Original Article
Yonsei Med J 2023 Feb;64(2):133-138
https://doi.org/10.3349/ymj.2022.0451
Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

Refractive Errors, Retinal Findings, and Genotype of Tuberous Sclerosis Complex: A Retrospective Cohort Study

Soyoung Ryu[1], Hoon-Chul Kang[2], Sung Chul Lee[3], Suk Ho Byeon[1], Sung Soo Kim[1], and Christopher Seungkyu Lee[1]

[1]The Institute of Vision Research, Department of Ophthalmology, Yonsei University College of Medicine, Seoul;
[2]Division of Pediatric Neurology, Department of Pediatrics, Severance Children's Hospital, Yonsei University College of Medicine, Seoul;
[3]Department of Ophthalmology, Konyang University Hospital, Konyang University College of Medicine, Daejeon, Korea.

Purpose: To examine the refractive errors, retinal manifestations, and genotype in tuberous sclerosis complex (TSC) patients in a Korean population.

Materials and Methods: A total of 98 patients with TSC were enrolled in Severance Hospital for a retrospective cohort study. The number of retinal astrocytic hamartoma and retinal achromic patch within a patient, as well as the size, bilaterality, and morphological type were studied. In addition, the refractive status of patients and the comorbidity of intellectual disability and epilepsy were also examined.

Results: Retinal astrocytic hamartoma was found in 37 patients, and bilateral invasion was observed in 20 patients (54%). TSC1 mutation was associated with myopia (p=0.01), while TSC2 mutation was associated with emmetropia (p=0.01). Retinal astrocytic hamartoma was categorized into three morphological types and examined as follows: type I (87%), type II (35%), and type III (14%). Single invasion of retinal astrocytic hamartoma was identified in 32% of the patients, and multiple invasions in 68%. The TSC1/TSC2 detection rate was 91% (41/45). Among them, TSC1 variant was detected in 23 patients (54%), whereas TSC2 variant was detected in 18 patients (40%). The results showed that TSC2 mutations are correlated with a higher rate of retinal astrocytic hamartoma involvement (all p<0.05), and multiple and bilateral involvement of retinal hamartomas (all p<0.05). However, the size of retinal astrocytic hamartomas, comorbidity of epilepsy, or intellectual disability did not show correlation with the genetic variant.

Conclusion: TSC1 variant patients were more myopic, while TSC2 variant patients showed association with more extensive involvement of retinal astrocytic hamartoma.

Key Words: Tuberous sclerosis, genotype, phenotype, hamartoma

INTRODUCTION

Tuberous sclerosis complex (TSC) is a neurocutaneous syndrome characterized by multiple forms of hamartoma in almost any organ or tissue, including the skin, heart, lungs, brain, kidneys, and eyes.[1] TSC is an autosomal dominant disorder that was first described by Bourneville in 1880 after the autopsy of a patient with intellectual disability, epilepsy, and sebaceous adenoma.[2] In 1908, Heinrich Vogt defined the classic triad of epilepsy, intellectual disability, and adenoma sebaceum (now known as angiofibromatosis).[3] The association between ophthalmic features and TSC was first described by Van der Hoeve,[4] who identified retinal hamartomas associated with TSC in 1921.

Multiple ophthalmic features have been reported in patients with TSC. These include retinal astrocytic hamartomas, hy-

Received: October 12, 2022 **Revised:** December 24, 2022
Accepted: December 28, 2022 **Published online:** January 18, 2023
Corresponding author: Christopher Seungkyu Lee, MD, PhD, The Institute of Vision Research, Department of Ophthalmology, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemungu, Seoul 03722, Korea.
E-mail: sklee219@yuhs.ac

•The authors have no potential conflicts of interest to disclose.

popigmented sectoral lesions of the iris and ciliary body, colobomas of the iris and choroid, angiofibromas of the eyelid, and strabismus.[5-7] The most common ophthalmic feature of TSC is the presence of retinal astrocytic hamartomas, which is also included as one of the major criteria for TSC diagnosis.[8] Based on morphological features, retinal astrocytic hamartomas are categorized into the following three types: type I hamartomas are defined as relatively smooth, flat, non-calcified, semi-translucent light grey or yellow lesions with indistinct margins (Fig. 1); type II hamartomas are defined as nodular, elevated, calcified, opaque lesions, which are often described as a 'mulberry lesion' or 'fish eggs' (Fig. 2); and type III hamartomas are defined as mixed, transitional lesions in-between types I and II. The base of the tumor may be flat and translucent with an elevated, nodular center.[9-11]

