Racial Differences in TSC Skin Manifestations

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March 14, 2023

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Four major TSC clinical diagnostic criteria are dermatological manifestations

Table 1. Clinical diagnostic criteria for tuberous sclerosis complex [reprinted under the terms of the Creative Commons Attribution-NonCommercial-No Derivatives License (CC BY NC ND) from the study by Northrup *et al.*].[3]

Major criteria	Minor criteria
Hypomelanotic macules (⩾3; at least 5 mm diameter)	'Confetti' skin lesions
Angiofibroma (⩾3) or fibrous cephalic plaque	Dental enamel pits (⩾3)
Ungual fibromas (⩾2)	Intraoral fibromas (⩾2)
Shagreen patch	Retinal achromic patch
Multiple retinal hamartomas	Multiple renal cysts
Multiple cortical tubers and/or radial migration lines	Nonrenal hamartomas
Subependymal nodule (⩾2)	Sclerotic bone lesions
Subependymal giant cell astrocytoma	
Cardiac rhabdomyoma	
LAM[a]	
Angiomyolipomas (⩾2)[a]	

LAM, lymphangioleiomyomatosis; TSC, tuberous sclerosis complex.
Definite TSC: two major features or one major feature with two minor features. Possible TSC: either one major feature or more than two minor features. Genetic diagnosis: A pathogenic variant in *TSC1* or *TSC2* is diagnostic for TSC (most TSC-causing variants are sequence variants that clearly prevent TSC1 or TSC2 protein production). Some variants compatible with protein production (e.g. some missense changes) are well-established as disease-causing; other variant types should be considered with caution.
[a]A combination of the two major clinical features LAM and angiomyolipomas without other features does not meet criteria for a definite diagnosis.

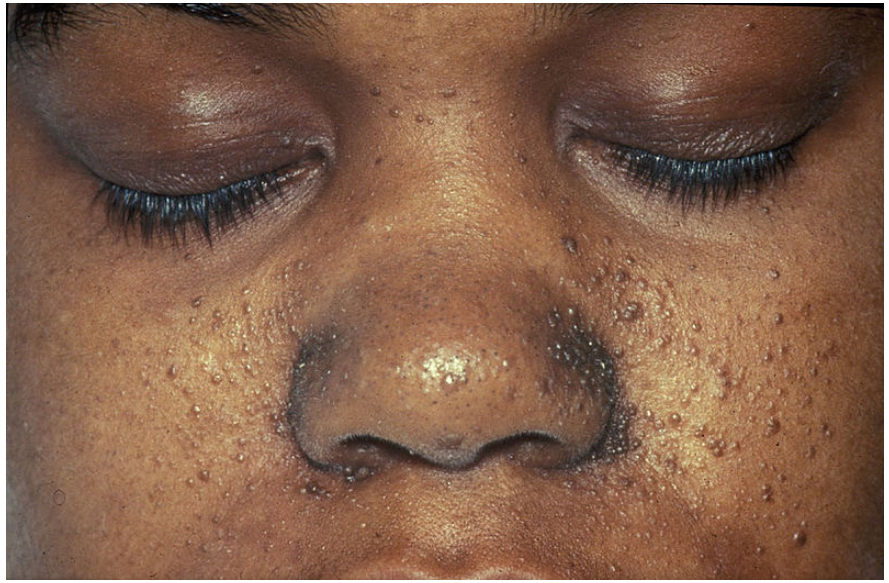
Anecdotal Reports

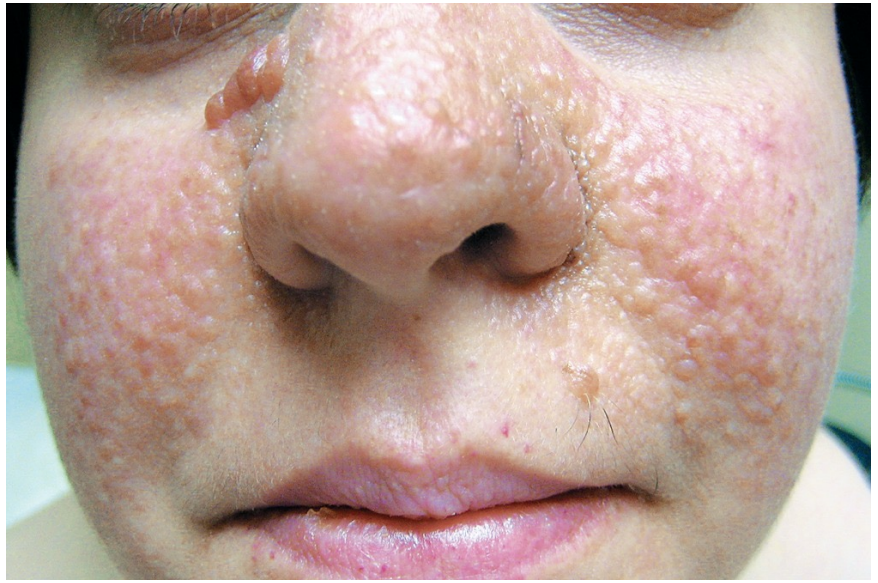
Racial disparities observed clinically

- Representation and diagnosis of Black individuals in TSC clinics and research studies.
- Age of diagnosis despite individuals having comparable numbers of TSC skin manifestations.
- Medical references and photographs of TSC skin manifestations, limiting clinicians' accuracy of assessment of darker skin tones.

