

Review

Genetic and Clinical Features of Tuberous Sclerosis Patients from the Republic of Bashkortostan

Rustam Nailevich Mustafin *

Federal State Budgetary Institution of Higher Education Bashkir State Medical University, 450008, Ufa, Lenin St., 3, Russia; E-Mail: ruji79@mail.ru; ORCID: 0000-0002-4091-382X

* **Correspondence:** Rustam Nailevich Mustafin; E-Mail: ruji79@mail.ru; ORCID: 0000-0002-4091-382X

Academic Editor: Andre Megarbane*OBM Genetics*

2026, volume 10, issue 1

doi:10.21926/obm.genet.2601323

Received: September 29, 2025**Accepted:** January 05, 2026**Published:** January 08, 2026

Abstract

Tuberous sclerosis (TS) is one of the most common hereditary tumor syndromes, occurring with an average incidence of 1 in 9,000 newborns worldwide. The disease manifests itself through the development of tumors of the brain, kidneys, heart, lungs, and skin, along with characteristic depigmented spots. Tuberous sclerosis is caused by germline variants in the *TSC1* (encoding hamartin) and *TSC2* (encoding tuberin) genes. The hamartin-tuberin protein complex, together with the TBC1D7 molecule, inhibits the serine/threonine protein kinase mTORC1 (mammalian target of rapamycin complex 1), which is essential for cell proliferation and growth. Accordingly, the use of mTOR inhibitors in the treatment of tuberous sclerosis affects the pathogenesis of the disease and tumor development. Meta-analyses have confirmed the efficacy of mTOR inhibitors in the treatment of tuberous sclerosis, making molecular genetic confirmation of the diagnosis essential for treatment planning. To analyze the clinical and genetic characteristics of tuberous sclerosis in the Republic of Bashkortostan (RB). A retrospective study of patients with tuberous sclerosis registered at the Republican Medical Genetic Center was conducted. 23 programs were used to assess the pathogenicity of newly discovered variants. The odds ratio (OR) was calculated manually using the formula: $OR = (A \times D) / (B \times C)$. Currently, 88 cases of tuberous sclerosis have been registered in RB, of which 5 patients had pathogenic variants in the *TSC1* gene, 19



© 2026 by the author. This is an open access article distributed under the conditions of the [Creative Commons by Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium or format, provided the original work is correctly cited.

had pathogenic variants in the *TSC2* gene, and 4 people had extensive deletions of the *TSC2* gene. Compared with global data, a statistically significantly lower incidence of subependymal nodules, cortical tubers, renal angiomyolipomas, gingival fibromas, pulmonary lymphangiomyomatosis, facial angiofibromas, cognitive impairment, and autism was determined. The significantly lower incidence of brain and internal organ tumors may be due to genetic factors affecting the disease in the region. In 28 of 88 patients with tuberous sclerosis (33%), the diagnosis was confirmed at the genetic level, which forms the basis for treatment with mTOR inhibitors, which is being administered to 8 patients.

Keywords

Hamartomas; *TSC1* gene; *TSC2* gene; tumors; depigmentation spots; tuberous sclerosis; fibromas

1. Introduction

Tuberous sclerosis (TS) is a hereditary tumor syndrome with an incidence of 1:6000 to 1:12000 (average 1:9000) newborns. The cause of TS is germline heterozygous pathogenic variants in the tumor suppressor genes *TSC1* and *TSC2* (the name is derived from the abbreviation Tuberous Sclerosis) with confirmed pathogenicity [1]. The disease is characterized by a variety of clinical manifestations in various organs and systems (Figure 1), the development of hamartomas (a type of benign tumor) of the brain in the form of subependymal nodes in 90% and cortical tubers in 85% of patients; renal angiomyolipomas in 75% [2] of patients with TS; cardiac rhabdomyomas in 90% of newborns [1], as well as pulmonary lymphangiomyomatosis in 40% [2, 3] of patients. Subependymal giant cell astrocytomas are detected in 5–20% of patients with TS [2]. Patients with TS are characterized by skin lesions, including depigmentation spots in 90% [3, 4], facial angiofibromas in 83%, shagreen plaques in 50%, and fibrous plaques on the forehead and scalp in 25% of patients [4]. Epilepsy is detected in 63–93% of patients with TS, which first appears during the first year of life and is closely associated with impaired neurocognitive development [1]. 30% of patients with TS have autism spectrum disorder (ASD), of which 90% have intellectual disability. For differential analysis of autism spectrum disorder, consultations with a psychiatrist and psychologist are necessary to exclude other mental disorders, such as attention deficit hyperactivity disorder, schizophrenia, anxiety disorders, and intellectual disability [5].

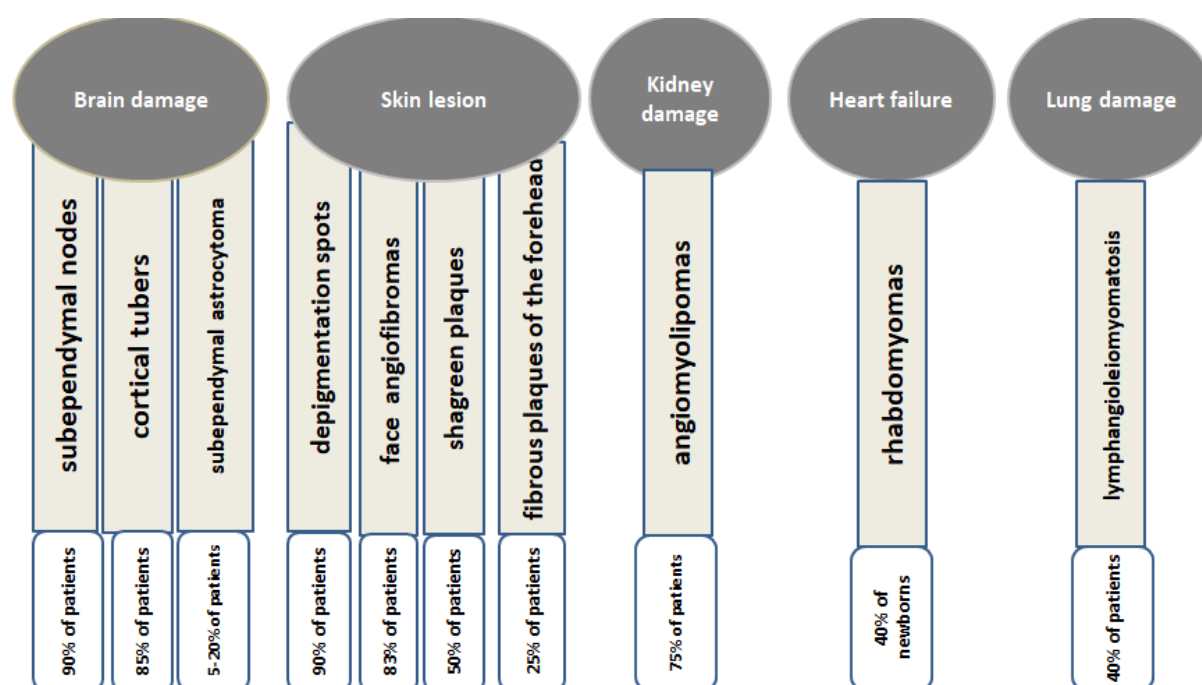


Figure 1 Clinical manifestations of tuberous sclerosis and their frequency.

