Table 5. TSC patients with identical mutations in the literature [iii]

Reference Patient	Heredity			DNA change	Protein	Age (year)	Sex	Mutation type	Intelligence	Autism	Seizure	Tuber	SEN	SEGA	HPM	AF	PUF	ShgP	AML	RCC	Renal cyst	CR	Others
Wilson (1996)																							
TSC-382	F	TSC2	exon 16	1849C>T	R611W			MM	MR		+		CT (+)		+	+	+	+	Renal ab (+)				Eye (–)
Ali (2004)																							
TS-07	S	TSC2	exon 16	1832G>A	R611Q	9		MM	MR (–)	NA	+	NA	NA	NA	+	+	–	+	NA			NA	
TS-23	S	TSC2	exon 16	1831C>T	R611W	2		MM	MR	+	+	+	+	–	+	–	–	+	NA			NA	
Hung (2006)																							
29	S	TSC2	exon 16	1832G>A	R611Q		f	MM	MR		+	+			+	–	–	+	–				
Zhang (1999)																							
22	F	TSC2	exon 16	1850G>A	R611Q	6	f	MM	MR(–)		+		+		+	–							
Beauchamp (1998)																							
F03-01	F	TSC2	exon 16	1832G>A	R611Q	5		MM	MR(–)		+	Brain findings (+)			+	–	–	–	–			–	
Hung (2006)																							
82	S	TSC2	exon 17	1939G>A	D647N		m	MM	MR (–)		+	–			–	–	–	–	–				
Zhang (1999)																							
32	S	TSC2	exon 17	1957G>A	D647N	2	m	MM	NA		+		+		+	NA							
Zhang (1999)																							
21	F	TSC2	exon 20	2324T>G	V769E	44	f	MM	MR (++)		NA		NA		+	+							
2	S	TSC2	exon 20	2324T>G	V769E	32	m	MM	MR (++)		+		+		+	+							
Verhoef (1999)																							
Family 3 sib 1	F	TSC2	intron 20	2374-2 A>C			f	SP	Moderate MR		+		(+)?		+	+		+				+	
Family 3 sib 2	F	TSC2	intron 20	2374-2 A>C			f	SP	Severe MR		+		(+)?			+	+		+			+	
Beauchamp (1998)																							
F08–01	F	TSC2	exon 23	2714G>A	R905Q	10		MM	MR (–)		+	Normal	Normal		+	+	+	+	NA			NA	
Jansen (2006)																							
Family A ($n = 25$)	F	TSC2	exon 23	2714G>A	R905Q	6 – 61		MM	MR (–) 12, LD 10, mild CI 3		15/25	5/15 WML	1	1	23/25				1		1	0/12	0/16
Family B ($n = 3$)	F	TSC2	exon 23	2714G>A	R905Q	NA		MM	MR (–) 1, mild CI 2		2	2			3	1			NA			NA	
Family C ($n = 9$)	F	TSC2	exon 23	2714G>A	R905Q	NA		MM	MR (–) 6, impaired 1, severe CI 1		6	1/1 examined			8	1	2	2				1/1 examined	
Family D ($n = 1$)	F	TSC2	exon 23	2714G>A	R905Q	NA		MM	MR (–)		+	–			+			+	NA		NA	NA	
Family E ($n = 1$)	F	TSC2	exon 23	2714G>A	R905Q	NA		MM	MR (–)		+	abn			+				–		–	–	
P1	S	TSC2	exon 23	2713C>T	R905W	NA		MM	NA		–	+	+		+	+			NA		NA	NA	
P2	S	TSC2	exon 23	2713C>T	R905W	NA		MM	Mild CI		Remitted	+	+		+	+		+	–		–	–	Retinal HM
P3	S	TSC2	exon 23	2713C>T	R905W	NA		MM	Moderate CI		Active	+	+		+				–		–	+	
P4	S	TSC2	exon 23	2713C>T	R905W	NA		MM	Severe CI		Active LGS	+	+		+				–		–	–	
P5	S	TSC2	exon 23	2713C>T	R905W	NA		MM	MR(–)		–	+		+	+	+					+	–	
P6	S	TSC2	exon 23	2713C>T	R905W	NA		MM	Severe CI		+	+	+		+	+			–			NA	
P7	S	TSC2	exon 23	2713C>T	R905W	NA		MM	Severe CI		+	NA	NA	NA					NA		NA	NA	
P8	S	TSC2	exon 23	2713C>T	R905W	NA		MM	Mild CI		Remitted IS	+	+		+	+	+	+	+		–	NA	