TSC is a genetic syndrome caused by a loss-of-function mutation in one of the following two genes: *TSC1* gene on chromosome 9q34 or the *TSC2* gene on chromosome 16p13.[12] These are known as tumor suppressor genes, and hamartin and tuberin are the gene products of *TSC1* and *TSC2*, respectively. They form a protein complex that regulates cellular hyperplasia by acting as an inhibitor of the mechanistic target of the rapamycin-mediated signaling pathway, which plays an important role in regulating cell growth and proliferation.[12] Previous studies have reported that clinical manifestations of TSC are more common and serious in patients with *TSC2* mutations than in those with *TSC1* mutations.[13,14] Likewise, Aronow, et al.[15] stated that patients with TSC with retinal hamartoma tend to have more frequent *TSC2* mutations than *TSC1* mutations.

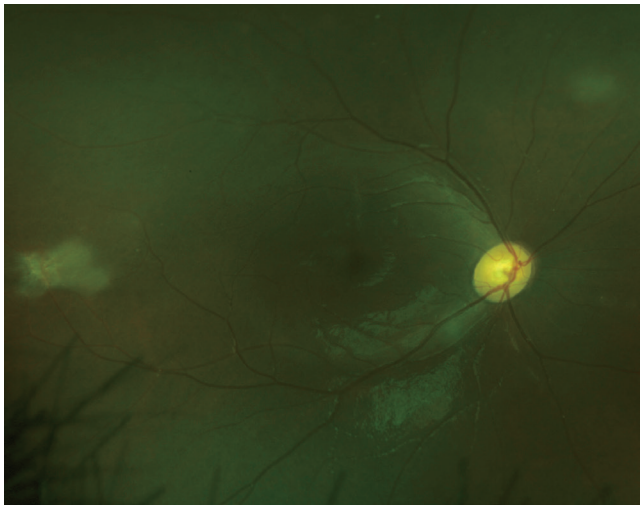

Fig. 1. Color fundus photo demonstrating type I retinal astrocytic hamartoma: relatively smooth, flat, non-calcified, semi-translucent lesions.

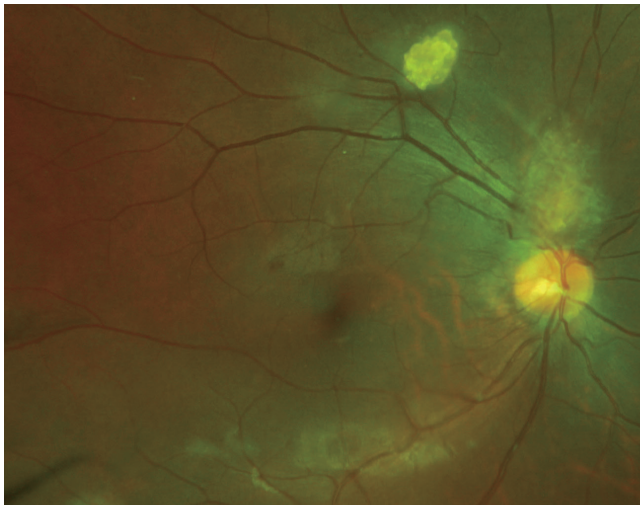

Fig. 2. Color fundus photo demonstrating type II retinal astrocytic hamartoma: nodular, elevated, calcified, opaque lesions, which are often described as a 'mulberry lesions'.

Previous studies have analyzed the prevalence of TSC ophthalmic manifestations in population-based studies in the USA, Japan, and UK.[10,16,17] There has been no previous study that examined the prevalence in Korean patients. Therefore, this study aimed to examine the prevalence of ophthalmic manifestations of TSC in a Korean population.