The *TSC1* and *TSC2* genes encode the proteins hamartin and tuberin, respectively, which, together with the TBC1D7 molecule, inhibit the serine/threonine protein kinase mTORC1 (mammalian target of rapamycin complex 1), which is essential for cell proliferation and growth. Therefore, pathogenic variants in the *TSC1* or *TSC2* genes lead to hyperactivation of mTORC1 and carcinogenesis [6]. Pathogenic variants in the *TSC1* and *TSC2* genes that cause TS exhibit extreme diversity and lack mutational hotspots. A meta-analysis of molecular genetic studies from different countries revealed no significant differences in the types of pathogenic variants. Among nucleotide substitutions, the ratio C>G/G>C was 3:1, and C>T/G>A was 2:1 [7]. The *TSC1* gene is located on 9q34.13, consists of 23 exons, and encodes a 1164-amino-acid protein with a molecular weight of 130 kDa. Pathogenic variants in the *TSC1* gene, primarily nonsense variants and small deletions, account for 10–15% of all TS cases worldwide. The *TSC2* gene is located on 6p13.3, spans 45 exons, and encodes the 200 kDa protein tuberin, which consists of 1807 amino acids. Pathogenic variants in the *TSC2* gene account for 75-80% of TS cases and are primarily represented by missense variants and deletions. A more severe course of TS was determined in patients with pathogenic variants in the *TSC2* gene [6]. A study of 325 patients with TS, identifying the characteristics of the clinical manifestations of the disease with different types of pathogenic variants, showed that patients with pathogenic variants in the *TSC2* gene had a greater number of depigmentation spots and more pronounced learning difficulties compared to patients with pathogenic variants in the *TSC1* gene (17% of all causes of TS in this sample) [8].

The ClinVar database currently contains data on 5,253 germline variants in the *TSC1* gene, of which 655 are pathogenic, 132 are likely pathogenic, 2,128 are of uncertain significance, 516 have conflicting pathogenicity data, 1,474 are likely benign, and 320 are benign. The majority of these variants—2,252—are missense variants, 224 are nonsense variants, and 141 are splice site alterations. In addition, 533 deletions, 263 duplications, and 329 insertions have been described.

The ClinVar database contains 11,587 germline variants in the *TSC2* gene, of which 1,237 are pathogenic, 291 are likely pathogenic, 4,066 are of uncertain significance, 1,391 have conflicting pathogenicity data, 3,701 are likely benign, and 984 are benign. Of these, 4,960 are missense variants, 362 are nonsense variants, 414 are splice site variants, 1,093 are deletions, 552 are duplications, and 725 are insertions (Figure 2). Identification of pathogenic variants in the *TSC1* and *TSC2* genes is important for confirming the diagnosis of TS and prescribing effective treatment with mTOR inhibitors, which include rapamycin (sirolimus) and its analogues (everolimus). According to meta-analyses, these drugs reduce the size of astrocytomas of the brain, angioliopomas of the kidneys [2], with a significant decrease in the frequency of seizures [9], including in children aged 1 year and older in relation to astrocytomas, angiofibromas of the face, and tumors of the optic nerves [10]. Moreover, the use of mTOR inhibitors by pregnant women with TS in their fetus reduces the size of cardiac rhabdomyomas in the fetus [11]. Sirolimus ointments are used for the treatment of facial angiofibromas, with a 0.2% concentration of the drug being most effective [12].

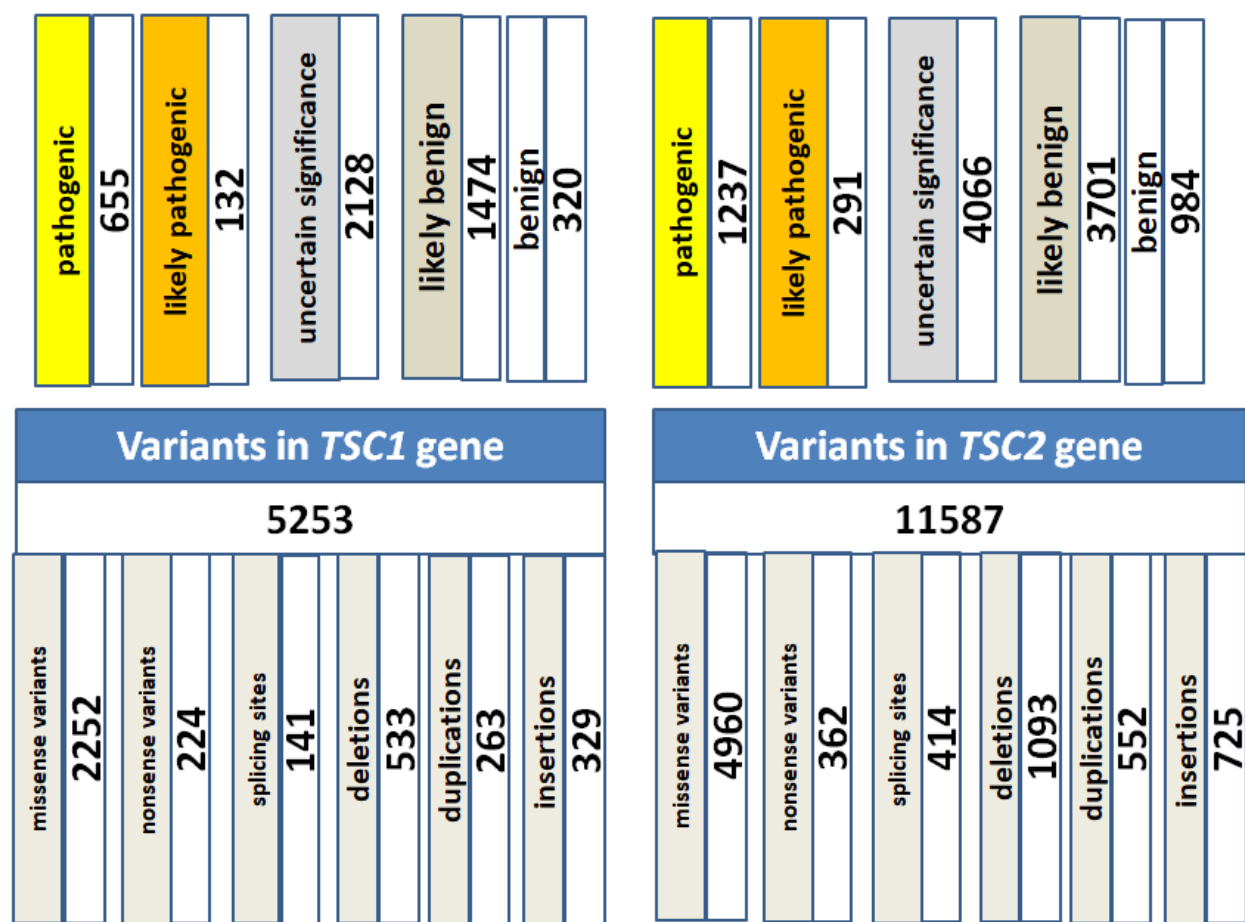


Figure 2 Spectrum of variants in the *TSC1* and *TSC2* genes worldwide, according to ClinVar data.