Table 5, continued to the next page. Footnotes, refer to Table 5 [vii], end of this table.

Table 5. TSC patients with identical mutations in the literature [iv]

Reference Patient	Heredity			DNA change	Protein	Age (year)	Sex	Mutation type	Intelligence	Autism	Seizure	Tuber	SEN	SEGA	HPM	AF	PUF	ShgP	AML	RCC	Renal cyst	CR	Others
Au (1998)																							
TS95-12		TSC2	exon 23	2713C>T	R905W			MM	MR		+	+	+		+	–	–	–	–		–	–	
Yamamoto (2002)																							
8	S	TSC2	exon 23	2713C>T	R905W	21	f	MM	IQ 40		+	+	+		+	+				Renal tumor			
Yamashita (2000)																							
1		TSC2	exon 23	2713C>T	R905T			MM	Moderate MR		IS				+	+							
Yamamoto (2002)																							
7	S	TSC2	exon 23	2713C>G	R905G	3	m	MM	Neurological symptoms (+)		IS	+	+		+							+	
Hung (2006)																							
64	S	TSC2	exon 26	2974C>T	Q992X		m	NM	MR (–)		+	+			+	–	–	–	–				
Beauchamp (1998)																							
S17-01	S	TSC2	exon 26	2974C>T	Q992X	5		NM	Moderate MR		+	Brain findings (+)			+	+	–	–	–			NA	Retinal findings (+)
The present study																							
Patient 4	S	TSC2	exon 28	3355C>T	Q1119X	8	f	NM	DQ 17	+	IS	+	+		+	+			–			+	
Feng (2004), the present study																							
4, Patient 5	S	TSC2	exon 28	3355C>T	Q1119X	23	f	NM	MR (–)	–	Febrile Sz	NA	+		–	–			+	Renal tumor			Liver AML
Humphrey (2004)																							
Twin A	F	TSC2	exon 29	3043delC	truncation 1210?	3	m	FS	DQ 45	+	Partial Sz	Extensive											
Twin B	F	TSC2	exon 29	3043delC	truncation 1210?	3	m	FS	DQ 71	Partial	IS	+											
Wilson (1996)																							
TSC-001-1 father	F	TSC2	exon 29	3616C>T	R1199W		m	MM		Beh/ LD (+)	+	MRI (–)	CT (–)		+	–	–	–					
TSC-001-2 sib	F	TSC2	exon 29	3616C>T	R1199W			MM				MRI (+)	CT (–)		+	+	–						
TSC-001-3 sib	F	TSC2	exon 29	3616C>T	R1199W			MM	MR		+	MRI (–)	CT (–)		+	–	–	+					Eye (–)
Lyczkowski (2007)																							
D-I-1	F	TSC2	exon 33	4422–4423del		NA	m	FS	NA		Controlled	NA	NA	NA	+				NA	NA	NA	NA	
D-II-2	F	TSC2	exon 33	4422–4423del		NA	m	FS	NA		Controlled	NA	NA	NA	+				NA	NA	NA	NA	
D-II-3	F	TSC2	exon 33	4422–4423del		NA	f	FS	NA		Controlled	NA	NA	NA	+				NA	NA	NA	NA	
D-III-1	F	TSC2	exon 33	4422–4423del		9	f	FS	NA		IS	39	+	+	+	+			–			+	
D-III-2	F	TSC2	exon 33	4422–4423del		6	f	FS	IQ 85		IS	+	+	+	+	+			–			+	
D-III-3	F	TSC2	exon 33	4422–4423del		3	m	FS	IQ 101		IS	49	+	+	+				+				

Table 5, continued to the next page. Footnotes, refer to Table 5 [vii], end of this table.