MATERIALS AND METHODS

Participants

This retrospective study was approved by the Institutional Review Board (IRB) of the Yonsei University College of Medicine (4-2022-0185), and was conducted in accordance with the tenets outlined in the Declaration of Helsinki. Informed consent was waived by the IRB of Yonsei University College of Medicine owing to the retrospective nature of the study. The study included individuals with TSC who were identified on a genetic or clinical basis by multiple specialists, such as ophthalmologists, neurologists, dermatologists, cardiologists, nephrologists, and pediatricians. TSC was confirmed based on the 2021 diagnostic criteria, with a clinical diagnosis of "definite TSC" requiring two major features or one major feature with two minor features at Severance Hospital in Seoul, Korea between January 1995 and March 2022.[18] A total of 104 patients had undergone ophthalmological evaluation, and 98 patients were enrolled in the study.

Ophthalmic examination

To identify hamartomas, all patients underwent a comprehensive ophthalmologic examination of the retina, which included dilated fundoscopy using indirect ophthalmoscopy with a 20D lens, retinal imaging via wide fundus photography, fluorescein and indocyanine green angiography, and fundus autofluorescence. The number of retinal astrocytic hamartomas per patient was studied, as well as their size, bilaterality, and morphological type. The total number of retinal astrocytic hamartomas per patient was divided into either the single or multiple groups. The size of the tumor was categorized as small when the height of retinal astrocytic hamartoma was <1 disc diame-

https://doi.org/10.3349/ymj.2022.0451

ter, and as large when the height of retinal astrocytic hamartoma was >1 disc diameter. Retinal astrocytic hamartoma was classified into three morphological categories as types I, II, and III. Refraction of both eyes was examined based on manifest refraction and autorefraction in patients who did not have the recordings of manifest refraction. The refraction test of each patient was performed at their first visit to the clinic. Along with previous population studies regarding the refractive results, hyperopia was defined as a spherical equivalent >+0.5D, myopia as a spherical equivalent <-0.5D, and emmetropia as a spherical equivalent between -0.5D and +0.5D.[10,19,20]

Genetic analyses

Blood samples were collected from patients after obtaining informed consent. The genetic information of two distinct variants of TSC genes (*TSC1* and *TSC2*) was collected through a targeted next-generation sequencing (NGS) approach in seven patients and a standard polymerase chain reaction (PCR) Sanger sequencing approach in 38 patients.

For NGS analysis, genomic DNA extracted from an individual's sample was used for library preparation and target capture using a custom panel that targeted candidate genes. Massive parallel sequencing was performed using the NextSeq 550Dx System (Illumina, San Diego, CA, USA). Analysis was performed using custom analysis pipeline, quality control, sequence analysis, and copy number. GRCh37 (hg19) was used as the reference sequence for mapping and variant calling. Databases used for analysis and variant annotation included the Online Mendelian Inheritance in Man, Human Gene Mutation Database, ClinVar, dbSNP, 1000 Genome, Exome Aggregation Consortium, Exome Sequencing Project, and Korean Reference Genome Database. Classification of variants followed the standards and guidelines established by the American College of Medical Genetics. Sanger sequencing further confirmed all pathogenic and likely pathogenic variants.

For standard PCR-sanger sequencing analysis, genomic DNA was extracted from peripheral blood lymphocytes using a standard phenol/chloroform extraction protocol from TSC-suspicious patients. The entire TSC1 and TSC2 coding exons and introns were amplified by PCR using the Sanger method with primers. Direct sequencing was performed using the BigDye Terminator Cycle Sequencing Ready Reaction Kit on an ABI Prism 3130 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA). The sequences were analyzed using the Sequencher program (Gene Codes Corporation, Ann Arbor, MI, USA), and were compared to reference sequences. Patient DNA sequences obtained were aligned with RefSeq sequences of *TSC1* (*NM_000368*) and *TSC2* (*NM_000548*) from the GenBank.

Statistical analyses

Data were analyzed using SPSS Statistics software (version 25; IBM Corporation, Armonk, NY, USA) and Microsoft Excel 2016 (Microsoft Corp, USA). Descriptive statistics, including standard deviations, means, medians, and frequencies, were determined. The chi-square test and odds ratio were used to test the association between the genetic variant and clinical manifestations, including retinal findings, comorbidity of intellectual disability, epilepsy, and refractive errors. The t-test was used to test the association between age and retinal lesions. *P* values<0.05 were considered statistically significant.