There is an evident lack of published resources for individuals with darker skin.

Only one picture of facial angiofibromas in dark skin found online

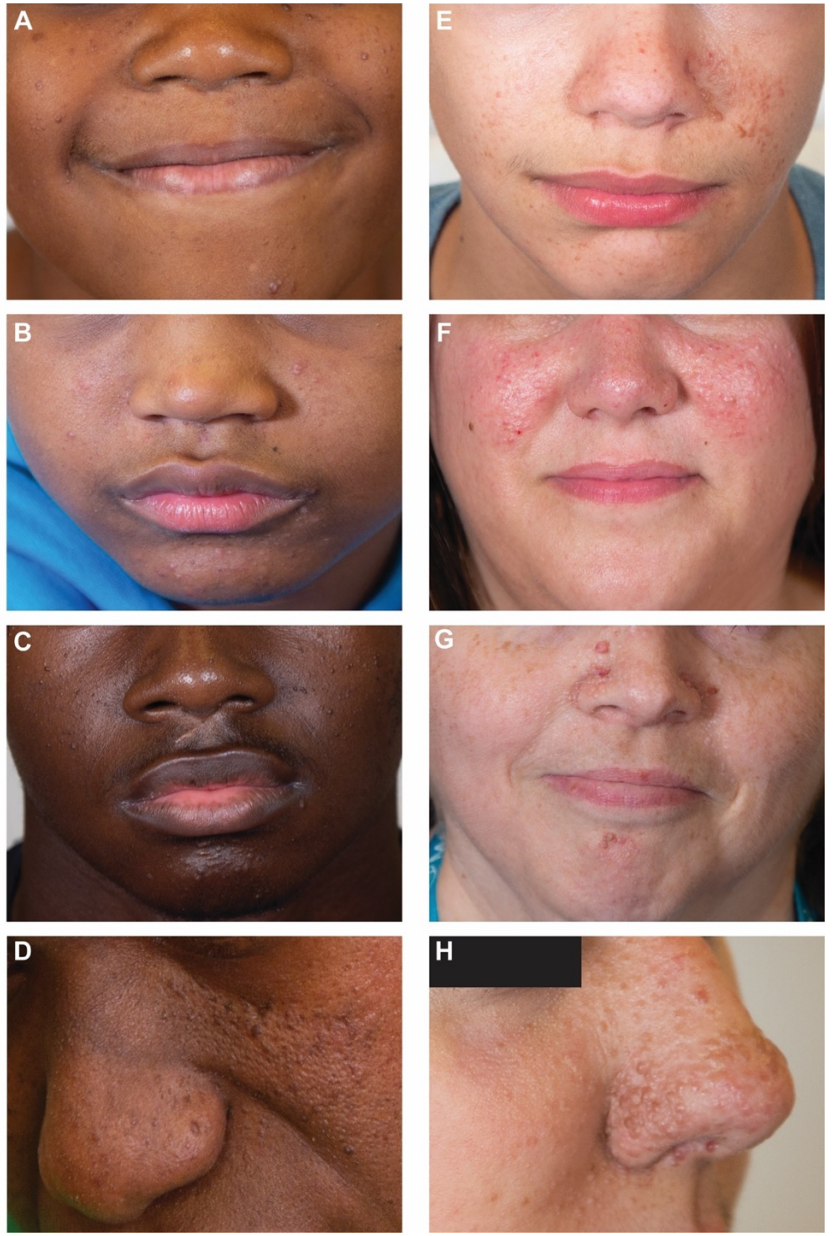




Collaboration with Dr. Gipson: Goals

- Create an infographic to share with clinicians showing TSC skin manifestations across patients of differing skin tones.
  - **This is currently being printed for distribution to clinics!**
- Raise awareness of identified disparities and the potential consequences.
- Publish data comparing age at TSC diagnosis and presence of skin manifestations in Black and White individuals.

Long-term goal: decrease time to diagnosis and prevent misdiagnosis.



Hypomelanotic Macules

- Hypomelanotic macules, also called ash-leaf spots, are the most common dermatologic feature of TSC in patients under the age of 1 year.
- A complete skin examination utilizing a wood's lamp is recommended to visualize these findings.
- They are often present on the limbs, trunk, and buttocks, but can be identified throughout the body.

