 9.4 Cell Lineage 171
- 9.5 mTOR Activation and Biallelic TSC Gene Inactivation 176
- 9.6 Alternative Signaling Cascades in TSC Brain Lesions 178
- 9.7 Structural Alterations in Nontuber Brain Areas 179
- 9.8 Conclusions and Future Directions 181
References 182
- 10 Epilepsy in TSC 187**
Elizabeth A. Thiele and Howard L. Weiner 187
- 10.1 Overview of Epilepsy in TSC 187
- 10.2 Role of Electroencephalography 187
- 10.3 Treatment of Epilepsy in TSC 191
 - 10.3.1 Pharmacologic Treatment 191
 - 10.3.2 Nonpharmacologic Treatment 192
 - 10.3.3 Epilepsy Surgery in TSC 193
- 10.4 Infantile Spasms 197
 - 10.4.1 Clinical Features of IS 198
 - 10.4.2 EEG Features of Infantile Spasms 199
 - 10.4.3 Treatment of Infantile Spasms in TSC 202
 - 10.4.4 Infantile Spasms in TSC: Outcome 203
- 10.5 Lennox–Gastaut Syndrome 203
- 10.6 Pathogenesis of Epilepsy in TSC 204
- 10.7 The Natural History of Epilepsy in TSC 205
References 206
- 11 Subependymal Giant Cell Astrocytomas 211**
David Neal Franz, Darcy A. Krueger, and M. Gregory Balko
- 11.1 Introduction 211
- 11.2 Pathology and Pathogenesis of SEGA 212
- 11.3 SENs Versus SEGAs 215
- 11.4 Diagnosis of SEGA Versus SEN 215
- 11.5 Current Management of SEGAs 218

11.6	Medical Management of SEGAs	220
11.7	Conclusion and Summary	225
	References	225
12	Neurodevelopmental, Psychiatric and Cognitive Aspects of Tuberous Sclerosis Complex	229
	<i>Petrus J. de Vries</i>	
12.1	Introduction	229
12.2	Different Levels of Investigation	229
12.2.1	The Behavioral Level	230
12.2.2	The Psychiatric Level	231
12.2.2.1	Developmental Disorders	232
12.2.2.2	Mood and Anxiety Disorders	234
12.2.2.3	Other Psychiatric Disorders	235
12.2.2.4	Are There Gender Differences in the Developmental and Psychiatric Disorders in TSC?	236
12.2.2.5	Psychiatric Level: Summary	236
12.2.3	The Intellectual Level	237
12.2.3.1	Two Intellectual Subgroups or Phenotypes in TSC	238
12.2.3.2	Is There a Predictable Pattern of Intellectual Strengths and Weaknesses in TSC?	239
12.2.3.3	The Association Between the Intellectual Level and the Behavioral/Psychiatric Levels	239
12.2.4	The Academic or Scholastic Level	239
12.2.5	The Neuropsychological Level	241
12.2.5.1	Overall Neuropsychological Profiles in TSC	241
12.2.5.2	Attentional Skills	242
12.2.5.3	Memory Skills	242
12.2.5.4	Language Skills	243
12.2.5.5	Visuospatial Skills	243
12.2.5.6	Executive Control Processes	243
12.2.5.7	Is There a Typical Pattern of Neuropsychological Deficits in TSC?	244
12.2.6	The Psychosocial Level	244
12.2.7	The Biological Level	245
12.3	Assessment and Management of Neurocognitive and Neurobehavioral Difficulties in TSC	246
12.3.1	Assessment	246
12.3.1.1	Assess the Individual Across all Levels of Investigation (Behavioral, Psychiatric, Intellectual, Academic, Neuropsychological Skills, Psychosocial, Biological)	246
12.3.1.2	Assessment is Likely to Require Multi-agency, Multi-disciplinary Involvement	246
12.3.1.3	Make Sure You Have an Understanding of the Patient/Individual at Each Level	250