RESULTS

Patient demographics and ophthalmological manifestation

Among 104 patients who had undergone ophthalmic evaluation, 98 patients were included for the analysis, as full retinal assessment was not possible due to poor cooperation caused by other medical conditions, such as intellectual disability, epilepsy, or young age. Patient demographics and ophthalmological manifestation are shown in Table 1. The mean age of the patients was 14.7±13.8 years, with 48 male and 50 female patients.

Retinal findings

Retinal astrocytic hamartoma was found in 37 patients, and bi-

Table 1. Patient Demographics (n=98)

Parameters	Value
Male/Female	48/50
Age (yr)	14.7±13.8
Patients with retinal hamartoma	37 (38)
Morphological type	
Type I	32 (87)
Type II	13 (35)
Type III	5 (14)
Bilaterality of retinal hamartoma	
Unilateral	17 (46)
Bilateral	21 (57)
Number of retinal hamartoma per patient	
Single	12 (32)
Multiple	25 (68)
Patients with retinal achromic patch	8 (8)
Patients with genetic screening	45 (46)
TSC1 mutation	23 (51)
TSC2 mutation	18 (40)
No *TSC1*/*TSC2* mutation	4 (9)
Patients with refractive examination	63 (126 eyes)
Myopia	56 (44)
Hyperopia	44 (35)
Emmetropia	26 (21)
Intellectual disability	52 (53)
Epilepsy	46 (47)

Results are expressed as means±standard deviation or n (%).

lateral involvement was observed in 21 patients (57%). When categorized into three morphological types, type I tumors were observed in 32 patients (87%), type II tumors were observed in 13 patients (35%), and type III tumors were observed in 5 patients (14%). Single involvement of retinal astrocytic hamartoma was seen in 12 patients (32%), and multiple involvement were identified in 25 patients (68%). There was no correlation between age and the presence of retinal astrocytic hamartoma (p=0.615). Furthermore, no correlation between age and each of the three morphological types was observed (p>0.05).

Retinal achromic patch was seen in eight of the 98 patients examined (8%). There was no correlation between age and retinal achromic patch (p=0.453). Genetic mutation data were available in only two patients with retinal achromic patch (one patient with the *TSC1* variant and the other with the *TSC2* variant).

Genetic analysis (*TSC1* and *TSC2* gene mutation)

In the 45 patients who underwent genetic screening, the *TSC1*/*TSC2* detection rate was 91% (41/45). The *TSC1* variant was detected in 23 patients (51%), whereas the *TSC2* variant was detected in 18 patients (40%). The types of mutations within each variant are described in Table 2.

The correlations between genetic variants (*TSC1* or *TSC2*) and medical conditions related to TSC are shown in Table 3. The results showed that *TSC2* mutations are correlated with a higher rate of retinal astrocytic hamartoma involvement (χ^2=7.1 with 1 df, p=0.01; odds ratio, 6.31). Furthermore, there was a correlation between genetic variants and number of retinal astrocytic hamartoma observed within a patient (χ^2=7.1 with 1 df, p=0.02). Multiple retinal astrocytic hamartomas within a patient were significantly more prevalent among carriers of the *TSC2* than among those with *TSC1* mutations (odds ratio, 30.0; p=0.03). Moreover, a correlation between genetic variants and bilaterality of retinal astrocytic hamartoma was observed (χ^2=6.2 with 1 df, p=0.02); bilateral involvement was significantly more frequent among carriers of *TSC2* than among those with *TSC1* mutations (odds ratio, 30.0; p=0.03). However, there was no correlation between genetic variant and size of retinal astrocytic hamartomas (χ^2=0.0 with 1 df, p>0.05), comorbidity of epilepsy (χ^2=0.6 with 1 df, p>0.05), or intellectual disability (χ^2=0.1 with 1 df, p>0.05).

Refractive examination

Reliable refractive examination results were available from 63 (126 eyes) out of 98 patients; 44% (56/126) of patients were myopic, 35% (44/126) were hyperopic, and 21% (26/126) were emmetropic. Furthermore, there was a correlation between genetic variants and the refractive status of TSC patients, whether they are myopic, hyperopic, or emmetropic (χ^2=8.10 with 2 df, p=0.02). The *TSC1* variant was associated with myopia (χ^2=6.6 with 1 df, p=0.01), while the *TSC2* variant was associated with emmetropia (χ^2=6.87 with 1 df, p=0.01).