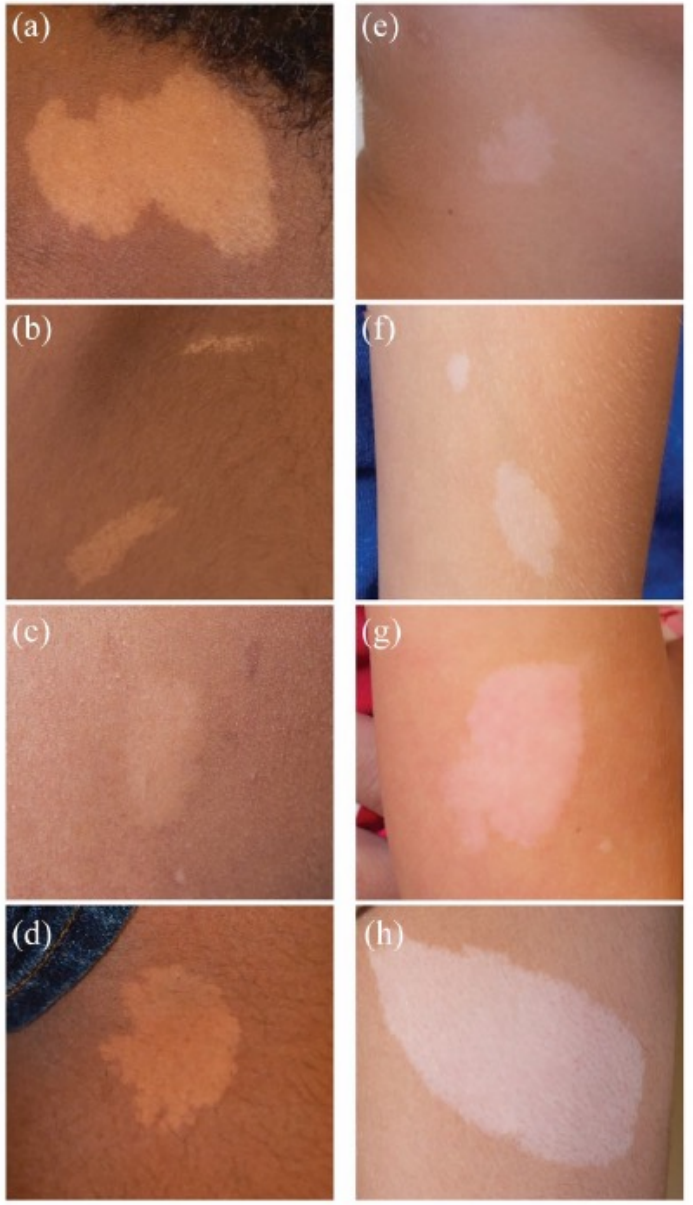


Figure 1. Hypomelanotic macules in Black and White individuals with TSC. (a–d) Black individuals with hypomelanotic macules. (a) Age 11 male, on forehead. (b) Age 11 male, on back. (c) Age 14 male, on cheek. (d) Age 14 male, on leg. (e–h) White individuals with hypomelanotic macules. (e) Age 8 male, on neck. (f) Age 7 female, on arm. (g) Age 4 female, on arm. (h) Age 15 male, on leg.

Facial Angiofibromas

- Facial angiofibromas occur in up to 75% of patients and become more prominent with age.
- Facial angiofibromas often appear erythematous, raised, and in a butterfly-shaped appearance across the nasolabial folds; however, in Black individuals, they are typically hyperpigmented.
- In Black individuals, facial angiofibromas may be confused for seborrheic keratoses or other benign epidermal growths or even other neurocutaneous disorders.

