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

Tuberous Sclerosis Complex

Genes, Clinical Features, and Therapeutics

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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.

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Contents

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that the traditional Tuberous Sclerosis Complex (TSC) book edited by Manuel Gomez was eight years old, and was already outdated then in several respects.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
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David J. Kwiatkowski
Elizabeth A. Thiele
Vicky H. Whittemore

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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).

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 "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]

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