Table 5. TSC patients with identical mutations in the literature [v]

Reference Patient	Heredity			DNA change	Protein	Age (year)	Sex	Mutation type	Intelligence	Autism	Seizure	Tuber	SEN	SEGA	HPM	AF	PUF	ShgP	AML	RCC	Renal cyst	CR	Others
Niida (1999)																							
171	S	TSC2	exon 33	4421–4422del	R1474fs 1521X			FS	MR		+	Brain image (+)			+	+	+	+	NA		NA	NA	
311	S	TSC2	exon 33	4422–4423del	R1474fs 1521X			FS	MR (–)		+	Brain image (+)			+	–	–	–	NA		NA	NA	
Niida (1999)																							
187	F	TSC2	exon 33	4375C>T	R1459X			NM	MR		+	Brain image (+)			+	+	–	+	–		–	+	Retinal HM
Zhang (1999), the present study																							
6, Patient 6	F	TSC2	exon 33	4393C>T	R1459X	18	m	NM	IQ 33	+	Controlled	+	+		NA	NA			+				
8, Patient 7	S	TSC2	exon 33	4393C>T	R1459X	19	f	NM	IQ 41	+	Surgery	+	+		+	+			+				
Smalley (1994)																							
n = 17	F	TSC2	exon 34	4508A>C	Q1503P			MM	IQ<70 4/17			(–) in 10	–										Psychiatric disorder 13/17
Wilson (1996)																							
TSC-422-1	F	TSC2	exon 34	4519–4547 dup	L1510fs 1541X			FS	MR		+		CT (+)		+	+	–	+	Renal ab (+)				Eye (–)
TSC-422-2	F	TSC2	exon 34	4519–4547 dup	L1510fs 1541X			FS	NA		–				+	+	+	+	Renal ab (+)				Eye (–)
Jansen (2006)																							
Family F II-3	F	TSC2	exon 35	4642G>A	E1542K			MM	MR (–)		–	+			+	+	+		+				
Family F III-3	F	TSC2	exon 35	4642G>A	E1542K			MM	MR (–)		–	+			+	+	–						
Family F III-5	F	TSC2	exon 35	4642G>A	E1542K			MM	MR (–)		–	+			+	+	–						
Family F IV-3	F	TSC2	exon 35	4642G>A	E1542K			MM	MR (–)		+	+			+	+	–						
Family F IV-4	F	TSC2	exon 35	4642G>A	E1542K			MM	MR (–)		–	+			+	+	–						
Family F IV-7	F	TSC2	exon 35	4642G>A	E1542K			MM	MR (–)		–	+		+	+	+	–						
Family F IV-8	F	TSC2	exon 35	4642G>A	E1542K			MM	MR (–)		–	+			+	+	–						
Family F IV-9	F	TSC2	exon 35	4642G>A	E1542K			MM	MR (–)		–	+			+	+	–						
Family F V-3	F	TSC2	exon 35	4642G>A	E1542K			MM	MR (–)		+	+			–	–	–						
Family F V-4	F	TSC2	exon 35	4642G>A	E1542K			MM	MR (–)		–	+			–	–	–						
Lyczkowski (2007)																							
E-I-1	F	TSC2	exon 35	4662G>A	1554Q	62	m	SP	IQ 106		NA	7	+	+					NA	NA	NA	NA	
E-II-1	F	TSC2	exon 35	4662G>A	1554Q	39	f	SP	IQ 115		NA	12	+						NA	NA	NA	NA	
E-II-2	F	TSC2	exon 35	4662G>A	1554Q	38	m	SP	NA		None		+	+		+			+		+		Hepatic cyst
E-II-4	F	TSC2	exon 35	4662G>A	1554Q	34	f	SP	IQ 105		NA	8	+						NA	NA	NA	NA	
E-III-1	F	TSC2	exon 35	4662G>A	1554Q	5	m	SP	IQ 102		Controlled	14	+	+	+	+		+	–	–	–	+	Retinal pigment
E-III-2	F	TSC2	exon 35	4662G>A	1554Q	3	m	SP	IQ 121		None	18	+	+	+	+			–	–	–	–	