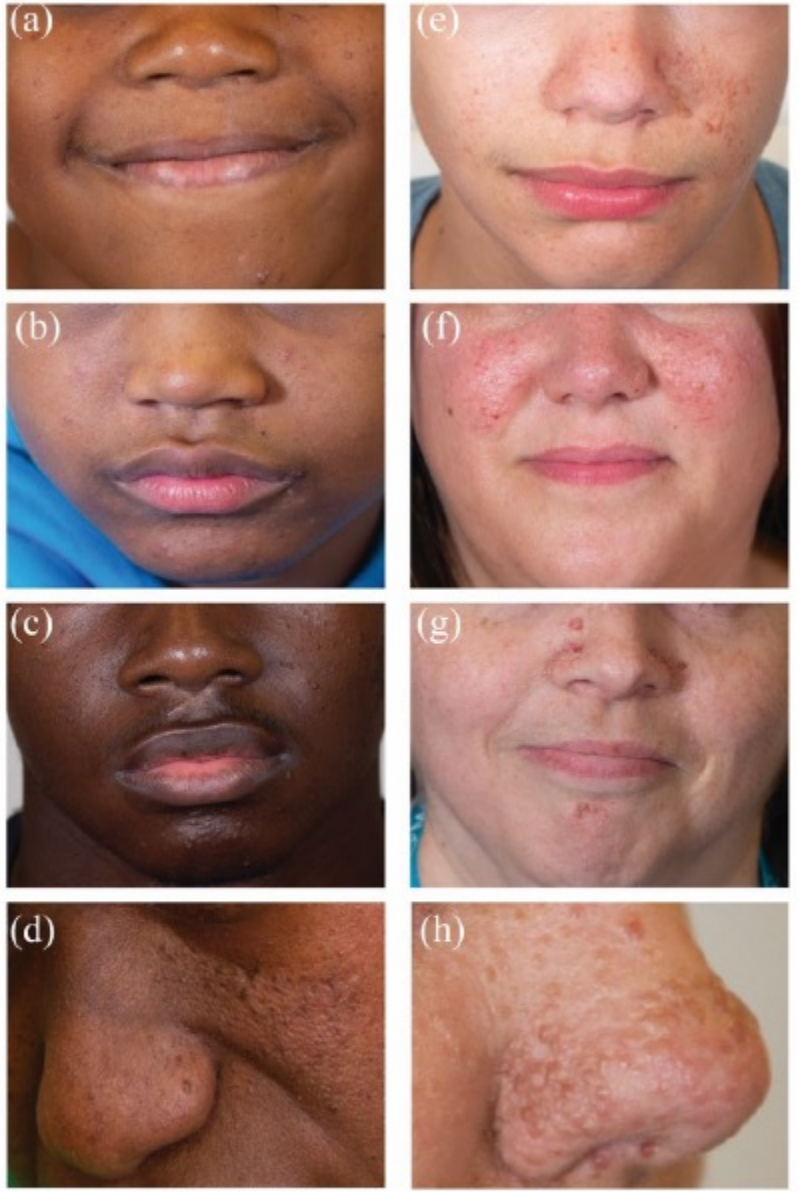


Figure 2. Facial angiofibromas in Black and White individuals with TSC. (a–d) Black individuals with facial angiofibromas, ages 11, 14, 16, and 28, respectively. (e–h) White individuals with facial angiofibromas, ages 13, 37, 39, and 28, respectively.

Cephalic Fibrous Plaques

- Fibrous cephalic plaques (FCPs) can be present from birth but are more noticeable during early childhood or adolescence.
- FCPs can be located on the face, scalp, or forehead and may appear rubbery to firm, smooth to bumpy, skin-colored, pink, red, or brown.
- Individuals with darker skin tones tend to have much darker lesions relative to surrounding skin than those with lighter skin tones.

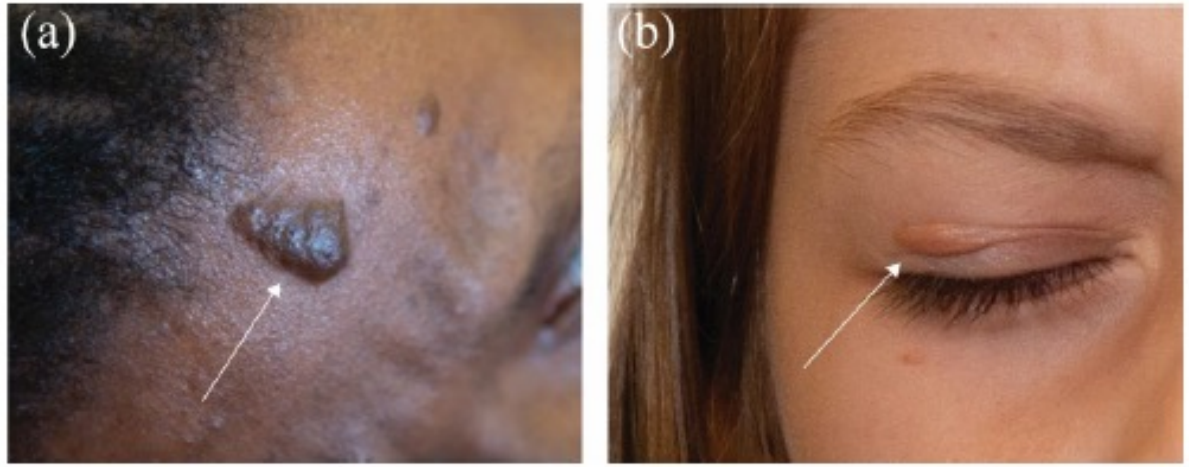


Figure 3. Cephalic fibrous plaques (CFPs) in Black and White individuals with TSC. (a) A 28-year-old Black female and (b) a 7-year-old White female with cephalic fibrous plaques (CFPs) on the forehead and eyelid, respectively. White arrows indicate location of CFPs.

Shagreen Patches

- Shagreen patches are a type of connective tissue nevus that typically appear as large, irregular, firm skin and colored to hypopigmented plaques across the lower back; however, they can appear throughout the upper and middle back, buttocks, and thighs.
- These lesions usually appear during early childhood.
- Black participants had a significantly increased probability of having shagreen patches and cephalic fibrous plaques as compared with White participants in the NHD.

