

Tuberous Sclerosis Complex

Genes, Clinical Features,
and Therapeutics

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



 WILEY-
BLACKWELL

Contents

Preface

List of Contributors

PART I: BASICS

1 THE HISTORY OF TUBEROUS SCLEROSIS COMPLEX

VICKY H. WHITTEMORE

1.1 DEFINITION

1.2 THE HISTORY OF TUBEROUS SCLEROSIS COMPLEX

1.3 HEREDITARY NATURE OF TSC

1.4 MOLECULAR MECHANISMS IN TSC

1.5 THE FUTURE OF TSC

REFERENCES

2 NATURAL HISTORY OF TUBEROUS SCLEROSIS COMPLEX AND OVERVIEW OF MANIFESTATIONS

ELIZABETH A. THIELE AND SERGIUSZ JÓŹWIAK

2.1 TSC: MULTISYSTEM INVOLVEMENT

2.2 TSC: A SPECTRUM ACROSS THE LIFE SPAN

2.3 TSC: A "MODEL" SYSTEM
REFERENCES

3 DIAGNOSTIC CRITERIA FOR TUBEROUS SCLEROSIS COMPLEX

E. STEVE ROACH AND STEVEN P. SPARAGANA

INTRODUCTION
REFERENCES

PART II: GENETICS

4 GENETICS OF TUBEROUS SCLEROSIS COMPLEX

DAVID J. KWIATKOWSKI

4.1 INTRODUCTION

4.2 HISTORICAL REVIEW OF LINKAGE ANALYSIS AND POSITIONAL CLONING OF THE TSC1 AND TSC2 GENES

4.3 THE TSC1 AND TSC2 GENES: GENOMIC STRUCTURE, SPLICING, PREDICTED SEQUENCES, AND DOMAINS

4.4 MUTATIONAL SPECTRUM OF TSC1 AND TSC2

4.5 FREQUENCY AND SIGNIFICANCE OF MOSAICISM IN TSC

4.6 CONSIDERATIONS IN PATIENTS IN WHOM NO MUTATION CAN BE IDENTIFIED

4.7 THE ROLE OF TSC1 AND TSC2 IN TUMOR DEVELOPMENT

4.8 THE FUTURE OF MOLECULAR DIAGNOSTICS IN TSC

ACKNOWLEDGMENTS

REFERENCES

5 GENOTYPE-PHENOTYPE STUDIES IN TSC AND MOLECULAR DIAGNOSTICS

KIT S. AU AND HOPE NORTHRUP

5.1 INTRODUCTION

5.2 COMPREHENSIVE GENOTYPE-PHENOTYPE REPORTS

5.3 GENOTYPE-PHENOTYPE CORRELATION

5.4 MOLECULAR DIAGNOSTIC METHODS

5.5 CONCLUSION

REFERENCES

PART III: BASIC SCIENCE

6 THE ROLE OF TARGET OF RAPAMYCIN SIGNALING IN TUBEROUS SCLEROSIS COMPLEX

BRENDAN D. MANNING

6.1 THE TARGET OF RAPAMYCIN: AN EVOLUTIONARILY CONSERVED REGULATOR OF CELL GROWTH AND PROLIFERATION

6.2 GENETIC AND BIOCHEMICAL STUDIES LINK THE TSC1-TSC2 COMPLEX TO CELL GROWTH CONTROL THROUGH MTORC1

6.3 THE TSC1-TSC2 COMPLEX AS A CRITICAL SENSOR OF CELLULAR GROWTH CONDITIONS

6.4 PRIMARY MTOR-RELATED SIGNALING DEFECTS TRIGGERED BY DISRUPTION OF THE TSC1-TSC2 COMPLEX

6.5 PATHOLOGICAL CONSEQUENCES OF MTOR DYSREGULATION IN TSC

6.6 THERAPEUTIC OPPORTUNITIES: RAPAMYCIN AND BEYOND

ACKNOWLEDGMENTS

REFERENCES

7 RAT AND MOUSE MODELS OF TUBEROUS SCLEROSIS

DAVID J. KWIATKOWSKI

7.1 INTRODUCTION