12.3.1.4	Draw Information Together into a “Formulation of Needs”	250
12.3.1.5	Discuss the Formulation and a Possible Plan of Action with the Family and the Individual with TSC	251
12.3.1.6	Re-assess at Appropriate Intervals as Set Out in the International Clinical Guidelines (Table 12.2)	251
12.3.1.7	Arrange or Perform an Urgent Reassessment When There is a History of Sudden Change in Learning, Behavior, or Mental Health	251
12.3.2	Management Options	251
12.3.2.1	Psycho-education	251
12.3.2.2	Behavioral Interventions	251
12.3.2.3	Cognitive Behavioral Interventions	252
12.3.2.4	Coaching Techniques	252
12.3.2.5	Psychodynamic Approaches	253
12.3.2.6	Interventions for Autism and Autism Spectrum Disorders	253
12.3.2.7	Other Non-pharmacological Approaches	253
12.3.2.8	Pharmacological Approaches	254
12.3.2.9	Educational Interventions	255
12.3.2.10	Social Interventions	256
12.4	Causes of the Neurocognitive and Neurobehavioral Features of TSC	256
12.4.1	Tuber Models	256
12.4.2	Seizure Models	257
12.4.3	Genotype–Phenotype Models	258
12.4.4	Molecular Models	259
12.5	Animal Models for Behavioral, Psychiatric, Intellectual, Learning, and Neuropsychological Deficits in TSC	260
12.6	Future Directions for the Understanding of Behavioral, Psychiatric, Intellectual, Academic, and Neuropsychological Deficits in TSC	261
12.7	How to Live a Positive Life with TSC	263
	References	264

Part V Other Organ Systems 269

13	Ophthalmic Manifestations	271
	<i>Shivi Agrawal and Anne B. Fulton</i>	
13.1	Introduction	271
13.2	Adnexa and Anterior Segment	271
13.3	Retinal Lesions	271
13.3.1	Hamartomas	271
13.3.1.1	Noncalcified Hamartomas	274
13.3.1.2	Calcified Hamartomas	275
13.3.1.3	Transitional Hamartomas	275
13.3.2	Complications and Treatment of Retinal Hamartomas	275
13.3.3	Chorioretinal Hypopigmented Lesions	277
13.3.4	Differential Diagnosis	278
13.4	Papilledema	279

13.5	Visual Field Defects	279
13.6	Cerebral Visual Impairment	280
13.7	Common Ophthalmic Issues	281
13.7.1	Refractive Error	281
13.7.2	Strabismus and Amblyopia	281
13.8	Summary and Recommendations	281
	References	282
14	Dermatologic Manifestations of Tuberous Sclerosis Complex (TSC)	285
	<i>Thomas N. Darling, Joel Moss, and Mark Mausner</i>	
14.1	Introduction	285
14.2	Types of TSC Skin Lesions	285
14.2.1	Hypomelanotic Macules	285
14.2.2	Facial Angiofibromas	287
14.2.3	Forehead Plaques	289
14.2.4	Shagreen Patch	289
14.2.5	Ungual Fibromas	291
14.2.6	Other Skin Lesions	292
14.2.7	Significance of Skin Lesions for Diagnosis of TSC	292
14.3	Pathogenesis of TSC Skin Lesions	293
14.4	Considerations for Surgical Treatment of TSC Skin Lesions	293
14.4.1	Patient Evaluation	293
14.4.2	Indications for Treatment and Preoperative Considerations	295
14.4.3	Patient, Family, and Caregiver Education	295
14.4.4	Insurance Issues	296
14.5	Treatment of Angiofibromas	297
14.5.1	Approaches	297
14.5.2	Timing of Treatment	297
14.5.3	Patient Preparation	298
14.5.4	Operating Room	299
14.6	Laser Treatments of Angiofibromas	299
14.6.1	CO ₂ Laser	299
14.6.2	CO ₂ Laser Postoperative Care	300
14.6.3	Complications and Risks of CO ₂ Laser Treatment	300
14.6.4	Limitations of CO ₂ Laser Treatment	301
14.6.5	Vascular Laser	302
14.6.6	Vascular Laser Postoperative Care	302
14.6.7	Complications and Risks of Vascular Laser Treatment	302
14.6.8	Limitations of Vascular Laser Treatment	303
14.7	Treatment of other TSC Skin Lesions	303
14.7.1	Facial and Scalp Plaques	303
14.7.2	Ungual Fibromas	303
14.7.3	Shagreen Patch	305
14.8	Future of Medical/Surgical Treatment of TSC Skin Lesions	305
	References	305