1.1 Purpose of the Study

To analyze the clinical and molecular genetic characteristics of tuberous sclerosis in the Republic of Bashkortostan (RB).

2. Materials and Methods

A retrospective analysis of data on patients with TS from RB, registered with geneticists at the Republican Medical Genetic Center (RMGC) with an established diagnosis of TS, was conducted. All studies were conducted in compliance with biomedical ethics and GCP (Good Clinical Practice) standards. The clinical manifestations of TS are described in patients from RB, as well as in patients with identified pathogenic variants in the *TSC1* and *TSC2* genes. Pathogenic variants were identified using next-generation sequencing (NGS) for intragenic pathogenic variants and multiplex ligase-dependent probe amplification (MLPA) for extended deletions. Blood samples were collected with the patients' consent and sent to molecular genetic laboratories. For qualitative binary data, statistical analysis was performed using an interactive 2×2 contingency table and the calculation of association statistics (Pearson's χ^2 test) with Yates's continuity correction developed by V.P. Leonov, as well as analysis of four-field contingency tables available at <https://medstatistic.ru/calculators/calchi.html>. The odds ratio (OR) was calculated manually using the formula: $OR = (A \times D)/(B \times C)$. All patients signed informed consent. The study protocol was approved by the Local Ethics Committee (Protocol No. 5 dated December 7, 2009). 23 programs were used for pathogenicity assessment for newly discovered variants: SIFT_pred; SIFT4G_pred; Polyphen2_HDIV_pred; Polyphen2_HVAR_pred; LRT_pred; MutationTaster_pred; MutationAssessor_pred; FATHMM_pred; PROVEAN_pred; MetaSVM_pred; MetaLR_pred; MetaRNN_pred; M-CAP_pred; PrimateAI_pred; DEOGEN2_pred; BayesDel_addAF_pred; BayesDel_noAF_pred; ClinPred_pred; LIST-S2_pred; ESM1b_pred; AlphaMissense_pred; fathmm-MKL_coding_pred; fathmm-XF_coding_pred. For the new variants we identified, pathogenicity has been determined according to most of these programs.

3. Results

In RB, 88 patients with TS (49 men and 39 women, ratio (1.26:1)) from 82 families were registered. The prevalence of TS was calculated for the entire period of TS patient registration at the Republican Medical Genetic Center—from 1996 to 2025—over the past 29 years. The age range of patients with tuberous sclerosis in the republic ranged from 1 to 61 years (average age 25 years). The age distribution of patients is shown in Figure 3. Taking into account the population of RB in 2025 - 4,046,094 people, the incidence rate was 1:46,000, and the prevalence of TS was 2.17:100,000 people, while the global average is 11:100,000 people (5.5 times more often). This discrepancy may be due to regional factors and to the lack of visits by TS patients to genetic counselors. Therefore, it is essential to report this condition to physicians across various specialties. Sporadic cases resulting from de novo pathogenic variants in parental germ cells accounted for the majority—85% (73 individuals) of patients with TS.

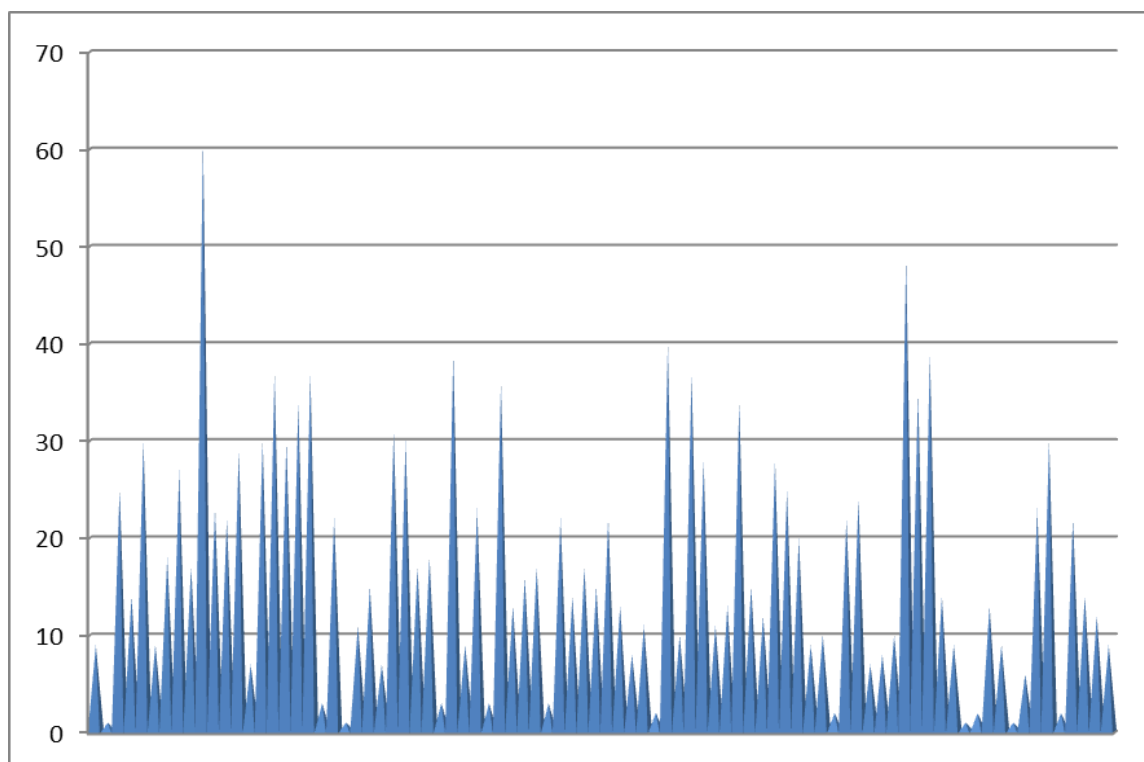


Figure 3 Distribution of patients with tuberous sclerosis by age in the Republic of Bashkortostan.

Analysis of the clinical manifestations of TS in RB reveals differences in the frequency of certain manifestations compared with global data (Table 1). Depigmentation spots were detected in 78 patients (88%), fibrous plaques on the forehead in 28 (31.8%), shagreen plaques on the skin in 36 (42%), subependymal giant cell astrocytoma in 16 (19%), and renal cysts in 19 (22%). Cardiac rhabdomyomas were detected in 6 of 8 patients with TS in children under 2 years of age (75%), in 30 of 78 patients over 2 years of age (38%). Epilepsy was diagnosed in 67% of patients with tuberous sclerosis from the Republic of Bashkortostan (58 people), which is not statistically significantly different from the data from a study of tuberous sclerosis in the world (78%), $p = 0.082$ [1]. Considering the average incidence of TS worldwide of 1:9000 [1] and the Earth's population of 8251771647, we can calculate the average number of patients with TS worldwide, which is 916864.

Table 1 Differences between clinical manifestations of tuberous sclerosis in patients from the RB and data from around the world.

