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Expanding the Genotypic Spectrum of Bathing Suit Ichthyosis.

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Expanding the Genotypic Spectrum of Bathing Suit Ichthyosis

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IMPORTANCE Bathing suit ichthyosis (BSI) is a rare congenital disorder of keratinization characterized by restriction of scale to sites of relatively higher temperature such as the trunk, with cooler areas remaining unaffected. Fewer than 40 cases have been reported in the literature. Bathing suit ichthyosis is caused by recessive, temperature-sensitive mutations in the transglutaminase-1 gene (*TGM1*). Clear genotype-phenotype correlations have been difficult to establish because several of the same *TGM1* mutations have been reported in BSI and other forms of congenital ichthyosis. We identify novel and recurrent mutations in 16 participants with BSI.

OBJECTIVE To expand the genotypic spectrum of BSI, identifying novel *TGM1* mutations in patients with BSI, and to use BSI genotypes to draw inferences about the temperature sensitivity of *TGM1* mutations.

DESIGN, SETTING, AND PARTICIPANTS A total of 16 participants with BSI from 13 kindreds were identified from 6 academic medical centers. A detailed clinical history was obtained from each participant, including phenotypic presentation at birth and disease course. Each participant underwent targeted sequencing of *TGM1*.

MAIN OUTCOMES AND MEASURES Phenotypic and genotypic characteristics in these patients from birth onward.

RESULTS Of the 16 participants, 7 were male, and 9 were female (mean age, 12.6 years; range, 1-39 years). We found 1 novel *TGM1* indel mutation (Ile469_Cys471delinsMetLeu) and 8 *TGM1* missense mutations that to our knowledge have not been previously reported in BSI: 5 have been previously described in non-temperature-sensitive forms of congenital ichthyosis (Arg143Cys, Gly218Ser, Gly278Arg, Arg286Gln, and Ser358Arg), and 3 (Tyr374Cys, Phe495Leu, and Ser772Arg) are novel mutations. Three probands were homozygous for Arg264Trp, Arg286Gln, or Arg315Leu, indicating that these mutations are temperature sensitive. Seven of 10 probands with a compound heterozygous *TGM1* genotype had a mutation at either arginine 307 or 315, providing evidence that mutations at these sites are temperature sensitive and highlighting the importance of these residues in the pathogenesis of BSI.

CONCLUSIONS AND RELEVANCE Our findings expand the genotypic spectrum of BSI and the understanding of temperature sensitivity of *TGM1* mutations. Increased awareness of temperature-sensitive *TGM1* genotypes should aid in genetic counseling and provide insights into the pathophysiology of *TGM1* ichthyoses, transglutaminase-1 enzymatic activity, and potential therapeutic approaches.

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Autosomal recessive congenital ichthyosis (ARCI) is a heterogeneous group of disorders of keratinization linked by the common finding of generalized hyperkeratosis and often accompanied by erythroderma. ARCI is rare, with an incidence of approximately 1 in 200 000 births.¹

The major phenotypic subtypes of ARCI include lamellar ichthyosis (LI), congenital ichthyosiform erythroderma, and harlequin ichthyosis. While ARCI is genetically heterogeneous, with at least 9 different genes causative for the most common forms,² approximately 30% of the heritability of ARCI is explained by mutations in the *TGMI* gene,³ which encodes transglutaminase-1 (TGase-1), an enzyme involved in the formation of the cornified envelope.⁴

While mutations in *TGMI* most commonly cause a spectrum of LI and congenital ichthyosiform erythroderma phenotypes of varying severity, they also underlie bathing suit ichthyosis (BSI), a very rare form of ARCI with fewer than 40 reported cases characterized by lamellar scaling restricted primarily to the trunk, neck and scalp. Affected infants are typically born as collodion babies and develop more localized scaling after shedding of the membrane. Bathing suit ichthyosis is due to the temperature sensitivity of certain *TGMI* mutations.⁵ Clear genotype-phenotype correlations have been difficult to establish owing to the rarity of BSI and because many of the BSI mutations have also been reported in individuals with more generalized forms of ARCI. The present study of 16 individuals from 13 kindreds expands the spectrum of *TGMI* mutations known to occur in patients with BSI and the understanding of mutations related to temperature sensitivity.

Methods

Participants and Samples

The study was approved by the Yale human investigation committee, consistent with the Declaration of Helsinki guidelines, and written informed consent was provided by all 16 participants (7 male and 9 female; mean age, 12.6 years; range, 1-39 years) or their parents. A detailed clinical history was obtained from each participant, including phenotypic presentation at birth and evolution of disease when available. Self-reporting of ethnicity was obtained to evaluate for a founder effect. Saliva samples were obtained from all participants for genetic analysis.

Genetic Analysis

Genetic analysis was performed on DNA isolated from the saliva of participants and both parents, if available. The DNA was extracted using standard procedures. Samples were analyzed in 1 of 2 ways: (1) they were screened for mutations in 11 genes (*ABCA12*, *ALOXE3*, *ALOX12B*, *CYP4F22*, *NIPAL4*, *PNPLA1*, *SPINK5*, *TGMI*, *KRT1*, *KRT2E*, and *KRT10*) via multiplex polymerase chain reaction and next-generation sequencing; or (2) the coding exons of *TGMI* were amplified using polymerase chain reaction and subsequently examined via Sanger sequencing.