7.2 THE EKER RAT

7.3 TSC MODELS IN THE MOUSE

7.4 CONCLUDING REMARKS

REFERENCES

8 ANIMAL MODELS OF TSC: INSIGHTS FROM DROSOPHILA

DUOJIA PAN

8.1 INTRODUCTION

8.2 CONNECTING TSC1-TSC2 TO THE INSULIN/PI3K SIGNALING PATHWAY

8.3 THE TSC1-TSC2 COMPLEX AS A NEGATIVE REGULATOR OF TORC1

8.4 IDENTIFICATION OF THE SMALL GTPASE RHEB AS A DIRECT TARGET OF THE TSC1-TSC2 COMPLEX

8.5 CONTROL OF AUTOPHAGY BY THE TSC-RHEB-TORC1 PATHWAY

8.6 CROSS TALK BETWEEN THE TSC-RHEB-TORC1 PATHWAY AND THE INSULIN PATHWAY

8.7 RELATIONSHIP BETWEEN TSC1-TSC2 AND AMINO ACIDS-MEDIATED TORC1 ACTIVATION

8.8 UPSTREAM OF THE TSC1-TSC2 COMPLEX

8.9 SUMMARY

ACKNOWLEDGMENTS

REFERENCES

PART IV: BRAIN INVOLVEMENT

9 PATHOGENESIS OF TSC IN THE BRAIN

**PETER B. CRINO, RUPAL MEHTA, AND
HARRY V. VINTERS**

9.1 INTRODUCTION

9.2 TUBERS

9.3 SENS AND SEGAS

9.4 CELL LINEAGE

**9.5 MTOR ACTIVATION AND BIALLELIC TSC
GENE INACTIVATION**

**9.6 ALTERNATIVE SIGNALING CASCADES IN
TSC BRAIN LESIONS**

**9.7 STRUCTURAL ALTERATIONS IN
NONTUBER BRAIN AREAS**

9.8 CONCLUSIONS AND FUTURE DIRECTIONS

ACKNOWLEDGMENTS

REFERENCES

10 EPILEPSY IN TSC

**ELIZABETH A. THIELE AND HOWARD L.
WEINER**

10.1 OVERVIEW OF EPILEPSY IN TSC

10.2 ROLE OF ELECTROENCEPHALOGRAPHY

10.3 TREATMENT OF EPILEPSY IN TSC

10.4 INFANTILE SPASMS

10.5 LENNOX-GASTAUT SYNDROME

10.6 PATHOGENESIS OF EPILEPSY IN TSC

**10.7 THE NATURAL HISTORY OF EPILEPSY IN
TSC**

REFERENCES

11 SUBEPENDYMAL GIANT CELL ASTROCYTOMAS

**DAVID NEAL FRANZ, DARCY A.
KRUEGER, AND M. GREGORY BALKO**

11.1 INTRODUCTION

**11.2 PATHOLOGY AND PATHOGENESIS OF
SEGA**

11.3 SENS VERSUS SEGAS

11.4 DIAGNOSIS OF SEGA VERSUS SEN

11.5 CURRENT MANAGEMENT OF SEGASS

11.6 MEDICAL MANAGEMENT OF SEGAS

11.7 CONCLUSION AND SUMMARY

ACKNOWLEDGMENTS

REFERENCES

12 NEURODEVELOPMENTAL, PSYCHIATRIC AND COGNITIVE ASPECTS OF TUBEROUS SCLEROSIS COMPLEX

PETRUS J. DE VRIES

12.1 INTRODUCTION

12.2 DIFFERENT LEVELS OF INVESTIGATION

**12.3 ASSESSMENT AND MANAGEMENT OF
NEUROCOGNITIVE AND NEUROBEHAVIORAL
DIFFICULTIES IN TSC**

**12.4 CAUSES OF THE NEUROCOGNITIVE AND
NEUROBEHAVIORAL FEATURES OF TSC**

12.5 ANIMAL MODELS FOR BEHAVIORAL, PSYCHIATRIC, INTELLECTUAL, LEARNING, AND NEUROPSYCHOLOGICAL DEFICITS IN TSC

12.6 FUTURE DIRECTIONS FOR THE UNDERSTANDING OF BEHAVIORAL, PSYCHIATRIC, INTELLECTUAL, ACADEMIC, AND NEUROPSYCHOLOGICAL DEFICITS IN TSC