15	Renal Manifestations of Tuberous Sclerosis Complex	311
	<i>John J. Bissler and Elizabeth P. Henske</i>	
15.1	Introduction	311
15.2	Angiomyolipomata	311
15.3	Epithelioid and Malignant Angiomyolipomata	314
15.4	Renal Cystic Disease	314
15.5	Oncocytoma	316
15.6	Renal Cell Carcinoma	316
15.7	Monitoring Renal Lesions	317
15.8	Treatment	317
15.9	Conclusions and Future Directions	321
	References	321
16	Cardiac and Vascular Manifestations	327
	<i>Sergiusz Józwiak and Maria Respondek-Liberska</i>	
16.1	Introduction	327
16.2	Prevalence and Natural History of Cardiac Rhabdomyomas	327
16.2.1	Prevalence of Cardiac Rhabdomyomas	327
16.2.2	Association Between Cardiac Rhabdomyomas and Tuberous Sclerosis Complex	328
16.2.3	Natural History of Cardiac Rhabdomyomas in TSC Patients	328
16.3	Clinical Manifestations	330
16.4	Pathology and Molecular Biology of Cardiac Tumors	332
16.5	Diagnosis	334
16.6	Fetal Cardiac Rhabdomyomas and Diagnosis of TSC	335
16.7	Treatment	337
16.8	Genotype–Phenotype Correlations with Rhabdomyomas	338
16.9	Vascular Abnormalities in TSC	338
	References	340
17	Lymphangi leiomyomatosis and Pulmonary Disease in TSC	345
	<i>Francis X. McCormack and Elizabeth P. Henske</i>	
17.1	Introduction	345
17.2	Historical Features of LAM	346
17.3	Epidemiology	346
17.4	Clinical Presentation	348
17.4.1	Physical Examination	348
17.5	Diagnosis	349
17.6	Pathology and Laboratory Studies	349
17.7	Physiology	350
17.8	Radiology	351
17.9	Clinical Course and Management	352
17.9.1	Pulmonary Function	352
17.9.2	Pleural Complications	352
17.9.3	Screening and Follow Up	353

17.9.4	Medical Treatment	353
17.9.5	Transplantation	354
17.9.6	Lifestyle and Miscellaneous Issues	355
17.10	Genetic Basis and Molecular Pathology	355
17.10.1	Tuberous Sclerosis Complex-Associated LAM	355
17.10.2	Sporadic LAM	356
17.10.3	LAM Cells Have Evidence of mTOR Activation	356
17.10.4	The Cell-of-Origin of LAM Is Unknown	358
17.10.5	Estrogen May Promote LAM Pathogenesis	358
17.10.6	Cystic Lung Disease in LAM	359
17.11	Challenges and Future Directions	360
	References	362

18 Endocrine, Gastrointestinal, Hepatic, and Lymphatic Manifestations of Tuberous Sclerosis Complex 369

Finbar J. O'Callaghan and John P. Osborne

18.1	Introduction and Summary	369
18.2	Endocrine Manifestations of TSC	370
18.2.1	Theoretical Relationship Between TSC and Neuroendocrine Tumors	370
18.2.2	Pituitary	370
18.2.3	Parathyroid	371
18.2.4	Thyroid	372
18.2.5	Pancreas	372
18.2.6	Adrenal	373
18.2.7	Gonads	374
18.2.8	Precocious Puberty and TSC	376
18.3	Gastrointestinal Manifestations of TSC	376
18.3.1	Mouth	376
18.3.2	Esophagus and Stomach	378
18.3.3	Small Bowel	379
18.3.4	Large Bowel and Rectum	379
18.4	Hepatic Manifestations of TSC	380
18.5	Splenic Manifestations of TSC	381
18.6	Lymphatic Manifestations of TSC	381
	References	382

Part VI Family Impact 387

19 Impact of TSC on the Family and Genetic Counseling Issues 389

Vicky H. Whittemore and Janine Lewis

19.1	Introduction	389
19.2	Impact on the Family	389
19.3	Finding Support	391
19.4	Tuberous Sclerosis Complex Organizations and Support Groups	391
19.5	Genetic Counseling Issues for Tuberous Sclerosis Complex	392

19.5.1	Adults with TSC	392
19.5.2	Parents of a Child with TSC	393
19.5.3	Siblings of an Individual with TSC	393
19.5.4	Family Members of an Individual with TSC	394
19.5.5	Reproductive Options and Decision Making	394
19.6	Summary	395
	References	395
	Index	397

Preface

It is a great pleasure and honor to present this book, *Tuberous Sclerosis Complex: From Genes to Therapeutics*, for your thoughtful reading. This book was conceived in the spring of 2007, by David and Vicky, as we realized that the traditional Tuberous Sclerosis Complex (TSC) book edited by Manuel Gomez was eight years old, and was already outdated then in several respects. We recruited Elizabeth as a third Editor, and began serious work at that time in developing the chapter outlines and recruiting the best authors for the chapters from TSC clinicians and investigators from around the world.