Criterion	frequency (number) in TS patients from the RB, n = 88	frequency (number) in patients with TS in the world, n = 916864	χ^2 test; OR
with subependymal nodes	66% (58)	90% [2] (825178)	$\chi^2 = 16.783$; 0.2148
without subependymal nodes	44% (30)	10% (91686)	
with angiofibromas of the face	56% (49)	83% [4] (760997)	$\chi^2 = 17.195$; 0.2447
without angiofibromas of the face	44% (39)	17% (155867)	
with cognitive impairment	47% (41)	75% [3] (687648)	$\chi^2 = 16.478$; 0.2908
without cognitive impairment	53% (47)	25% (229216)	
with cortical tubers	43% (38)	85% [2] (779334)	$\chi^2 = 38.281$; 0.13412
without cortical tubers	57% (50)	15% (137530)	
with renal angiomyolipomas	43% (38)	75% [2] (687648)	$\chi^2 = 21.166$; 0.2533
without renal angiomyolipomas	57% (50)	25% (229216)	
with gingival fibromas	5% (4)	35% [3] (320902)	$\chi^2 = 28.125$; 0.0884
without gingival fibromas	95% (84)	65% (595962)	
with pulmonary lymphangioleiomyomatosis	1.2% (1)	40% [2, 3] (366746)	$\chi^2 = 46.664$; 0.0172
without pulmonary lymphangioleiomyomatosis	98.8% (87)	60% (550118)	
with autism spectrum disorder	1.2% (1)	30% [5] (275059)	$\chi^2 = 32.105$; 0.0268
without autism spectrum disorder	98.8% (87)	70% (641805)	

Molecular genetic studies to detect mutations in the *TSC1* and *TSC2* genes were performed on 28 patients with TS. Pathogenic variants in the *TSC1* gene were identified in 5 patients (Table 2), accounting for 18% of the 28 patients with molecular confirmation of the disease. Mutations in the *TSC2* gene were identified in 23 patients with TS (Table 3), representing 82% of the 28 patients with a molecularly confirmed diagnosis of TS.

Table 2 Features of clinical manifestations of tuberous sclerosis in patients with pathogenic variants in the *TSC1* gene from the Republic of Bashkortostan.

N	Identified variant (pathogenicity type according to ACMG criteria)	Exon	Gender, age	Clinical manifestations	Described earlier
1.	NM_000368:c.530_531delTC NP_000359.1:p.Leu177fs (pathogenic)	exon 7	male/12	DPS, FAF, SP, cognitive deficit, SEGCA	
2.	NM_000368:c.587C>T: NP_000359.1:p.Pro196Leu (uncertain significance)	exon 7	female/22	FAF, periungual fibromas, epilepsy, SEN	
3.	NM_000368:c.682C>T: NP_000359.1:p.Arg228Ter (pathogenic)	exon 8	female/22	DPS, FAF, cognitive deficit, BCT, CRM, SEGCA, SP	Germany [13]
4.	NM_000368:c.936C>G: NP_000359.1:p.Tyr312Ter (pathogenic)	exon 10	male/3	DPS, RAML, CRM, brain cyst, epilepsy, SEN	
5.	NM_000368:c.2287C>T: NP_000359.1:p.Gln763Ter (pathogenic)	exon 18	male/2	venous angioma of the right hemisphere of the brain, epilepsy, SEN	USA [8], Netherlands [14], Brazil [15]

List of abbreviations for the table: RAML – renal angiomyolipomatosis, FAF – facial angiofibromas, BCT – brain cortical tubers, DPS – depigmentation spots, CRM – cardiac rhabdomyomas, SEGCA – subependymal giant cell astrocytoma, SEN – subependymal nodes, FFP – forehead fibrous plaques, SP – shagreen plaques.

Table 3 Features of clinical manifestations of tuberous sclerosis in patients with pathogenic variants in the *TSC2* gene from the Republic of Bashkortostan.

N	Identified variant (pathogenicity type according to ACMG criteria)	Exon	Gender, age	Clinical manifestations	Described earlier
1.	NM_000548.5:c.43delT: NP_000539.2:p.Phe15fs (pathogenic)	exon 1	male, 13	DPS, hair depigmentation, RAML, FAF, cognitive deficit, cerebellar tonsils ectopia, SEN, SP	
2.	NM_000548.5:c.268C>T: NP_000539.2:p.Glu90Ter (pathogenic)	exon 3	female, 9	DPS, CRM, cognitive deficit, epilepsy, SEN	USA [8, 16-18], China [19]
3.	NM_000548.5:c.707T>C: NP_000539.2:p.Leu236Pro (likely pathogenic)	exon 7	female, 10	epilepsy, BCT	
4.	NM_000548.5:c.767G>T: NP_000539.2:p.Cys256Phe (uncertain significance)	exon 7	female, 11	DPS, CRM, atrial septal defect, epilepsy, SEN, BCT, brain venous cavernomas	
5.	NM_000548.5:c.931_932del: NP_000539.2:p.Ser311fs (likely pathogenic)	exon 9	female, 16	DPS, RAML, CRM, cognitive deficit, epilepsy, dysgenesis of the corpus callosum, SEGCA	
6.	NM_000548.5:c.973C>T: NP_000539.2:p.Gln325Ter (pathogenic/likely pathogenic)	exon 9	male, 2	DPS, CRM, atrial septal defect, epilepsy, BCT	
7.	NM_000548.5:c.976-15G>A: (likely pathogenic)	exon 10	male, 2	DPS, CRM, SEN	USA [17], Germany [20], USA [21]
8.	NM_000548.5:c.1225G>T: NP_000539.2:p.Glu409Ter (pathogenic/likely pathogenic)	exon 11	male, 30	DPS, RAML, polycystic kidney disease, FAF, BCT, periungual fibromas, SEN, SP, cognitive deficit	

9.	NM_000548.5:c.1831C>T: NP_000539.2:p.Arg611Trp (pathogenic)	exon 17	male, 14	DPS, RAML, kidney cysts, FAF, CRM, atrial septal defect, FFP	USA [8, 21], India [22], China [23], Mexico [24]
10.	NM_000548.5:c.1840-1G>A: (pathogenic)	exon 18	female, 14	DPS, FAF, periungual fibromas, FFP, CRM, atrial septal defect, cognitive deficit, epilepsy, BCT	
11.	NM_000548.5:c.2083C>T: NP_000539.2:p.Gln695Ter (pathogenic)	exon 19	male, 10	DPS, FAF, FFP, kidney cysts, cognitive deficit, epilepsy	USA [8], G.B. [25], China [26]
12.	NM_000548.5:c.2380C>T: NP_000539.2:p.Gln794Ter (pathogenic)	exon 22	male, 1	CRM, kidney cysts, SEN, BCT	
13.	NM_000548.5:c.2707dupC: NP_000539.2:p.Leu902fs (pathogenic)	exon 24	female, 7	DPS, RAML, kidney cysts, FAF, FFP, SP, CRM, epilepsy, cognitive deficit	
14.	NM_000548.5:c.3095G>C: NP_000539.2:p.Arg1032Pro (pathogenic/likely pathogenic)	exon 26	male, 2	DPS, SP, liver hemangioma, epilepsy	Neth. [27]
15.	NM_000548.5:c.3610+1G>A: (pathogenic)	exon 30	male, 7	DPS, RAML, kidney cysts, CRM, epilepsy, SEGCA	USA [17], G.B. [25]
16.	NM_000548.5:c.3610+6G>A: (likely pathogenic)	exon 30	female, 23	DPS, RAML, FAF, FFP, CRM, SEGCA, SP	
17.	NM_000548.5:c.4161_4162del: NP_000539.2:p.Ser1387fs (likely pathogenic)	exon 34	female, 11	DPS, RAML, kidney cysts, CRM, epilepsy, SEGCA, cognitive deficit	
18.	NM_000548.5:c.4174C>T: NP_000539.2:p.Gln1392Ter (pathogenic)	exon 34	female, 9	DPS, RAML, FAF, FFP, CRM, SP, cognitive deficit, epilepsy, BCT, SEN	Mexico [24], China [28]