Table 5, continued to the next page. Footnotes, refer to Table 5 [vii], end of this table.

Table 5. TSC patients with identical mutations in the literature [vi]

Reference Patient	Heredity		DNA change	Protein	Age (year)	Sex	Mutation type	Intelligence	Autism	Seizure	Tuber	SEN	SEGA	HPM	AF	PUF	ShgP	AML	RCC	Renal cyst	CR	Others
Mayer (2007)																						
IV-3	F	TSC2 exon 36	4684G>A	G1556S	3	m	MM	MR (–)		–		–		+							+	
IV-1	F	TSC2 exon 36	4684G>A	G1556S	12	m	MM	MR (–)?		+	–	–		+				–				
III-3	F	TSC2 exon 36	4684G>A	G1556S		m	MM	MR (–)		–		–		+			+					
III-2	F	TSC2 exon 36	4684G>A	G1556S		f	MM	MR (–)				–		+				+				
Verhoef (1998)																						
Family A	S	TSC2 exon 36	4882 delTT	1628X	14	m	FS	MR (–)		±		+		+	+	+	–	–	–		–	Dental pits
Family B	F	TSC2 exon 36	4882 delTT	1628X	18	f	FS	MR (–)		+		+		+	+	+	+	+	–		+	
Family B mother	F	TSC2 exon 36	4882 delTT	1628X	40	f	FS	MR (–)		+		+		+	+	+	+	+	–		+	
Niida (1999)																						
185	S	TSC2 exon 37	4858C>T	H1620Y			MM	MR		+	Brain image (+)			+	+	–	+	–		–	NA	
Au (1998)																						
TS94–53		TSC2 exon 37	4859A>T	N1620I			MM	MR	Beh/ LD (+)	+	+	NA		+	+	–	–	–		±	–	Eye (–)
Maheshwar (1997)																						
$n = 4$, unrelated	S	TSC2 exon 38	5042C>T	P1675L			MM	MR (–) 1, moderate MR 1, severe MR 2		3								1/1 examined				
Niida (1999)																						
277	S	TSC2 exon 38	5024C>T	P1675L			MM	MR		+	Brain image (+)			+	–	–	–	+		–	+	Retinal HM
Zhang (1999)																						
28	S	TSC2 exon 38	5042C>T	P1675L	3	f	MM	MR		+		+		+	NA							
Feng (2004)																						
7	F	TSC2 exon 38	5042C>T	P1675L	15	f	MM	Severe MR														
Hung (2006)																						
4	S	TSC2 exon 40	5227C>T	R1743W		m	MM	MR (–)		+	+			+	+	–	+	(+)?				
50	S	TSC2 exon 40	5227C>T	R1743W		m	MM	MR		+	+			+	+	–	+	NA				
Choi (2006)																						
12	S	TSC2 exon 40	5227–5244 del	R1743–K1748 del		m	IF			+	Tuber/ SEN (–)			+						+	+	Retinal HM
13	S	TSC2 exon 40	5227–5244 del	R1743–K1748 del		m	IF			+	Tuber/ SEN (+)			+							+	
Martin (2003)																						
Twin M	F	TSC2 exon 40	5256–73 del	1740–1745 del	6	m	IF	Severe MR		IS		+		+	+			+		+		
Twin T	F	TSC2 exon 40	5256–73 del	1740–1745 del	6	m	IF	Severe MR		Partial Sz	+	+		+	+		+	+			+	

Table 5, continued to the next page. Footnotes, refer to Table 5 [vii], end of this table.