We have sought to make the presentation in this book both scholarly and scientifically accurate, and understandable to the average TSC family member. We hope that it will find use to research scientists interested in the clinical details of this syndrome, clinicians caring for individuals with TSC, and individuals with TSC patients and their family members. We apologize in advance if the presentation is too technical in some areas.

TSC clinical and basic investigation has made great strides in the past 10 years. The identification of the two genes, TSC1 and TSC2, and the discovery of the main signaling pathway in which they play a important role, the mTOR pathway, has opened up an increasing flood of investigation into their role in cellular growth control and the mechanism by which inactivation of either gene leads to hamartoma development in individuals with TSC. Although there remain many unanswered questions of great importance, these findings have led to the introduction of rational therapy for TSC lesions, directed at the abnormal activation of the mTORC1 complex, in the form of rapamycin and analogues. Although there is much hope for these compounds, they are the subject of current clinical trials and ongoing investigation, so it is not yet clear what their long term benefits versus side-effects and toxicities will be. Fortunately, even if these compounds fail to work as well as desired, many related compounds have been or will be generated in the coming years, based upon our expanding knowledge of this pathway, providing additional therapeutic molecules to be tested in the clinic. These developments, combined with the general current concept of personalized medicine, provide much optimism about the long-term reduction in both morbidity and mortality due to TSC.

We have divided the book into 6 sections: Basics, Genetics, Basic Science, Brain Involvement, Other Organ Systems, and Family Impact. The Basics section provides information on the history of TSC clinical description and research, an overview of the clinical manifestations of TSC, and diagnostic criteria. The Genetics section covers the two TSC genes in great detail, as well as correlations between different mutations and clinical features. The Basic science section describes the biochemical function of the TSC1 and TSC2 proteins and their role in mTOR regulation, as well as insights from the fly mouse and rat models of TSC. The Brain Involvement section covers the many different aspects of brain involvement in TSC, including pathological and clinical. The Other Organs Section covers all the other organs commonly involved by TSC. Finally, the Family Impact chapter describes effects of TSC on the family and the importance of genetic counseling in TSC.

Our literature review for this book, as well as our own experience, has made it clear that there are many issues in regard to TSC management in the family for which there has been both relatively little investigation and little well-founded guidance. These issues fall largely in the neurocognitive sphere, and include: attention deficit hyperactive disorder (ADHD), autism spectrum disorder, tantrums and behavioral outbursts, intellectual disability, and sleep disturbance. In some instances, these issues are understood to be due in part to chronic seizures. However, this is not the case for all individuals with TSC. This is an area of great importance to TSC individuals and their families, and we hope to be able to report in a revised edition of this book in the future that there has been significant progress in both understanding and management of these issues.

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Part I
Basics

1

The History of Tuberous Sclerosis Complex

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There are very few rare genetic disorders where the research has moved from clinical descriptions and case reports to identification of the disease-causing genes, to an understanding of the underlying mechanisms of disease, and finally to clinical trials in just 12 years. Research on tuberous sclerosis complex (TSC) has done just that with the identification of the *TSC1* and *TSC2* genes in 1993 and 1997, respectively, identification of the role of the genes in an important cell signaling pathway, and launching of clinical trials with drugs that specifically target the molecular defect in individuals with TSC.

1.1

Definition

Tuberous sclerosis complex is a genetically determined multisystem disorder that may affect any human organ system. Skin, brain, retina, heart, kidneys, and lungs are most frequently involved with the growth of noncancerous tumors, although tumors can also be found in other organs such as the gastrointestinal tract, liver, and reproductive organs. There may also be manifestations of TSC in the central nervous system (CNS), including tubers (disorganized areas of the cerebral cortex that contain abnormal cells), scattered abnormal cells throughout the CNS, and other lesions. The majority of individuals with TSC have learning disabilities that range from mild to severe, and may include severe intellectual disability and autism spectrum disorder. In addition, the majority of individuals with TSC will have epilepsy beginning in early childhood or at any point in the individual's life. Psychiatric issues including attention deficit, depression, and anxiety disorder may significantly impair the life of an individual with TSC and their family, and may impair their ability to live an independent life. However, there are many very able individuals with TSC who can carry on healthy and productive lives.