NM_000548.5:c.4242dupT:				DPS, hair depigmentation, RAML, FAF, FFP,	USA [8]
19.	NP_000539.2:p.Lys1415fs (pathogenic)	exon 34	male, 17	periungual fibromas, CRM, cognitive deficit, epilepsy, SEN, SEGCA	
20.	extended gene deletion		male, 18	DPS, RAML, kidney cysts, FAF, SP, CRM, cognitive deficit, SEGCA, BCT	
21.	extended gene deletion		female, 3	DPS, RAML, kidney cysts, cognitive deficit, CRM, FFP, SP, epilepsy, brain cyst, BCT, SEN	
22.	extended gene deletion		male, 3	DPS, CRM, epilepsy, BCT, SEN	
23.	extended gene deletion		male, 6	DPS, FAF, CRM, kidney cysts, SEGCA, cognitive deficit, epilepsy	

List of abbreviations for the table: RAML – renal angiomyolipomatosis, FAF – facial angiofibromas, BCT – brain cortical tubers, DPS – depigmentation spots, CRM – cardiac rhabdomyomas, SEGCA – subependymal giant cell astrocytoma, SEN – subependymal nodes, FFP – forehead fibrous plaques, SP – shagreen plaques.

For patients with identified mutations, disease severity was assessed based on age and the presence of epilepsy. In patients with *TSC1* gene mutations (aged 2 to 22 years, with a mean age of 12 years), no significant correlation was found between disease symptom severity and age. For patients with epilepsy, an association was found with the presence of subependymal nodes, suggesting that the cause of epilepsy is an organic brain tumor. In patients with *TSC2* gene mutations (aged 1 to 30 years, with a mean age of 10 years), no significant association between the severity of tuberous sclerosis and age was found. Of the 23 patients in this group, epilepsy was diagnosed in 16 (70%). However, epilepsy was associated with a higher incidence of cognitive impairment (63% compared to 43% in patients without epilepsy). The incidence of other symptoms, including brain tumors, was comparable between the two groups.

Statistically significantly less frequently, compared to global data, facial angiofibromas, pulmonary lymphangiomyomatosis, brain hamartomas, gingival fibromas, and autism spectrum disorders were registered in patients with TS from RB. However, a statistically similar frequency of detection of such manifestations characteristic of TS as depigmentation spots ($\chi^2 = 0$, $p = 1$), fibrous plaques on the head ($\chi^2 = 1.554$; $p = 0.213$), shagreen plaques on the skin ($\chi^2 = 3.998$; $p = 0.046$), cardiac rhabdomyomas ($\chi^2 = 7.792$; $p = 0.006$), subependymal giant cell astrocytoma ($\chi^2 = 1.339$; $p = 0.248$), polycystic kidney disease ($\chi^2 = 1.663$; $p = 0.198$), epilepsy (67%, $\chi^2 = 3.034$; $p = 0.082$) was determined.

An analysis of the characteristics of TS manifestations in patients with pathogenic variants in the *TSC2* gene compared to those in patients with pathogenic variants in the *TSC1* gene, as well as between patients with extended deletions and point pathogenic variants of *TSC2*, did not reveal any significant differences. In all patients, pathogenic variants were identified across multiple gene loci, indicating the absence of mutagenesis hotspots and genotypic correlations. A pathogenic variant in the *TSC1* gene: exon8:c.682C>T(p.Arg228Ter) was previously detected in a TS patient from Germany [13]. Pathogenic variant *TSC1*:exon18:c.2287C>T(p.Gln763Ter), rs118203671, has been described in patients with TS from the Netherlands [14], the USA [8], and Brazil [15]. Figure 4 shows the localization of pathogenic variants in the *TSC1* gene identified in this study.

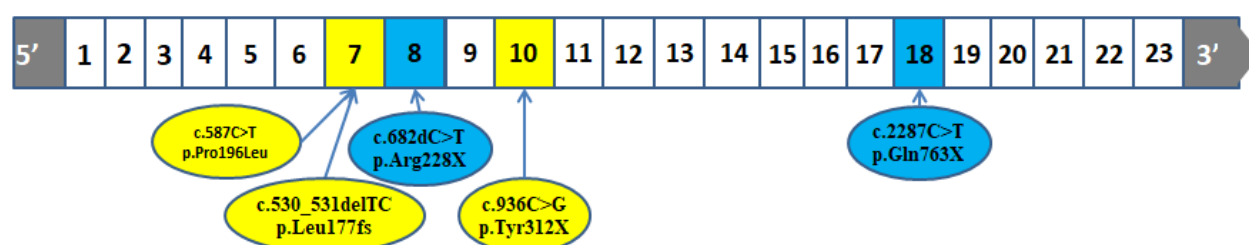


Figure 4 Localization of the described pathogenic variants in patients with TS from the Republic of Bashkortostan in relation to the exons of the *TSC1* gene.

The pathogenic variant *TSC2*:exon3:c.268C>T (p.Gln90X) was previously identified in TS patients from the USA [8, 16, 17], Taiwan [18], and China [19]. Variant *TSC2*:exon9:c.976-15G>A was also identified in Germany [20] and the USA [17, 21]. Variant *TSC2*:exon17:c.1831C>T (p.Arg611Trp) has been previously identified in TS patients from India [22], the USA [8, 21], China [23], and Mexico [24]. Variant *TSC2*:NM_00548:exon19:c.2083C>T (p.Gln695X) was described in TS patients from the UK [25], China [26], and the USA [8]. The pathogenic variant

TSC2:exon26:c.3095G>C(p.Arg1032Pro) was described in TS patients from the Netherlands [27]. Splice site mutation TSC2:exon30:c.3610+1G>A was previously described in TS patients from the UK [25] and the USA [17]. Nonsense mutation TSC2:exon34:c.4174C>T(p.Gln1392X) was previously described in TS patients from China [28] and Mexico [24]. Pathogenic frameshift variant TSC2:exon34:c.4242dupT(p.Lys1415fs) was previously described in a TS patient from the USA [8]. Figure 5 shows the localization of pathogenic variants in the *TSC2* gene identified in the present study.