12.7 HOW TO LIVE A POSITIVE LIFE WITH TSC

REFERENCES

PART V: OTHER ORGAN SYSTEMS

13 OPHTHALMIC MANIFESTATIONS

SHIVI AGRAWAL AND ANNE B. FULTON

13.1 INTRODUCTION

13.2 ADNEXA AND ANTERIOR SEGMENT

13.3 RETINAL LESIONS

13.4 PAPILLEDEMA

13.5 VISUAL FIELD DEFECTS

13.6 CEREBRAL VISUAL IMPAIRMENT

13.7 COMMON OPHTHALMIC ISSUES

13.8 SUMMARY AND RECOMMENDATIONS

REFERENCES

14 DERMATOLOGIC MANIFESTATIONS OF TUBEROUS SCLEROSIS COMPLEX (TSC)

**THOMAS N. DARLING, JOEL MOSS,
AND MARK MAUSNER**

14.1 INTRODUCTION

14.2 TYPES OF TSC SKIN LESIONS

14.3 PATHOGENESIS OF TSC SKIN LESIONS

**14.4 CONSIDERATIONS FOR SURGICAL
TREATMENT OF TSC SKIN LESIONS**

14.5 TREATMENT OF ANGIOFIBROMAS

**14.6 LASER TREATMENTS OF
ANGIOFIBROMAS**

**14.7 TREATMENT OF OTHER TSC SKIN
LESIONS**

**14.8 FUTURE OF MEDICAL/SURGICAL
TREATMENT OF TSC SKIN LESIONS**

ACKNOWLEDGMENTS

REFERENCES

15 RENAL MANIFESTATIONS OF TUBEROUS SCLEROSIS COMPLEX

**JOHN J. BISSLER AND ELIZABETH P.
HENSKE**

15.1 INTRODUCTION

15.2 ANGIOMYOLIPOMATA

15.3 EPITHELIOID AND MALIGNANT ANGIOMYOLIPOMATA

15.4 RENAL CYSTIC DISEASE

15.5 ONCOCYTOMA

15.6 RENAL CELL CARCINOMA

15.7 MONITORING RENAL LESIONS

15.8 TREATMENT

15.9 CONCLUSIONS AND FUTURE DIRECTIONS

REFERENCES

16 CARDIAC AND VASCULAR MANIFESTATIONS

SERGIUSZ JÓŹWIAK AND MARIA RESPONDEK-LIBERSKA

16.1 INTRODUCTION

16.2 PREVALENCE AND NATURAL HISTORY OF CARDIAC RHABDOMYOMAS

16.3 CLINICAL MANIFESTATIONS

16.4 PATHOLOGY AND MOLECULAR BIOLOGY OF CARDIAC TUMORS

16.5 DIAGNOSIS

16.6 FETAL CARDIAC RHABDOMYOMAS AND DIAGNOSIS OF TSC

16.7 TREATMENT

16.8 GENOTYPE-PHENOTYPE CORRELATIONS WITH RHABDOMYOMAS

16.9 VASCULAR ABNORMALITIES IN TSC

REFERENCES

**17 LYMPHANGIOLEIOMYOMATOSIS
AND PULMONARY DISEASE IN TSC**

**FRANCIS X. MCCORMACK AND
ELIZABETH P. HENSKE**

17.1 INTRODUCTION

17.2 HISTORICAL FEATURES OF LAM

17.3 EPIDEMIOLOGY

17.4 CLINICAL PRESENTATION

17.5 DIAGNOSIS

**17.6 PATHOLOGY AND LABORATORY
STUDIES**

17.7 PHYSIOLOGY

17.8 RADIOLOGY

17.9 CLINICAL COURSE AND MANAGEMENT

**17.10 GENETIC BASIS AND MOLECULAR
PATHOLOGY**

**17.11 CHALLENGES AND FUTURE
DIRECTIONS**

REFERENCES

**18 ENDOCRINE, GASTROINTESTINAL,
HEPATIC, AND LYMPHATIC
MANIFESTATIONS OF TUBEROUS
SCLEROSIS COMPLEX**

FINBAR J. O'CALLAGHAN AND JOHN P. OSBORNE

18.1 INTRODUCTION AND SUMMARY

18.2 ENDOCRINE MANIFESTATIONS OF TSC

18.3 GASTROINTESTINAL MANIFESTATIONS OF TSC

18.4 HEPATIC MANIFESTATIONS OF TSC

18.5 SPLENIC MANIFESTATIONS OF TSC

18.6 LYMPHATIC MANIFESTATIONS OF TSC

REFERENCES

PART VI: FAMILY IMPACT

19 IMPACT OF TSC ON THE FAMILY AND GENETIC COUNSELING ISSUES

VICKY H. WHITTEMORE AND JANINE LEWIS

19.1 INTRODUCTION

19.2 IMPACT ON THE FAMILY

19.3 FINDING SUPPORT

19.4 TUBEROUS SCLEROSIS COMPLEX ORGANIZATIONS AND SUPPORT GROUPS

19.5 GENETIC COUNSELING ISSUES FOR TUBEROUS SCLEROSIS COMPLEX

19.6 SUMMARY

REFERENCES

Index

Related Titles

Gires, O., Seliger, B. (eds.)

Tumor-Associated Antigens

Identification, Characterization, and Clinical Applications

2009

ISBN: 978-3-527-32084-4

Allgayer, H., Rehder, H., Fulda, S. (eds.)

Hereditary Tumors

From Genes to Clinical Consequences

2009

ISBN: 978-3-527-32028-8

Nothwang, H., Pfeiffer, E (eds.)

Proteomics of the Nervous System

2008

ISBN: 978-3-527-31716-5

Müller, H. W. (ed.)

Neural Degeneration and Repair

Gene Expression Profiling, Proteomics and Systems Biology