Results

The BSI phenotypes and *TGMI* genotypes of each participant are summarized in the Table. Representative photographs are pro-

Key Points

Question Can targeted sequencing of 13 kindreds with bathing suit ichthyosis (BSI) reveal novel mutations and provide evidence of temperature sensitivity of specific *TGMI* mutations?

Findings We report 1 novel *TGMI* indel mutation (Ile469_Cys471delinsMetLeu) and 8 *TGMI* missense mutations that have not been previously found in BSI: 5 have been previously described in non-temperature-sensitive forms of congenital ichthyosis, and 3 are novel mutations. We also provide evidence for temperature sensitivity of Arg264Trp, Arg286Gln, Arg307Gly, Arg315Leu, Arg315His, and Phe495Leu, highlighting the importance of these residues in the pathogenesis of BSI.

Meaning Our findings expand the genotypic spectrum of BSI.

vided in Figure 1 (patients 8 and 15), and the locations of the mutations relative to *TGMI* protein domains are shown in Figure 2.

Homozygous *TGMI* Mutations and Temperature Sensitivity: Arg264Trp, Arg286Gln, and Arg315Leu *TGMI* Mutations in BSI

Patient 1 was the child of first cousins. He was born with a collodion membrane and later developed large brown scales on the back, chest, and groin, with sparing of the face and extremities. He was homozygous for a *TGMI* Arg286Gln missense mutation, which has been previously reported in a compound heterozygous state with Gly278Arg in LI⁶ (and also found in patient 9), but to our knowledge has not been previously reported in BSI.

Patients 2 and 3 were siblings and the children of second cousins. Both were born with normal skin at birth and no collodion membrane and went on to develop platelike scale restricted to the neck, scalp, trunk, and flexural areas of the upper extremities. Nonscarring alopecia was present in both patients, and both siblings were homozygous for a *TGMI* Arg264Trp missense mutation, which has previously been found in a compound heterozygous state in a patient with BSI.⁵ It was also found in a heterozygous state in patient 4, a female with *TGMI* mutations Arg264Trp and Gly278Arg. The Gly278Arg mutation has been previously described in both LI⁶ and in self-healing ichthyosis, a rare form of ARCI characterized by the presence of a collodion membrane at birth with spontaneous healing of the phenotype within the first few weeks.^{7,8}

Patients 5 and 6 were African American siblings with no known consanguinity in the family. Both were born with a collodion membrane and later developed platelike scale restricted to the scalp and trunk. They were both homozygous for a *TGMI* Arg315Leu mutation, which has been reported in a cohort of 8 South African patients with BSI.^{9,10}

The observation of homozygous mutations in these 5 patients with BSI provides evidence that these *TGMI* mutations (Arg264Trp, Arg286Gln, and Arg315Leu) occurred with temperature sensitivity. All fall within the catalytic core of the transglutaminase-1 enzyme (Figure 2).

Temperature-Sensitive Substitutions at R315 *TGMI*: Common Compound Heterozygous Mutations in BSI

Patients 7 and 8 were siblings. Both were born with a collodion membrane and were noted to have thickened, fragile skin

Table. *TGM1* Mutations in Patients With BSI

Patient No./Sex/Age, y	Ethnicity	Presentation at Birth	Study Presentation ^a				Zygoty	Mutation in Coding DNA	Protein Effect ^b
			Scalp	Neck	Trunk	Extremities			
1/M/4	Middle Eastern	Collodion membrane	o	x	x	o	HOM	c.857 G>A	Arg286Gln ^c
2/F/37	Middle Eastern	Normal skin at birth, no collodion membrane	x	x	x	x (Flexural)	HOM	c.790 C>T	Arg264Trp
3/F/32	Middle Eastern	Normal skin at birth, no collodion membrane	x	x	x	x (Flexural)	HOM	c.790 C>T	Arg264Trp
4/F/39	White	Collodion membrane	x	x	x	o	HET	c.790 C>T c.832G>A	Arg264Trp Gly278Arg ^c
5/M/4	African American	Collodion membrane, thickened skin	x	o	x	o	HOM	c.944 G>T	Arg315Leu
6/F/9	African American	Collodion membrane, thickened skin	x	o	x	o	HOM	c.944 G>T	Arg315Leu
7/F/11	African American	Collodion membrane, thickened, fragile skin	x	x	x	x (Very mild)	HET	c.944 G>T c.2316 C>A	Arg315Leu Ser772Arg ^{c,d}
8/M/8	African American	Collodion membrane, thickened, fragile skin	x	x	x	x (Mild)	HET	c.944 G>T c.2316 C>A	Arg315Leu Ser772Arg ^{c,d}
9/M/8	Turkish	Collodion membrane, ectropion as a neonate	x	x	x	x (Flexural)	HET	c.944 G>A c.832G>A	Arg315His Gly278Arg ^c
10/M/1	White	Collodion membrane, thickened skin	x	o	x	o	HET	c.944 G>A c.876 + 2 t > C	Arg315His splice site
11/F/4	Irish	Collodion membrane	x	x	x	o	HET	c.919 C>G c.877-2 A>G	Arg307Gly splice site
12/M/21	Hispanic	Collodion membrane	x	x	x	o	HET	c.919 C>G c.652 G>A	Arg307Gly Gly218Ser ^c
13/F/9	Northern European	Collodion membrane	x	x	x	o	HET	c.919 C>G c.1074 C>G	Arg307Gly Ser358Arg ^c
14/F/1	White	Collodion membrane, thickened, fragile skin	x	o	x	o	HET	c.919 C>G c.1121 A>G	Arg307Gly Tyr374Cys ^{c,d}
15/M/13	White	Collodion membrane	x	x	x	x (Flexural)	HET	c.427 C>T c.1483 t > C	Arg143Cys ^c Phe495Leu ^{c,d}
16/F/1	White	Collodion membrane	x	x	x	o	HET	c.872 G>A c.1407_1416del10ins GCTCTGT	Gly291Asp I469_C471 delinsML ^{c,d}