Table 5. TSC patients with identical mutations in the literature [vii]

Reference Patient	Heredity			DNA change	Protein	Age (year)	Sex	Mutation type	Intelligence	Autism	Seizure	Tuber	SEN	SEGA	HPM	AF	PUF	ShgP	AML	RCC	Renal cyst	CR	Others
Rok (2005)																							
Patient A	S	TSC2	exon 40	5238–5255 del	del 1746 HIKRLR	10	f	IF	MR(+)		Partial Sz	+	+		+	+	–	–	+		–	+	
Patient B	S	TSC2	exon 40	5238–5255 del	del 1746 HIKRLR	9	m	IF	MR(+)		IS	+	+		+	+	–	–	+		–	–	Retinal HM
Patient C	S	TSC2	exon 40	5238–5255 del	del 1746 HIKRLR	9	f	IF	MR(–)		IS	+	+		+	+	–	+	+		–	+	
Patient D	S	TSC2	exon 40	5238–5255 del	del 1746 HIKRLR	1.5	?	IF	MR(–)		IS	+	+		+	–	–	–	–		–	+	
Dabora (2001)																							
n = 9		TSC2	exon 40	5238–5255 del	del 1746 HIKRLR	7 – 28		IF	MR none–severe		All (+)					None–severe			None–extensive				
Niida (1999)																							
113	S	TSC2	exon 40	5328–5255 del	H1746Q/ 1747–52 del			MM/ IF	MR (–)		–	NA			+	+	+	–	+		–	–	
Hung (2006)																							
10	S	TSC2	exon 40	5238–5255 del			f		LD		+	+			+	+	–	–	–				
25	S	TSC2	exon 40	5238–5255 del			m		LD		+	+			+	+	–	+	–				
Beauchamp (1998)																							
S18-01	S	TSC2	exon 40	5328–5255 del	H1746Q/ 1747–52 del	9		MM/ IF	Mild MR		+	Brain findings (+)			+	+	+	+	+			+	
The present study																							
Patient 8	S	TSC2	exon 40	5238–5255 del	del 1746 HIKRLR	3	m	IF	Moderate–severe MR	–	IS	+	+		+	+			–			+	
Patient 9	S	TSC2	exon 40	5238–5255 del	del 1746 HIKRLR	6	f	IF	Severe MR	+	IS, partial Sz	+	+		+	–			–				
Patient 10	S	TSC2	exon 40	5238–5255 del	del 1746 HIKRLR	13	m	IF	Moderate MR	Partial	IS	+	+		+	–			–		+		
Lyczkowski (2007)																							
B-II-1 (twin)	F	TSC2	IVS1, exon 1	1838 bp del		6	f	del	IQ 85		Occasional	65	+		+	+			+		+	+	
B-II-2 (twin)	F	TSC2	IVS1, exon 1	1838 bp del		6	f	del	IQ < 42		IS	60	+			+		+	+		+	+	

–, absent; +, present; ab, abnormality; AF, angiofibroma; AML, angiomyolipoma; Beh, behavioral problems; CI, cognitive impairment; CR, cardiac rhabdomyoma; DQ, developmental quotient; f, female; F, familial; FS, frameshift; HM, hamartoma; HPM, hypopigmented macule; IF, in-frame deletion; IS, infantile spasms; IVS, intervening sequence within an intron; LD, learning disability; LGS, Lennox-Gastaut syndrome; m, male; MM, missense mutation; MR, mental retardation; NA, not available; NM, nonsense mutation; PUF, periungual fibroma; RCC, renal cell carcinoma; S, sporadic; SEGA, subependymal giant cell astrocytoma; SEN, subependymal nodule; s/o, suspect of; ShgP, Shagreen patch; SP, splice mutation; Sz, seizure; TSC, tuberous sclerosis complex; Var, variable; WML, white matter lesion.