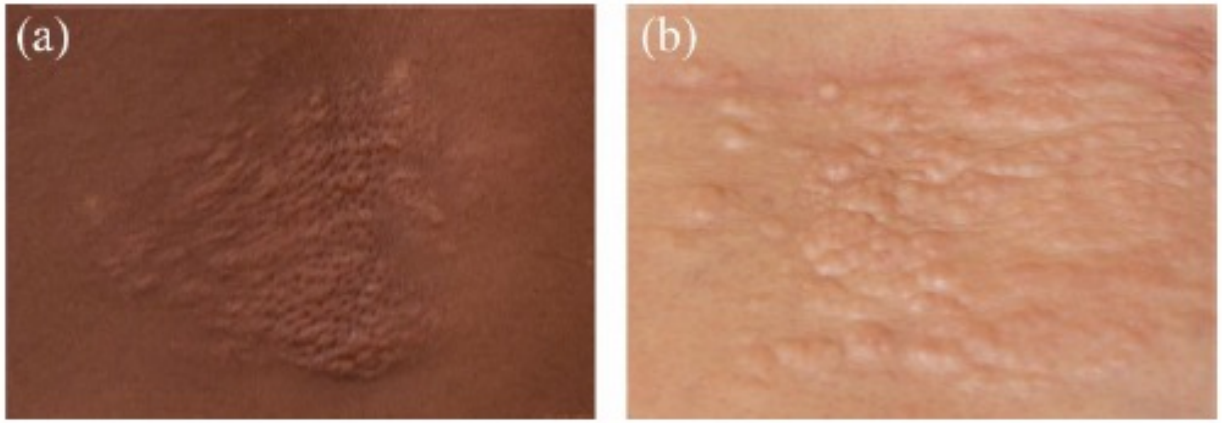
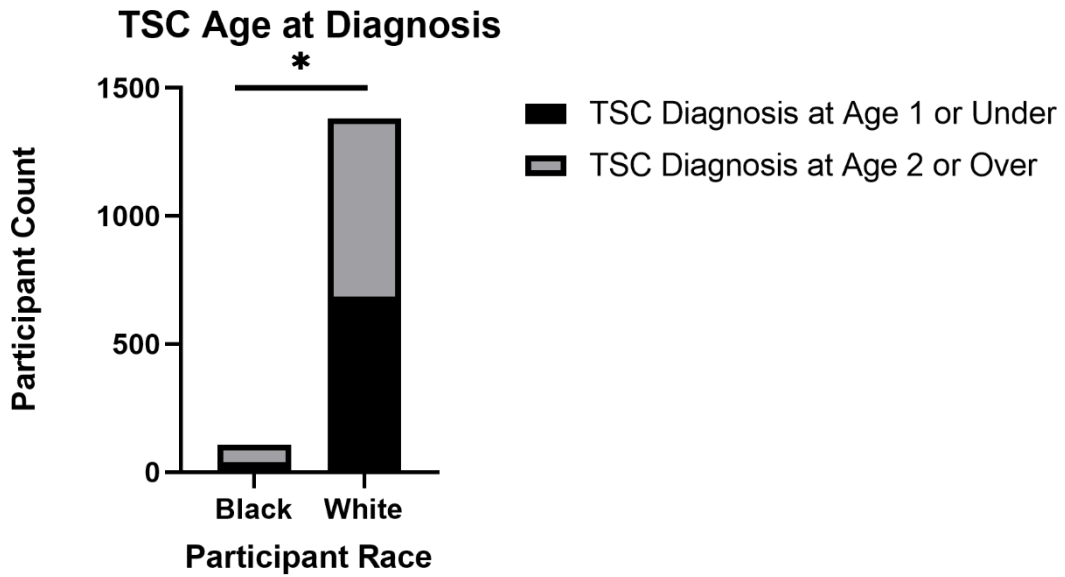


Figure 4. Shagreen patches in a Black and White individual with TSC. (a) An 11-year-old Black male with a shagreen patch on the back and (b) a 37-year-old White female with a shagreen patch on the back.

Age at TSC Diagnosis: TSC Center of Excellence Clinic Cohort and NHD Participants

- A trend was observed showing that Black patients were less likely to be diagnosed at an earlier age with 50% (9/18) diagnosed at ≤1 year compared to 70% (16/23) of White patients in the TSCOE cohort, although this finding was not statistically significant.
- A total of 107 (71%) Black and 1380 (76%) White participants had an age of diagnosis recorded in the NHD.
- Average age of diagnosis did not differ between Black (age 5.4) and White (age 5.7) individuals.