TSC can be inherited in an autosomal dominant manner, but the majority of cases are thought to be sporadic mutations with no family history of the disease. As our clinical understanding of the disease has improved over the last century, it is clear

that the disease is variably expressed, even in the same family and even in two individuals from different families who have the same genetic mutation in one of the two TSC genes.

1.2

The History of Tuberous Sclerosis Complex

The first documented descriptions of TSC date back to the early 1800s. Rayer [1] illustrated the skin lesions on a young man's face in his atlas in 1835. These skin lesions had the characteristic distribution and appearance of the facial angiofibromas frequently seen in individuals with TSC. The pathological findings of a newborn who died shortly after birth was provided by von Recklinghausen in 1862, and is the first documented report of a child with cardiac tumors (called "myomata") and a "great number of scleroses" in the brain [2] (Table 1.1).

The first detailed description of the neurological symptoms and the gross pathology in the central nervous system of three individuals with TSC was provided by Bourneville in 1880 [3]. He used the term "tuberous sclerosis of the cerebral convolutions" to describe the CNS pathology in a child with seizures and learning disability [3]. Moolten first used the term "tuberous sclerosis complex" to describe the multisystem genetic disorder that may predominantly include involvement of the skin, heart, brain, kidneys, lungs, eyes, and liver, but can also involve other organ systems (e.g., the gastrointestinal tract and reproductive organs) [4].

In 1881, Bourneville and Brissaud [5] described a 4-year-old boy with seizures, limited verbal skills, and a cardiac murmur who subsequently stopped eating and drinking and died. At autopsy, the brain showed sclerotic, hypertrophic convolutions, and they described many small sclerotic tumors covering the lateral walls of the ventricles – the first description of what later became known as subependymal nodules. They also described small yellowish-white tumors in the kidneys and proposed the association between the CNS and renal manifestations of TSC. Balzer and Menetrier [6] and then Pringle [7] described the facial lesions illustrated much earlier by Rayer and called them "congenital adenoma sebaceum." It was not until 1962 that Nickel and Reed [8] showed that the sebaceum glands were not enlarged in the facial lesions in TSC, but that they were often absent or atrophic. However, these lesions were only renamed facial angiofibromas after additional pathological descriptions of the lesions showed that the term adenoma sebaceum was a misnomer [9].

For many years, Vogt's triad of seizures, learning disability, and "adenoma sebaceum" (facial angiofibromas) was used to diagnose TSC [10]. Vogt also noted that cardiac and renal tumors were part of the disease.

In 1920, van der Hoeve coined the term phakomatoses to describe disorders that were characterized by the presence of circumscribed lesions or phakomas that had the potential to enlarge and form a tumor [11]. The three phakomatoses included TSC, neurofibromatosis, and von Hippel–Lindau disease. All three diseases have a spotty distribution of the lesions and the lesions can grow as benign tumors.

Table 1.1 Historical milestones of the tuberous sclerosis complex.

Clinicopathological developments

1835	First illustration of facial angiofibromas in atlas [1]
1862	Cardiac “myomata” described in newborn [2]
1879	Cortical “tuberousities” identified [3]
1885	Report of “adenoma sebaceum” [6]
1908	Diagnostic triad proposed [10]
1910	Hereditary nature of TSC described [20]
1912	Hereditary nature of TSC [21]
1913	Forme fruste with normal intelligence [22]
1920	Retinal phakoma identified [11]
1932	Review of clinical aspects and discovery of hypomelanotic macules [12]
1942	First use of the term “tuberous sclerosis complex” [4]
1967	Significant number of individuals with TSC found to have average (normal) intelligence [17]
1979	New criteria for diagnosis of TSC, decline of Vogt’s triad [18]
1987	Full spectrum of psychiatric issues described [14–16]
1988	Revised diagnostic criteria for TSC [18]
1998	Diagnostic criteria revised [19]
1999	Phenotype/genotype correlations [30]
2001	Phenotype/genotype correlations [31]
2007	Phenotype/genotype correlations [32]