Table 2. Description of the Types of Mutations Detected

	Deletion	Missense	Splicing error	Not specified	Total
TSC1	4 (17)	15 (65)	2 (9)	2 (9)	23
TSC2	2 (11)	12 (67)	3 (17)	1 (5)	18
No *TSC1*/*TSC2*					4

Data are presented as n (%).

DISCUSSION

TSC is a complex, multi-system disorder, which results in a wide array of clinical manifestations depending on where benign tumors (hamartomas) are located.[21] Although the eye is one of the organs in which hamartomas are most frequently located, the signs of its involvement can be subtle, and further assessment can be challenging.

In an attempt to understand the nature of TSC, there have been a few population-based studies reviewing the prevalence of its ophthalmic manifestations.[9,10,17] However, varying results had been reported regarding the prevalence, bilaterality, and morphological types of retinal astrocytic hamartomas. In the

Table 3. Association between Genetic Variants and Clinical Manifestation of TSC

	TSC1	TSC2	Odds ratio	TSC1 vs. TSC2 (p value)
Retinal hamartoma			6.31	0.01*
Yes	7	13		
No	17	5		
Bilaterality of hamartoma			30	0.02*
Unilateral	6	1		
Bilateral	1	5		
Multiplicity of hamartoma			30	0.03*
Single	5	1		
Multiple	1	6		
Size of hamartoma			2	0.61
≤1 dd	5	5		
>1 dd	1	2		
Refraction (eyes)				
Hyperopia	5	5	0.90	0.89
Myopia	17	7	4.59	0.01*
Emmetropia	4	12	0.18	0.01*
Intellectual disability			0.87	0.82
Yes	12	8		
No	13	10		
Epilepsy			1.22	0.77
Yes	17	13		
No	8	5		

Association between genetic variant and each clinical manifestation using odds ratio.
*p<0.05.

https://doi.org/10.3349/ymj.2022.0451

largest reported population-based study regarding ophthalmic manifestations of TSC patients from the USA (Mayo clinic), the overall prevalence of retinal astrocytic hamartomas was 49%. In a study based on the UK population, the overall prevalence of retinal astrocytic hamartomas was 44%.[9,10] A study from Tokyo reported an overall prevalence as high as 87%.[6] Our study showed a slightly lower prevalence (38%) compared with the previously reported studies. Reports on the bilaterality of retinal astrocytic hamartoma have also varied. The prevalence of bilateral involvement of retinal astrocytic hamartoma in the USA (Mayo clinic), UK, and the present study were 49%, 44%, and 57%, respectively. In terms of the prevalence of each morphological type of retinal astrocytic hamartoma in this study, type I tumors were the most common, followed by type II and type III tumors, which is consistent with previous literature.

Regarding retinal achromic patches, there have been varying results regarding its clinical significance to TSC and its detection rate in TSC patients. In a population-based study of 100 TSC patients, Rowley, et al.[10] reported 39% of retinal achromic patch, whereas Shields, et al.[22] reported a frequency of 12%. Our study reported a slightly lower percentage (8%) of retinal achromic patch compared with the previous studies. This may be attributed to the fact that the initial presentation of type I tumors, which are small, flat, and semi-lucent, may not be easily distinguished from the retinal achromic patch, especially since not all of our study population underwent comprehensive retinal examination, including fluorescein and indocyanine green angiography and fundus autofluorescence, owing to young age and lack of cooperation due to general physical condition.

TSC is recognized as a disorder with a well-established genetic cause. Therefore, a few previous population-based studies have analyzed the relationship between genetic variants (*TSC1* or *TSC2*) and the prevalence of retinal hamartoma in TSC patients and reported that clinical manifestations of TSC are more frequent in patients with *TSC2* mutations than in patients with *TSC1* mutations.[13-15] Likewise, Aronow, et al.[15] reported that *TSC2* mutations are more frequent in patients with retinal astrocytic hamartoma than in those without retinal findings. However, no previous studies have compared the association between the genetic variant and the degree of retinal astrocytic hamartoma involvement, such as the number or bilaterality of hamartoma. Interestingly, we have shown a statistically significant association between *TSC2* mutation and the number of retinal astrocytic hamartoma observed, as well as between *TSC2* mutation and bilaterality of retinal astrocytic hamartoma involvement. These results add value to the widely-established postulation that patients with *TSC2* mutations tend to exhibit more severe clinical manifestations.