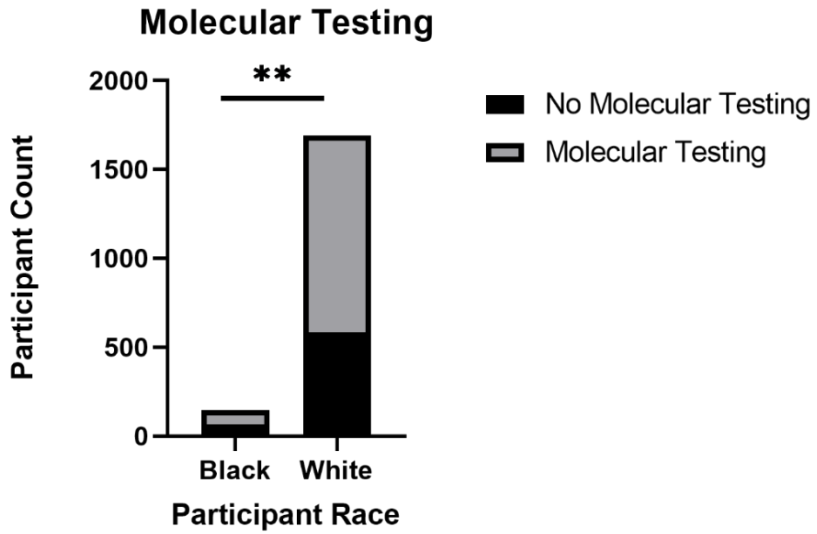
A significant difference was observed with 38% of Black participants diagnosed at age ≤1 year while 50% of White participants were diagnosed at age ≤1 year.

Participation in Recorded TSC Clinical Trials in the TSC Natural History Database

Black or African American	
0 clinical trials	142 (94.7%)
1 clinical trial	8 (5.3%)
White	
0 clinical trials	1599 (88.0%)
1 clinical trial	192 (10.6%)
2 clinical trials	22 (1.2%)
3 clinical trials	3 (0.2%)

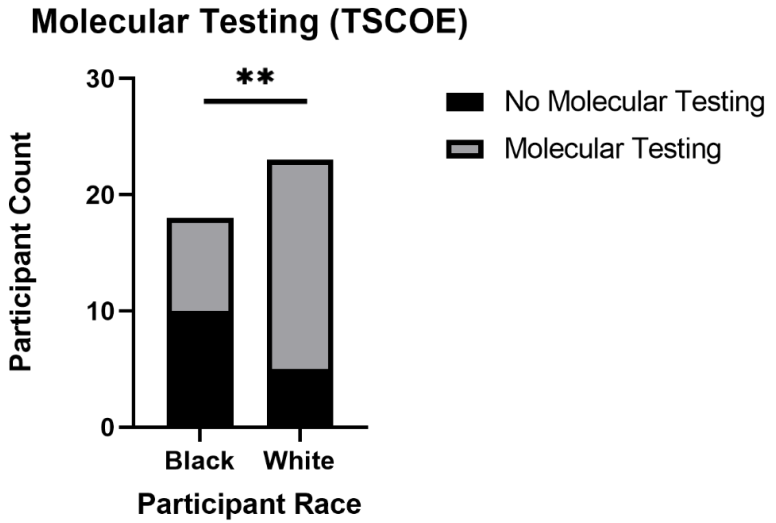
217 (11.9%) of White participants have participated in at least one clinical trial recorded in the TSC Natural History Database vs. only 8 (5.3%) of Black participants.

Disparity in Molecular Testing in the NHD and TSC Center of Excellence



A significant difference was observed in the frequency of molecular testing in the NHD:

54.5% of Black participants and 65.5% of White participants received molecular testing, respectively.



A significant difference was observed in the frequency of molecular testing in the TSCOE:

8 Black participants had molecular testing noted in the medical record (44%) vs. 18 White participants (78%).

A greater % of White individuals utilized topical rapamycin

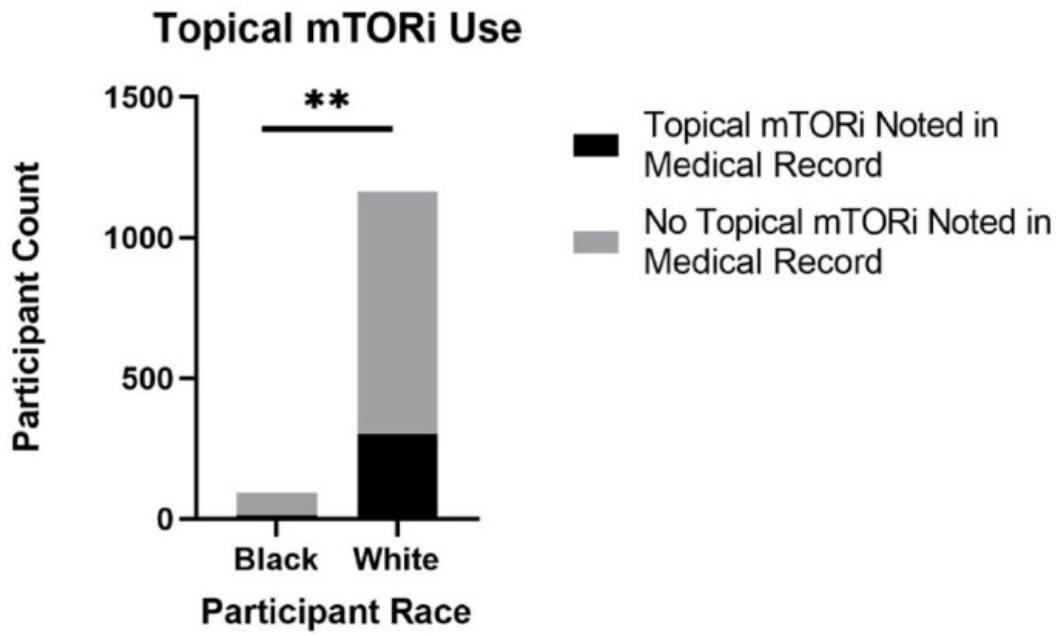


Figure 11. Use of topical rapamycin for facial angiofibroma in Black and White participants in the TSC natural history database.
A total of 92 Black participants and 1166 White participants had a recorded answer for the use of the topical mTORi rapamycin. A Fisher's exact test yielded a significant ($p = 0.006$) difference in the frequency of topical rapamycin use to treat facial angiofibroma in Black and White participants in the NHD cohort.

- 26% of White participants utilized a topical mTOR inhibitor vs. only 13% of Black participants in the NHD.
- Potential variables include the lack of FDA approval for topical rapamycin at the time of data collection and variable participation in clinical trials for topical creams.

Black individuals were underrepresented in the TSC Natural History Database

Race	Count of Race in NHD	% of Total NHD Participants	% in US population (US Census)
American Indian or Native Alaskan	**12**	**0.51%**	**1.3%**
Asian	**68**	**2.86%**	**5.9%**
Black or African American	**150**	**6.32%**	**13.4%**
Multi-Racial	92	3.87%	2.8%
Native Hawaiian or other Pacific Islander	4	0.17%	0.2%
Other	68	2.86%	N/A
Unknown	165	6.95%	N/A
White	1816	76.46%	60.1%
Grand Total	**2375**	**100.00%**	

**Data from January 2022 export*

Black individuals are still underrepresented in the TSC Natural History Database (2023)

Race	Count of Race in NHD	% of Total NHD Participants	% in US population (US Census)
American Indian or Native Alaskan (no change)	**12**	**0.51%**	**1.3%**
Asian (+2 in 2022)	**70**	**2.72%**	**5.9%**
Black or African American (+4 in 2022)	**154**	**5.98%**	**13.4%**
Multi-Racial (+3 in 2022)	95	3.69%	2.8%
Native Hawaiian or other Pacific Islander	4	0.17%	0.2%
Other	70	2.72%	N/A
Unknown	249	9.67%	N/A
White	1921	74.60%	60.1%
Grand Total	**2575**	**100.00%**	

**Data from March 2023 export*

We encourage anyone interested in research to reach out to us at biosample@tscalliance.org

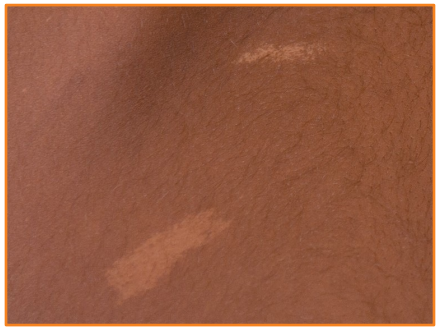
Summary

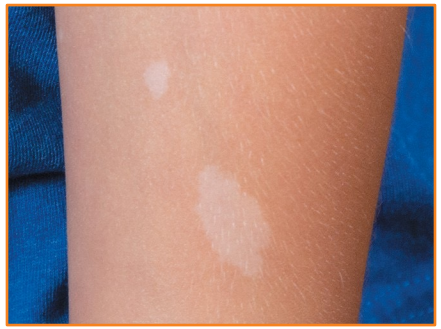
- Black individuals are underrepresented within the TSC Natural History Database, in TSC clinical trials, and within a TSC Center of Excellence clinic cohort.
- We discovered a trend where Black individuals are diagnosed later than White individuals and do not get molecular testing as frequently.
- There is a lack of published references of TSC skin manifestations in darker skinned individuals. Our infographic aims to improve this knowledge gap.

Racial differences in the dermatological manifestations of TSC

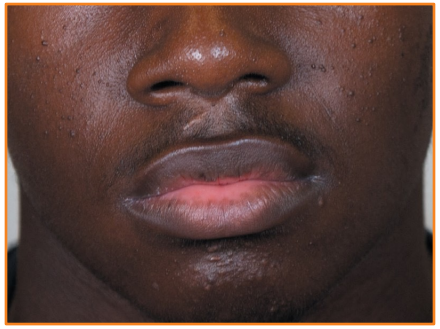
Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous disorder of non-malignant tumor growths throughout major organ systems and neurological, neuro- psychiatric, renal, and pulmonary co-morbidities. Clinical diagnosis of TSC is based on the presence of a specific combination of major and minor features, of which four major and one minor are dermatological manifestations. Medical photographs of such manifestations are commonly shown as examples from White individuals, creating a potential barrier to accurately identifying these features in skin of color. Cutaneous manifestations are often the only visual manifestation of TSC for individuals with mild to moderate phenotypes of TSC. The aim of this infographic is to raise awareness of dermatological manifestations associated with TSC and compare the appearance of the four major skin manifestations between Black and White individuals with TSC.