2008

Hardcover

ISBN: 978-3-527-31707-3

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

Tuberous Sclerosis Complex

Genes, Clinical Features, and Therapeutics

 **WILEY-BLACKWELL**

The Editors

Dr. David J. Kwiatkowski Brigham & Women's Hospital
Dana Farber Cancer Institute Harvard Medical School 1
Blackfan Circle Boston, MA 02115 USA

Dr. Vicky Holets Whittemore Tuberous Sclerosis Alliance
801 Roeder Road Silver Spring, MD 20910 USA

Dr. Elizabeth A. Thiele Carol & James Herscot Center For
TCS Massachusetts General Hospital Department of
Neurology 175 Cambridge Street Boston, MA 02114 USA

Cover: Tuberous sclerosis complex (TSC) affects people of all races, ages, and sexes. The cover shows photographs of individuals with TSC, provided by Rick Guidotti, New York, NY (www.positiveexposure.org) and MGH Photography (www.massgeneral.org/photography), Boston, Massachusetts.

Limit of Liability/Disclaimer of Warranty: While the publisher and author have used their best efforts in preparing this book, they make no representations or warranties with respect to the accuracy or completeness of the contents of this book and specifically disclaim any implied warranties of merchantability or fitness for a particular purpose. No warranty can be created or extended by sales representatives or written sales materials. The Advice and strategies contained herein may not be suitable for your situation. You should consult with a professional where appropriate. Neither the publisher nor authors shall be liable for any loss of profit or any other commercial damages, including but not limited to special, incidental, consequential, or other damages.

Library of Congress Card No.: applied for

British Library Cataloguing-in-Publication Data A catalogue record for this book is available from the British Library.

Bibliographic information published by the Deutsche Nationalbibliothek

The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at <http://dnb.d-nb.de>.

© 2010 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany

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.

All rights reserved (including those of translation into other languages). No part of this book may be reproduced in any form – by photoprinting, microfilm, or any other means – nor transmitted or translated into a machine language without written permission from the publishers. Registered names, trademarks, etc. used in this book, even when not specifically marked as such, are not to be considered unprotected by law.

ISBN: 978-3-527-32201-5

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.

Boston and Silver Spring
February 2010

*David J. Kwiatkowski
Elizabeth A. Thiele
Vicky H. Whittemore*

Acknowledgements

The Editors give many thanks to: all of the chapter authors for their contributions to this book; our families for their perseverance and understanding; our grant support enabling this work (DJK-NIH/NCI 1P01CA120964, NIH NINDS 2R37NS031535, NIH NINDS 1P01NS24279; ET-NIH NINDS 1P01NS24279; the Carol and James Herscot Center for TSC); the continuing support of the Tuberous Sclerosis Alliance, and other TSC support groups worldwide; and individuals with TSC and families who have not only permitted but facilitated, encouraged, and even funded in part many studies on this condition for several decades.

