

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

additional loci [26]. This led to the identification of a second linkage to chromosome 16p13 [27], designated as the *TSC2* locus. The *TSC2* gene was cloned first by the European Chromosome 16 Consortium [28] in 1993, with the *TSC1* gene cloned in 1997 [29].

A molecular diagnostic test for TSC was launched in the early 2000s, and is used today for confirmation of a clinical diagnosis of TSC, to assist in the diagnosis of TSC, and for reproductive decision making, including prenatal diagnosis and preimplantation genetic diagnosis combined with *in vitro* fertilization. Several studies have attempted to correlate the phenotype (the clinical manifestations of the disease expressed) with the genotype (the specific genetic mutation) for individuals with TSC, with reinforcement of the notion that TSC is variably expressed even in individuals with the exact genetic mutation [30–32].

1.4

Molecular Mechanisms in TSC

Little was known about the cause of TSC prior to identification of the *TSC1* and *TSC2* genes in the 1990s. A naturally occurring rat mutation in *Tsc2*, the Eker rat model, had been used extensively to study TSC, but it was not until the *Drosophila* homologues, *Tsc1* and *Tsc2*, were found to be involved in regulation of cell and organ size [33–35] that significant progress could be made. Finding that the *TSC2* gene product, tuberin, was a target in an important cell signaling pathway [36] and the identification that the *TSC1* and *TSC2* gene products worked together in a complex [37] led to finding the critical role of the TSC genes in regulation of the mTOR pathway [38]. mTOR activation has been confirmed in renal angiomyolipomas from individuals with TSC [39], and an mTOR inhibitor, rapamycin, has been shown to reduce renal tumors in Eker rats [40] and TSC mouse models [41] and, more recently, to reduce the size of subependymal giant cell astrocytomas [42] and renal angiomyolipomas [43] in individuals with TSC.

1.5

The Future of TSC

Significant progress has been made in TSC research, but there are still many questions left unanswered. The clinical trials look promising, but may or may not be effective for treatment of both the CNS manifestations and tumor growth in various organ systems without very early treatment and/or chronic drug therapy. Yet another revision of the diagnostic criteria is needed to include those individuals who do not meet criteria for a diagnosis based on the previous criteria, but are found to have a disease-causing variation in either the *TSC1* or *TSC2* gene. The future holds much promise for improving the quality of life for individuals with TSC, and for reaching an even more complete understanding of the underlying mechanisms that result in the many and variable manifestations of the disease.

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