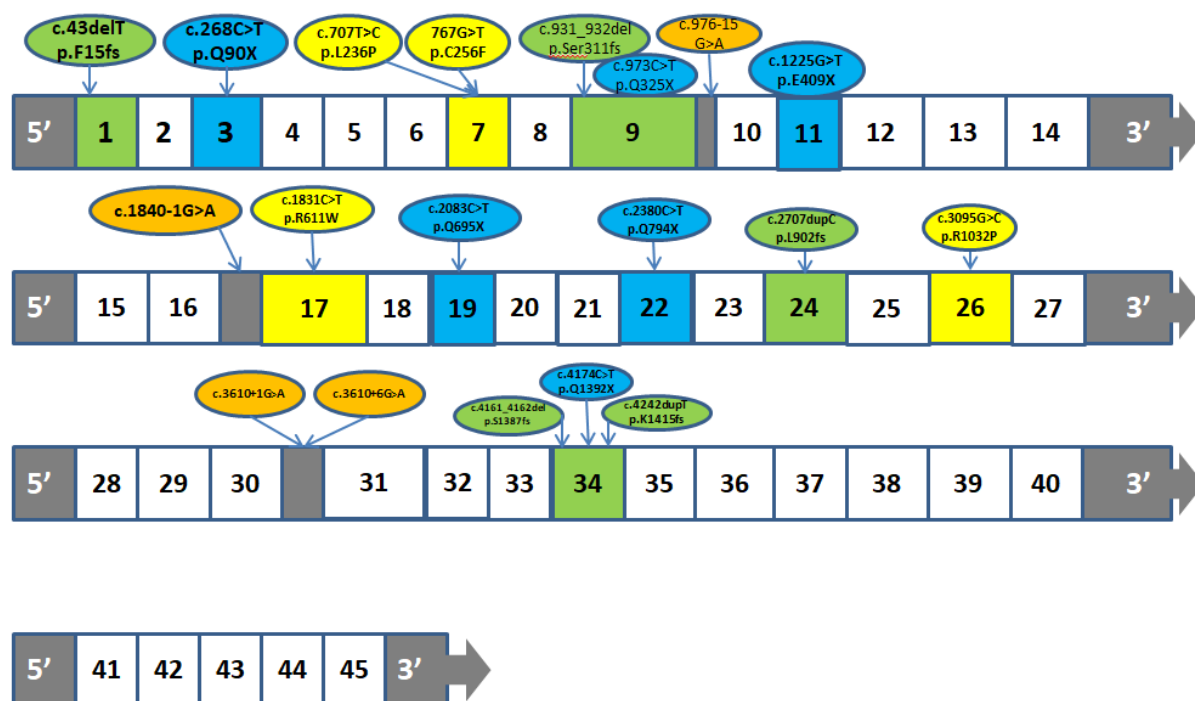


Figure 5 Localization of the described pathogenic variants in patients with TS from the Republic of Bashkortostan in relation to the exons of the *TSC2* gene. Green color indicates frameshift variants, blue color indicates nonsense variants, yellow color indicates missense variants, and orange color indicates splicing variants.

Thus, of the 5-point variants in the *TSC1* gene identified in TS patients from RB, 3 have not previously been described in the literature. The variants are distributed across different exons, without hotspots of mutagenesis, and include 1 double-nucleotide deletion, 1 missense variant, and 3 nonsense variants. Of the 19 point variants in the *TSC2* gene identified in TS patients from RB, 8 have also been reported in the literature in TS patients from other countries, and 11 are previously undescribed. Variants in the *TSC2* gene in patients with RB are distributed across different exons without hotspots of mutagenesis and include 6 nonsense variants, 4 splice-site variants, 4 missense variants, 3 deletions, and 2 duplications.

It should be noted that 8 of the 28 TS patients with identified pathogenic variants are receiving the mTOR inhibitor everolimus, a rapamycin analogue. Patient follow-up is planned to assess the drug's effectiveness and document the observed results. This requires repeat ultrasound examinations of internal organs, a brain MRI, echocardiography, a brain EEG, and consultations with a neurologist, an epileptologist, a psychotherapist, and a psychologist. Since a comparative analysis (see Table 1) of the manifestations of TS in patients from RB compared with data from

around the world revealed a statistically significant lower incidence of subependymal nodes, cortical tubers, and tumors of the kidneys and lungs, repeated instrumental examinations of patients are necessary. To accurately identify cognitive impairments and autism spectrum disorders, all TS patients must be consulted by psychologists, neurologists, and psychotherapists, with the data recorded in their outpatient records and their progress monitored. The use of mTOR inhibitors in TS patients in RB with a molecularly confirmed diagnosis demonstrates a high level of patient care. Given that, according to the scientific literature [2, 9-12], mTOR inhibitors have shown effectiveness against tumor and convulsive syndromes in patients with TS, it is planned to screen for pathogenic variants in the *TSC1* and *TSC2* genes in all patients prescribed these drugs.

The frequency of clinical signs of TS in the RB was compared not only with average indicators but also with the lowest reported frequencies in individual publications (Table 4). As can be seen from the Table 5, according to data from various researchers, there are statistical results similar to the frequency of occurrence in RB for such clinical manifestations of TS as subependymal nodes [15], facial angiofibromas [8, 14, 28], cognitive impairment and cortical tubers [14], and renal angiomyolipomas [8, 23, 28]. Therefore, it can be assumed that the differences observed from the global average in this study may reflect regional characteristics associated with the influence of pathogenic variants in the *TSC1/TSC2* genes that cause TS in RB.

Table 4 Differences in clinical manifestations of tuberous sclerosis in patients from RB with data from around the world.

criterion	frequency (number) in TS patients from RB, n = 88	frequency (number) in TS patients according to different authors, n = 325 [8], n = 65 [13], n = 225 [14], n = 53 [15], n = 224 [17], n = 117 [23], n = 174 [28]	frequency in TS patients in the world, n = 916864
subependymal nodes	66% (58)	58% (31) [15], 83% (270) [8], 84% (189) [14], 86% (100) [23], 92% (206) [17]	90% [2] (825178)
Angiofibromas of the face	56% (49)	60% (195) [8], 60% (70) [28], 63% (142) [14], 73% (39) [15], 75% (168) [17]	83% [4] (760997)
cognitive impairment	47% (41)	47% (106) [14], 59% (38) [13], 61% (32) [15], 68% (118) [28], 73% (85) [23], 76% (247) [8]	75% [3] (687648)
cortical tubers	43% (38)	38% (86) [14], 81% (43) [15], 84% (273) [8], 88% (197) [17], 92% (108) [23]	85% [2] (779334)
renal angiomyolipomas	43% (38)	28% (49) [28], 32% (37) [23], 47% (153) [8], 55% (123) [17], 70% (37) [15]	75% [2] (687648)
gingival fibromas	5% (4)	18% (10) [15], 19% (62) [8]	35% [3] (320902)
pulmonary lymphangioleiomyomatosis	1.2% (1)	5% (3) [15], 11% (25) [17]	40% [2, 3] (366746)
autism spectrum disorder	1.2% (1)	25% (29) [23], 25% (44) [28], 31% (20) [13]	30% [5] (275059)

Table 5 Comparison of clinical manifestations of TS in patients from the RB compared with global data.