List of Contributors

Shivi Agrawal Boston Children's Hospital and Harvard Medical School Boston, MA 02115 USA

Kit S. Au The University of Texas Medical School at Houston Division of Medical Genetics Department of Pediatrics Houston, TX 77030 USA

M. Gregory Balko Wright State University Boonshoft School of Medicine Dayton, OH USA

John J. Bissler University of Cincinnati College of Medicine Cincinnati Children's Hospital Medical Center Division of Nephrology and Hypertension Cincinnati, OH 45435 USA

Peter B. Crino University of Pennsylvania PENN Epilepsy Center Philadelphia, PA 19104 USA

Petrus J. de Vries University of Cambridge Cambridgeshire & Peterborough NHS Foundation Trust Developmental Psychiatry Section Douglas House Cambridge CB2 8AH UK

Thomas N. Darling Uniformed Services University of the Health Sciences Department of Dermatology Bethesda, MD 20814 USA

David Neal Franz University of Cincinnati College of Medicine Cincinnati Children's Hospital Medical Center Cincinnati, OH 45229 USA

Anne B. Fulton Boston Children's Hospital and Harvard Medical School Boston, MA 02115 USA

Elizabeth P. Henske Harvard Medical School Brigham and Women's Hospital Center for LAM Research and Patient Care Boston, MA 02115 USA

Sergiusz Jóźwiak The Children's Memorial Health Institute Department of Pediatric Neurology and Epileptology Warsaw Poland

Darcy A. Krueger University of Cincinnati College of Medicine Cincinnati Children's Hospital Medical Center Cincinnati, OH 45229 USA

David J. Kwiatkowski Brigham & Women's Hospital Dana Farber Cancer Institute Harvard Medical School Boston, MA 02115 USA

Janine Lewis The Genetic and Rare Disease Information Center National Institute of Health Gaithersburg, MD 20898 USA

Brendan D. Manning Harvard University, School of Public Health Department of Genetics and Complex Diseases Boston, MA 02115 USA

Mark Mausner Mausner Plastic Surgery Center Bethesda, MD 20817 USA

Francis X. McCormack The University of Cincinnati Division of Pulmonary, Critical Care and Sleep Medicine Cincinnati, OH 45219 USA

Rupal Mehta David Geffen School of Medicine at UCLA Department of Pathology & Laboratory Medicine Los Angeles, CA 90095 USA

Joel Moss National Institutes of Health National Heart, Lung, and Blood Institute Translational Medicine Branch Bethesda, MD 20892 USA

Hope Northrup The University of Texas Medical School of Houston Division of Medical Genetics Department of Pediatrics Houston, TX 77030 USA

Finbar J. O'Callaghan University of Bristol Institute of Child Life and Health, Education Centre Bristol UK

John P. Osborne University of Bath UK

Duoja Pan Johns Hopkins University School of Medicine Howard Hughes Medical Institute Department of Molecular Biology and Genetics Baltimore, MD 21205 USA

Maria Respondek-Liberska Medical University of Łódź and Research Institute Polish Mother's Memorial Hospital Department for Diagnosis and Prevention of Fetal Malformations Łódź Poland

E. Steve Roach Ohio State University College of Medicine Division of Child Neurology Columbus, OH 43205 USA

Steven P. Sparagana Texas Scottish Rite Hospital for Children Dallas, TX 75219 USA

Elizabeth A. Thiele Massachusetts General Hospital Carol & James Herscot Center for TSC Department of Neurology Boston, MA 02114 USA

Harry V. Vinters David Geffen School of Medicine at UCLA Department of Pathology & Laboratory Medicine Los Angeles, CA 90095 USA

Howard L. Weiner Massachusetts General Hospital Carol & James Herscot Center Boston, MA 02114 USA

Vicky H. Whittemore Tuberous Sclerosis Alliance Silver Spring, MD 20910 USA

PART I
BASICS

1

THE HISTORY OF TUBEROUS SCLEROSIS COMPLEX

Vicky H. Whittemore

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](#)).

[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 “tuberosities” 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 *TSC1* gene to chromosome 9q34.3 [25]
- 1992 Finding of nonlinkage to chromosome 9 [26]; mapping of the *TSC2* gene to chromosome 16p13.3 [27]
- 1993 Cloning of the *TSC2* gene; its protein product is called tuberin [28]
- 1997 Cloning of the *TSC1* gene; its protein product is called hamartin [29]
- 2001 *Drosophila* homologues *Tsc1* and *Tsc2* 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]

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