Refractive errors in patients with TSC have been studied to establish whether there is a significant difference compared to a population without TSC. Rowley, et al.[10] reported that the refractive errors of TSC patients are broadly comparable to those of the normal population in the UK, as follows: 27% of myopia, 22% of hyperopia, and 51% of emmetropia. Compared with the previous study in the UK, our results showed a comparatively high percentage of myopic TSC patients. Overall, 44% of eyes were myopic, 35% were hyperopic, and 21% were emmetropic. This may be attributed to the higher prevalence of myopia in the East Asian population compared to the Caucasian population.[23] In addition to the prevalence of refractive findings in the TSC population, our study documented the correlation between genetic variants and refractive status. We found an association between *TSC1* mutation and myopia, as well as an association between *TSC2* mutation and emmetropia. Although there was no statistically significant difference between the age of patients with *TSC1* and *TSC2* ($p>0.05$), this result should be interpreted with caution, as the refractive status may change during the aging process, especially as myopia tends to develop with the aging of children.

This study has some limitations. First, not all TSC patients included in the study underwent genetic screening. However, patients with more clinical manifestations are likely to undergo a thorough examination, including genetic screening. Therefore, further prospective studies with comprehensive genetic screening in patients with TSC would be helpful in terms of elucidating the relationship between genetic variants and the ophthalmic manifestation of TSC. Second, the refractive results were based on manifested refraction or autorefraction rather than the use of cycloplegics. Therefore, accommodative power, especially in young patients, could have affected the results of our analysis. Lastly, although only patients with retinal examination results were included in the study, not all patients were able to undergo wide fundus photography due to problems of cooperation. However, this may have contributed to the underestimation of the prevalence of fundus findings, especially chorioretinal hypopigmentation located at the periphery.

In conclusion, our study is the first population-based study to investigate the ophthalmic manifestations of TSC patients in Korea. Our preliminary results align with previous literature, apart from the higher prevalence of myopic patients. Our study also demonstrates that TSC patients with *TSC2* mutation tend to have more extensive involvement of retinal astrocytic hamartoma with an increased number of retinal astrocytic hamartomas and a higher number of bilateral involvement of retinal astrocytic hamartoma. Further studies involving more eyes with genetic information are necessary to elucidate the connection between TSC gene variants and clinical manifestations.

ACKNOWLEDGEMENTS

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) under 2019R1A2C2002393 (C.S.L.).

AUTHOR CONTRIBUTIONS

Conceptualization: Christopher Seungkyu Lee. Data curation: Sung Soo Kim. Formal analysis: Christopher Seungkyu Lee and Soyoung Ryu. Funding acquisition: Christopher Seungkyu Lee. Investigation: Christopher Seungkyu Lee and Soyoung Ryu. Methodology: Christopher Seungkyu Lee. Project administration: Christopher Seungkyu Lee. Resources: Christopher Seungkyu Lee. Software: Christopher Seungkyu Lee. Supervision: Christopher Seungkyu Lee, Hoon-Chul Kang, and Sung Chul Lee. Validation: Christopher Seungkyu Lee. Visualization: Soyoung Ryu. Writing—original draft: Soyoung Ryu. Writing—review & editing: all authors. Approval of final manuscript: all authors.