Discussion

Previous studies report that either TSC1 or TSC2 mutations are found in 70% to 80% of TSC patients (Hung et al., 2006; Au et al., 2007). The relatively low proportion of positive results in our series may have resulted from a selection bias that doctors in charge of patients with ambiguous clinical phenotype tend to ask the genetic analysis to confirm the diagnosis. However, mutations could be detected even in individuals with partial expression of TSC phenotype, for example, Patient 5 who did not show any cutaneous symptoms.

Some factors have been elucidated that could explain the variability of clinical manifestations in TSC patients, particularly neurological symptoms. These include the mutated gene (TSC1 versus TSC2) (Dabora et al., 2001; Lewis et al., 2004; Sancak et al., 2005; Au et al., 2007), somatic mosaicism, history of infantile spasms (Lewis et al., 2004), and the number and volume of cortical tubers (Jansen et al., 2008). Higher prevalence of severe intellectual disability in TSC patients with TSC2 mutations rather than TSC1 mutations may be related to the fact the tuberin plays a critical role in the phosphorylation of mTOR through its GAP activity and hamartin binds to tuberin and stabilizes the latter (Chong-Kopera et al., 2006). Somatic mosaicism in parents can explain the emergence of more severe phenotypes in their children (Rose et al., 1999). Certain aspects of the data in our series of patients with identical mutations may be related to these mechanisms. However, somatic mosaicism cannot explain the mild phenotype of Patient 2, who was born to an affected TSC mother. In addition, the basis for the differential manifestation of epilepsy and cortical tuber load between siblings, monozygotic twins, and members within a single family, remains unclear. As for the two-hit theory, the second hit as somatic mutations have been detected in angiomyolipoma and giant cell astrocytoma of TSC patients, but not in ungual fibroma, pulmonary lymphangiomyolipomatosis, and cortical tubers (Niida et al., 2001; Mizuguchi et al., 2004). Pathogenic significance of haploinsufficiency in tumor-suppressive genes has been also assumed in neurofibromatosis 1 (Easton et al., 1993; Henske et al., 1996), where marked intrafamilial variation is prevalent similarly to TSC. Apparently there are other factors that modulate the phenotype of individual TSC genotypes. These may include somatic mutation in other factors within the mTOR and other signaling pathways, and genetic background related to the epileptogenesis, or activation of the inflammatory system (Boer et al., 2008). In addition, the significance and pathogenesis of mTOR pathway in the synaptic plasticity (Kelleher et al., 2004), and decreased volume of subcortical gray matter (Ridler et al., 2007) in TSC patients need to be further explored to understand the variability of neurological manifestations.

Most of the TSC1 mutations, and 2/3 of TSC2 mutations, causes truncation of the gene product proteins (Au et al., 2007). The data in the identical mutation list (Table 5) correlate with this overall tendency. As shown in this list, most of the mutations of TSC1/TSC2 genes in patients with mild intellectual disability are missense mutations. Relatively preserved tuberin-hamartin complex function may explain the mild phenotype in certain cases with missense mutations (Jansen et al., 2006). In addition, given that the proportion of missense mutations is relatively high in the GAP domain (Au et al., 2007), which has an essential role in the tuberin function, this type of mutations outside the GAP domain might remain subclinical and regarded as polymorphism. On the other hand, various truncating mutations of TSC2 gene, whose GAP domain either preserved or untranslated, can result in both mild and severe intellectual and behavioral disabilities. This again supports that other factors than the truncated gene product itself play critical roles in the determination of neurological phenotype.

Accumulation of mutation data with detailed clinical information is mandatory for a better understanding of genotype-phenotype correlation and the exploration of background mechanism. However, the mutation database and individual journal articles are often insufficient for collecting

clinical data and draw reliable conclusion. Due to the aforementioned modifying factors of TSC phenotypes, interpretation of mutation data in individual patient is most confusing. We hope that the review data in this article would help the assessment of mutations and provide research interest by doctors and investigators.

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