Criterion	frequency (number) in TS patients from the RB, n = 88	frequency (number) in patients with TS in the world, n = 916864	χ^2 test; OR
with epilepsy	67% (59)	78% [1] (715154)	3.034; 0.5738
without epilepsy	33% (29)	22% (201710)	
with DPS	88% (78)	90% [3, 4] (825178)	0.204; 0.8666
without DPS	12% (10)	10% (91686)	
with FFP	32% (28)	25% [4] (229216)	1.202; 1.4000
without FFP	68% (60)	75% (687648)	
with shagreen plaques	42% (36)	50% (458432)	1.288; 0.6923
without shagreen plaques	58% (52)	50% (458432)	
with SEGCA	19% (16)	13% [2] (119192)	1.339; 1.4872
without SEGCA	81% (72)	87% (797672)	
with renal cysts	22% (19)	30% [1] (275059)	1.663; 0.6425
without renal cysts	78% (69)	70% (641805)	

List of abbreviations for the table: DPS – depigmentation spots, SEGCA – subependymal giant cell astrocytoma, FFP – forehead fibrous plaques.

4. Discussion and Conclusion

Clinical manifestations of TS in RB are highly diverse and show a similar frequency of occurrence for most disease features compared to global data. Statistically significant differences in the identified subependymal nodules, facial angiofibromas, cortical tubers, renal angiomyolipomas, gingival fibromas, and pulmonary lymphangiomyomatosis from global data are likely due to the specific genetic causes of TS in RB (the nature of pathogenic variants). This is evidenced by comparing the frequency of TS features in RB with data from individual original studies. Molecular genetic confirmation of the TS diagnosis was obtained in 28 of 86 patients from RB (33%). Of the five pathogenic variants in the *TSC1* gene previously not described in the scientific literature, three were identified. Of the 19 pathogenic point variants in the *TSC2* gene, 11 were also previously unidentified by other researchers, demonstrating the importance of studying TS in RB not only for effective patient treatment but also for scientific research. Molecular genetic confirmation of the TS diagnosis in patients from RB allowed eight patients to begin treatment with mTOR inhibitors. The plan is to prescribe the drug to all TSC patients in need through the "Circle of Goodness" program, according to the organization's established criteria: children with a detected mutation in the *TSC1* or *TSC2* genes, children with cognitive impairment or dysphagia under 18 years of age, and children with the tuberous sclerosis symptom complex. This requires searching for pathogenic variants in the *TSC1/TSC2* genes using sequencing and MLPA in all TSC patients, with a description of the results. Accordingly, an algorithm for monitoring TS patients can be proposed for physicians of all specialties (Figure 6).

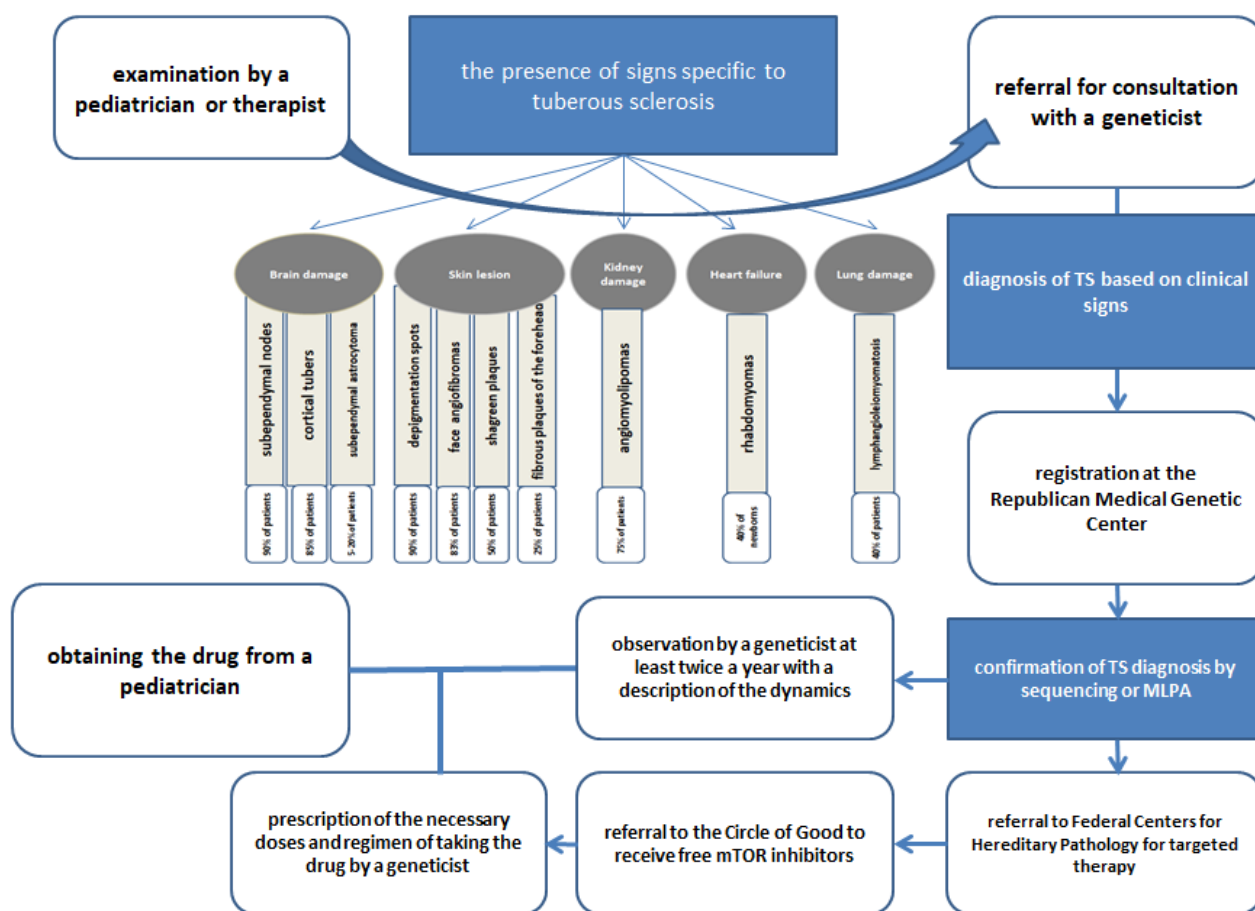


Figure 6 Scheme of the algorithm for monitoring patients with TS.

Author Contributions

The author did all the research work for this study.

Competing Interests

The author has declared that no competing interests exist.

References

1. Robinson J, Uzun O, Loh NR, Harris IR, Woolley TE, Harwood AJ, et al. The association of neurodevelopmental abnormalities, congenital heart and renal defects in a tuberous sclerosis complex patient cohort. BMC Med. 2022; 20: 123.
2. Sasongko TH, Ismail NF, Nik Abdul Malik NM, Zabidi-Hussin ZA. Rapamycin and its analogues (rapalogs) for Tuberous Sclerosis Complex-associated tumors: A systematic review on non-randomized studies using meta-analysis. Orphanet J Rare Dis. 2015; 10: 95.
3. Portocarrero LK, Quental KN, Samorano LP, Oliveira ZN, Rivitti-Machado MC. Tuberous sclerosis complex: Review based on new diagnostic criteria. An Bras Dermatol. 2018; 93: 323-331.