ORCID iDs

Soyoung Ryu	https://orcid.org/0000-0002-1278-9024
Hoon-Chul Kang	https://orcid.org/0000-0002-3659-8847
Sung Chul Lee	https://orcid.org/0000-0001-9438-2385
Suk Ho Byeon	https://orcid.org/0000-0001-8101-0830
Sung Soo Kim	https://orcid.org/0000-0003-3049-9554
Christopher Seungkyu Lee	https://orcid.org/0000-0001-5054-9470

REFERENCES

1. Randle SC. Tuberous sclerosis complex: a review. Pediatr Ann 2017;46:e166-71.
2. Jansen FE, van Nieuwenhuizen O, van Huffelen AC. Tuberous sclerosis complex and its founders. J Neurol Neurosurg Psychiatry 2004;75:770.
3. Vogt HW, Weygandt W. Zeitschrift für die Erforschung und Behandlung des jugendlichen Schwachsinns auf wissenschaftlicher Grundlage. G. Fischer; 1910.
4. Van der Hoeve J. Eye symptoms in tuberous sclerosis of the brain. Trans Ophthalmol Soc UK 1920;40:329-34.
5. Kranias G, Romano PE. Depigmented iris sector in tuberous sclerosis. Am J Ophthalmol 1977;83:758-9.
6. Lucchese NJ, Goldberg MF. Iris and fundus pigmentary changes in tuberous sclerosis. J Pediatr Ophthalmol Strabismus 1981;18:45-6.
7. Williams R, Taylor D. Tuberous sclerosis. Surv Ophthalmol 1985;30:143-54.
8. Roach ES, Gomez MR, Northrup H. Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. J Child Neurol 1998;13:624-8.
9. Robertson DM. Ophthalmic manifestations of tuberous sclerosis. Ann N Y Acad Sci 1991;615:17-25.
10. Rowley SA, O'Callaghan FJ, Osborne JP. Ophthalmic manifestations of tuberous sclerosis: a population based study. Br J Ophthalmol 2001;85:420-3.
11. Hodgson N, Kinori M, Goldbaum MH, Robbins SL. Ophthalmic manifestations of tuberous sclerosis: a review. Clin Exp Ophthalmol 2017;45:81-6.
12. Henske EP, Rasooly R, Siroky B, Bissler J. Tuberous sclerosis complex, mTOR, and the kidney: report of an NIDDK-sponsored workshop. Am J Physiol Renal Physiol 2014;306:F279-83.
13. 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;64:1305-15.
14. Jones AC, Daniells CE, Snell RG, Tachataki M, Idziaszczyk SA, Krawczak M, et al. Molecular genetic and phenotypic analysis reveals differences between TSC1 and TSC2 associated familial and sporadic tuberous sclerosis. Hum Mol Genet 1997;6:2155-61.
15. Aronow ME, Nakagawa JA, Gupta A, Traboulsi EI, Singh AD. Tuberous sclerosis complex: genotype/phenotype correlation of retinal findings. Ophthalmology 2012;119:1917-23.
16. Nyboer JH, Robertson DM, Gomez MR. Retinal lesions in tuberous sclerosis. Arch Ophthalmol 1976;94:1277-80.
17. Shelton RW. The incidence of ocular lesions in tuberous sclerosis. Ann Ophthalmol 1975;7:771-4.
18. Northrup H, Aronow ME, Bebin EM, Bissler J, Darling TN, de Vries PJ, et al. Updated international tuberous sclerosis complex diagnostic criteria and surveillance and management recommendations. Pediatr Neurol 2021;123:50-66.
19. Attebo K, Ivers RQ, Mitchell P. Refractive errors in an older population: the Blue Mountains Eye Study. Ophthalmology 1999;106:1066-72.
20. Wang Q, Klein BE, Klein R, Moss SE. Refractive status in the Beaver Dam Eye Study. Invest Ophthalmol Vis Sci 1994;35:4344-7.
21. Wan MJ, Chan KL, Jastrzembski BG, Ali A. Neuro-ophthalmological manifestations of tuberous sclerosis: current perspectives. Eye Brain 2019;11:13-23.
22. Shields CL, Reichstein DA, Bianciotto C, Shields JA. Retinal pigment epithelial depigmented lesions associated with tuberous sclerosis complex. Arch Ophthalmol 2012;130:387-90.
23. Tan CS, Chan YH, Wong TY, Gazzard G, Niti M, Ng TP, et al. Prevalence and risk factors for refractive errors and ocular biometry parameters in an elderly Asian population: the Singapore Longitudinal Aging Study (SLAS). Eye (Lond) 2011;25:1294-301.

https://doi.org/10.3349/ymj.2022.0451