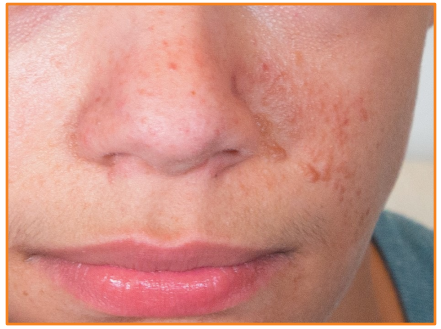
Hypomelanotic macules: Also called ash-leaf spots, these are the most common dermatologic feature of TSC in patients under the age of 1 year. They are often present on the limbs, trunk, and buttocks, but can be identified throughout the body. Hypomelanotic macules are typically present at birth and remain throughout life. A complete skin examina- tion utilizing a Wood's lamp is recommended to visualize these findings across all races as mild hypopigmentation may be difficult to detect in darker skin.





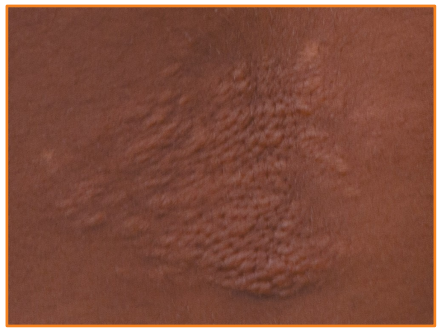
Facial Angiofibroma: Later in childhood, facial angiofibromas, also referred to as adenoma sebaceum, are a hallmark feature of TSC. Facial angiofibromas occur in up to 75% of patients and become more prominent with age. Facial angiofibromas often appear erythematous, raised, in a butterfly-shaped appearance across the nasolabial folds, and are more likely to appear hyperpigmented in darker skinned individuals. In Black individuals, facial angiofibro- mas may be confused for seborrheic keratoses or other benign epidermal growths or even other neurocutaneous disorders.

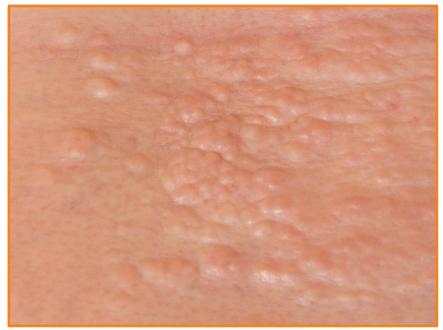




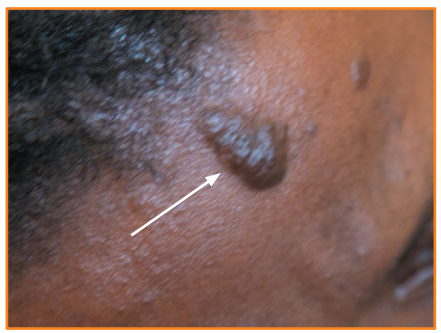
Shagreen Patches: Shagreen patches are a type of connective tissue nevus that typically appear as large, irregular, firm skin and colored to hypopigmented plaques across the lower back; however, they can appear throughout the upper and middle back, buttocks, and thighs. These lesions usually appear during early childhood.
In the examples below, both patches are located on the lower back.

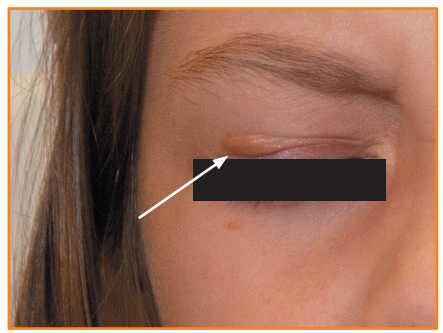
Scan the QR code to see common locations of shagreen patches.





Fibrous Cephalic Plaque: Fibrous cephalic plaques (FCPs) can be present from birth but are more noticeable during early childhood or adolescence. FCPs can be located on the face, scalp, or forehead and may appear rubbery to firm, smooth to bumpy, skin-colored, pink, red, or brown. Individuals with darker skin tones tend to have much darker lesions relative to surrounding skin than those with lighter skin tones. FCPs on the scalp were associated with decreased hair density in the location of the lesion. The size and distribution of FCPs is still not well understood; however, between 1-5 cm is commonly noted throughout the literature.





Photographs also shown in Pounders, Rushing et. al., Therapeutic Advances in Rare Disease. Infographic prepared by Ashley Pounders, FNP-C, Director, Medical Affairs, and Gabrielle Rushing, PhD, Director, Research, at the TSC Alliance. The authors kindly thank Dr. Tom Darling and Dr. Oyetewa Oyerinde for their thoughtful review and feedback and the individuals with TSC who allowed their photographs to be used.

Scan the QR code to read the *Therapeutic Advances in Rare Disease* article.

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This infographic made possible by support from Nobelpharma and an EveryLife Rare Giving Tools & Resources grant.

Q&A

TSC Alliance

Hope no matter how complex