4. Northrup H, Krueger DA, Roberds S, Smith K, Sampson J, Korf B, et al. Tuberous sclerosis complex diagnostic criteria update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatr Neurol.* 2013; 49: 243-254.
5. Mitchell RA, Mitchell M, Williams K. The autism spectrum disorder phenotype in children with tuberous sclerosis complex: A systematic review and meta-analysis. *Dev Med Child Neurol.* 2022; 64: 1214-1229.
6. Wang S, Ma R, Gao C, Tian YN, Hu RG, Zhang H, et al. Unraveling the function of *TSC1-TSC2* complex: Implications for stem cell fate. *Stem Cell Res Ther.* 2025; 16: 38.
7. Jóźwiak J, Sontowska I, Płoski R. Frequency of *TSC1* and *TSC2* mutations in American, British, Polish and Taiwanese populations. *Mol Med Rep.* 2013; 8: 909-913.
8. Au KS, Williams AT, Roach ES, Batchelor L, Sparagana SP, Delgado MR, et al. Genotype/phenotype correlation in 325 individuals referred for a diagnosis of tuberous sclerosis complex in the United States. *Genet Med.* 2007; 9: 88-100.
9. Li M, Zhou Y, Chen C, Yang T, Zhou S, Chen S, et al. Efficacy and safety of mTOR inhibitors (rapamycin and its analogues) for tuberous sclerosis complex: A meta-analysis. *Orphanet J Rare Dis.* 2019; 14: 39.
10. Yang G, Yang L, Yang X, Shi X, Wang J, Liu Y, et al. Efficacy and safety of a mammalian target of rapamycin inhibitor in pediatric patients with tuberous sclerosis complex: A systematic review and meta-analysis. *Exp Ther Med.* 2015; 9: 626-630.
11. Mustafa HJ, Javinani A, Morning ML, D'Antonio F, Pagani G, Puranik PM, et al. Characteristics and outcomes of fetal cardiac rhabdomyoma with or without mTOR inhibitors, a systematic review and meta-analysis. *Prenat Diagn.* 2024; 44: 1251-1267.
12. Lin YT, Yu CL, Tu YK, Chi CC. Efficacy and safety of topical mechanistic target of rapamycin inhibitors for facial angiofibromas in patients with tuberous sclerosis complex: A systematic review and network meta-analysis. *Biomedicines.* 2022; 10: 826.
13. Rendtorff ND, Bjerregaard B, Frödin M, Kjaergaard S, Hove H, Skovby F, et al. Analysis of 65 tuberous sclerosis complex (TSC) patients by *TSC2* DGGE, *TSC1/TSC2* MLPA, and *TSC1* long-range PCR sequencing, and report of 28 novel mutations. *Hum Mutat.* 2005; 26: 374-383.
14. van Slegtenhorst M, Verhoef S, Tempelaars A, Bakker L, Wang Q, Wessels M, et al. Mutational spectrum of the *TSC1* gene in a cohort of 225 tuberous sclerosis complex patients: No evidence for genotype-phenotype correlation. *J Med Genet.* 1999; 36: 285-289.
15. Rosset C, Vairo F, Bandeira IC, Correia RL, De Goes FV, Da Silva RT, et al. Molecular analysis of *TSC1* and *TSC2* genes and phenotypic correlations in Brazilian families with tuberous sclerosis. *PLoS One.* 2017; 12: e0185713.
16. Choy YS, Dabora SL, Hall F, Ramesh V, Niida Y, Franz D, et al. Superiority of denaturing high performance liquid chromatography over single-stranded conformation and conformation-sensitive gel electrophoresis for mutation detection in *TSC2*. *Ann Hum Genet.* 1999; 63: 383-391.
17. Dabora SL, Jozwiak S, Franz DN, Roberts PS, Nieto A, Chung J, et al. Mutational analysis in a cohort of 224 tuberous sclerosis patients indicates increased severity of *TSC2*, compared with *TSC1*, disease in multiple organs. *Am J Hum Genet.* 2001; 68: 64-80.
18. Hung CC, Su YN, Chien SC, Liou HH, Chen CC, Chen PC, et al. Molecular and clinical analyses of 84 patients with tuberous sclerosis complex. *BMC Med Genet.* 2006; 7: 72.

19. Yuan CD, Chang XL, Wu YQ, Liu Q, Gao M, Xiao FL, et al. Analysis of gene mutations in two patients with tuberous sclerosis complex. *Acta Acad Med Sin.* 2007; 29: 205-208.
20. Mayer K, Ballhausen W, Rott HD. Mutation screening of the entire coding regions of the *TSC1* and the *TSC2* gene with the protein truncation test (PTT) identifies frequent splicing defects. *Hum Mutat.* 1999; 14: 401-411.
21. Tyburczy ME, Dies KA, Glass J, Camposano S, Chekaluk Y, Thorner AR, et al. Mosaic and intronic mutations in *TSC1/TSC2* explain the majority of TSC patients with no mutation identified by conventional testing. *PLoS Genet.* 2015; 11: e1005637.
22. Ali M, Girimaji SC, Markandaya M, Shukla AK, Sacchidanand S, Kumar A. Mutation and polymorphism analysis of *TSC1* and *TSC2* genes in Indian patients with tuberous sclerosis complex. *Acta Neurol Scand.* 2005; 111: 54-63.
23. Yang G, Shi Z, Meng Y, Shi X, Pang L, Ma S, et al. Phenotypic and genotypic characterization of Chinese children diagnosed with tuberous sclerosis complex. *Clin Genet.* 2017; 91: 764-768.
24. Reyna-Fabián ME, Hernández-Martínez NL, Alcántara-Ortigoza MA, Ayala-Summano JT, Enríquez-Flores S, Velázquez-Aragón JA, et al. First comprehensive *TSC1/TSC2* mutational analysis in Mexican patients with Tuberous Sclerosis Complex reveals numerous novel pathogenic variants. *Sci Rep.* 2020; 10: 6589.
25. Jones AC, Shyamsundar MM, Thomas MW, Maynard J, Idziaszczyk S, Tomkins S, et al. Comprehensive mutation analysis of *TSC1* and *TSC2*—and phenotypic correlations in 150 families with tuberous sclerosis. *Am J Hum Genet.* 1999; 64: 1305-1315.
26. Chen H, Lin X, Lian S, Zhu W. Novel nonsense mutation of the *TSC2* gene in a case of tuberous sclerosis complex. *Eur J Dermatol.* 2016; 26: 295-296.
27. Hoogeveen-Westerveld M, Wentink M, van den Heuvel D, Mozaffari M, Ekong R, Povey S, et al. Functional assessment of variants in the *TSC1* and *TSC2* genes identified in individuals with tuberous sclerosis complex. *Hum Mutat.* 2011; 32: 424-435.
28. Ding Y, Wang J, Zhou S, Zhou Y, Zhang L, Yu L, et al. Genotype and phenotype analysis of Chinese children with tuberous sclerosis complex: A pediatric cohort study. *Front Genet.* 2020; 11: 204.