Genetic and scientific developments

1987	Positional cloning: mapping of the <i>TSC1</i> gene to chromosome 9q34.3 [25]
1992	Finding of nonlinkage to chromosome 9 [26]; mapping of the <i>TSC2</i> gene to chromosome 16p13.3 [27]
1993	Cloning of the <i>TSC2</i> gene; its protein product is called tuberin [28]
1997	Cloning of the <i>TSC1</i> gene; its protein product is called hamartin [29]
2001	<i>Drosophila</i> homologues <i>Tsc1</i> and <i>Tsc2</i> involved in regulation of cell and organ size [33–35]
2002	Tuberin found as a target of the PI3k/akt pathway [36]; TSC1/2 protein complex described [37]
2002	Activation of mTOR pathway in TSC described [38]
2003	mTOR activation confirmed in renal angiomyolipomas from individuals with TSC [39]
2005	Rapamycin (mTOR inhibitor) reduces renal tumors in Eker rats [40] and mouse models [41]
2006	Rapamycin shown to reduce the size of subependymal giant cell astrocytomas [42]
2008	Rapamycin reduces size of renal angiomyolipomas [43]

It was not until 1932 that the significance of the white spots (hypomelanotic macules) on the skin of individuals was noted as helpful in the diagnosis of TSC [12]. They also described autistic behavior in some of the 29 individuals with TSC they observed. Kanner [13] described “early infantile autism” 11 years later, but it was not until far more recently that the link between TSC and autism spectrum disorder was truly recognized [14–16].

A very important shift in our understanding and diagnosis of TSC occurred in 1967 when Lagos and Gomez [17] reported their findings from a family with 71 affected

individuals in which five generations were affected by TSC. In this family, 38% of the 69 individuals, where information on their intellectual abilities was known, had average intelligence, while 62% had learning disabilities. These data led to the new diagnostic criteria that were first published in 1988 [18], although many clinicians still used Vogt's triad to diagnose TSC for many years, incorrectly and inappropriately referring to individuals with TSC as persons with "fits, zits and who are nitwits." The diagnostic criteria were revised again in 1998 [19] and will continue to be revised as more knowledge is gained about the clinical and genetic aspects of the disease.

The hereditary nature of TSC was recognized in the early 1900s through the observation of families that had multiple affected individuals in two or more generations [20, 21]. Schuster [22] confirmed that TSC was a hereditary disease, but also described individuals with only the "adenoma sebaceum" component of Vogt's triad, with no seizures or intellectual disability. Initially, these individuals were described as having *forme fruste* TSC (from the French fluster, or defaced), a term that was not clearly defined but was used for individuals with "incomplete" phenotypes who did not meet diagnostic criteria.

With the improvement of technology to image the human body starting in the mid-1970s, it became possible to diagnose individuals with TSC who had manifestations of the disease but who were clinically asymptomatic. The development of computed tomography (CT) of the head allowed the imaging of subependymal nodules, subependymal giant cell tumors (SGCTs), and calcified tubers starting in 1974. This was followed by echocardiography to image cardiac rhabdomyomas and renal ultrasound to image renal tumors in individuals with TSC. However, the development of magnetic resonance imaging (MRI) in 1982 provided the means to much more accurately and explicitly image cortical tubers and other manifestations of TSC. As new technologies are developed and applied to the study of the clinical manifestations of TSC, our knowledge of the disease and our ability to diagnose TSC will significantly improve.

1.3

Hereditary Nature of TSC

Kirpicznik [20] first recognized TSC as a genetic condition after reporting on a family with affected individuals in three generations, including identical and fraternal twins. Adenoma sebaceum (correctly termed facial angiofibromas) were reported to be inherited in families [6, 7]. Berg [21] also described the hereditary nature of TSC in 1913, and Schuster [22] confirmed this and noted the exceptional individual with only the facial lesions without intellectual disability.

The dominant inheritance of TSC and its high mutation rate were demonstrated [23, 24], but very little progress was made until genetic linkage analysis identified a probably TSC gene on chromosome 9q34 in 1987 [25], identified as the *TSC1* locus. Numerous linkage analysis publications narrowed the search for the TSC gene(s), with a group in the United States showing that there some families with TSC had a linkage to chromosome 9, but that there were certainly one or more