Abbreviations: BSI, bathing suit ichthyosis; HET, heterozygous; HOM, homozygous; o, absence of scaling; x, presence of scaling.

^a No patient had facial involvement.

^b Boldface indicates temperature-sensitive mutations.

^c Mutations not previously found in BSI.

^d Novel mutations.

at birth. They developed dark platelike scaling, most prominent on the back, chest, and neck. Both were compound heterozygous for *TGM1* Arg315Leu, a temperature-sensitive mutation, and Ser772Arg, a novel mutation falling within the β -barrel 2 domain (Figure 2).

Patient 9 was born with a collodion membrane and ectropion. At the time of the study he had brown platelike scales most prominent on the neck, scalp, and trunk, with sparing of the face and the extremities. He also exhibited attention-deficit/hyperactivity disorder and developmental delay. He was compound heterozygous for *TGM1* (Arg315His and Gly278Arg). While both mutations fall within the catalytic core, Arg315His affects the same residue as Arg315Leu (found in patients 5-8) and has been commonly reported in patients with BSI.^{5,11} The Gly278Arg mutation was also found in patient 4.

Patient 10 was born with a collodion membrane and later developed scaling restricted to the scalp and trunk. He had *TGM1* mutations Arg315His and c.876 + 2 T > C, a mutation within the donor splice site of exon 5 previously described in generalized ARCI.¹²

The observation of a missense mutation at R315 in 6 of the 16 participants highlights the prevalence of substitutions at this

site in BSI and contributes to evidence that such mutations are temperature sensitive.

Temperature-Sensitive *TGM1* Arg307Gly: A Common BSI Mutation

Patient 11 was born with a collodion membrane that peeled at a few weeks of age, and she developed thick dark scale on the scalp, neck, axillae, and groin by age 1 year. She was compound heterozygous for *TGM1* Arg307Gly, which has been commonly described in BSI,^{5,11} and c.877-2 A>G, a mutation within the acceptor splice site of exon 6, which has previously been found in BSI in conjunction with Arg307Gly (as in patient 11) as well as with Arg264Trp and Arg315His in the present cohort.^{5,11}

Patient 12 was born with a collodion membrane. At the time of the study he had brown platelike scales most prominent on the neck, scalp, axillae, and trunk. He was compound heterozygous for *TGM1* Gly218Ser and Arg307Gly. The Gly218Ser mutation has been previously reported in an individual with LI with a collodion membrane at birth and later development of thick scales and ectropion.¹³

Patient 13 was born with a collodion membrane. At the time of the study she had thick dark scale restricted to the neck,

Figure 1. Clinical Features of Bathing Suit Ichthyosis (BSI)



Representative photographs of the BSI phenotype, notable for platelike scaling of the trunk and back, with sparing of the extremities and buttocks.

scalp, and trunk. She had *TGM1* mutations Arg307Gly and Ser358Arg. The Ser358Arg mutation has been previously reported in 2 siblings with LI who were born with collodion membranes and later developed generalized scaling with facial and palmoplantar involvement.^{14,15}

Patient 14 was born with a collodion membrane and later developed scaling restricted to the trunk and scalp. She had *TGM1* mutations Arg307Gly and Tyr374Cys. The Tyr374Cys mutation was within the catalytic domain and to our knowledge has not been described previously.

The observation of the Arg307Gly mutation in 4 out of the 16 study participants contributes to evidence that Arg307Gly is relatively common in BSI and is a temperature-sensitive mutation.

***TGM1* Phe495Leu: A Temperature-Sensitive Mutation**

Patient 15 was born with a collodion membrane. At the time of the study he had thick scale restricted to the neck, scalp, and trunk, as well as flexural involvement of the extremities. He has *TGM1* mutations Arg143Cys and Phe495Leu. Homozygosity for the Arg143Cys mutation has been previously described in 2 patients with LI.¹³ We therefore pre-

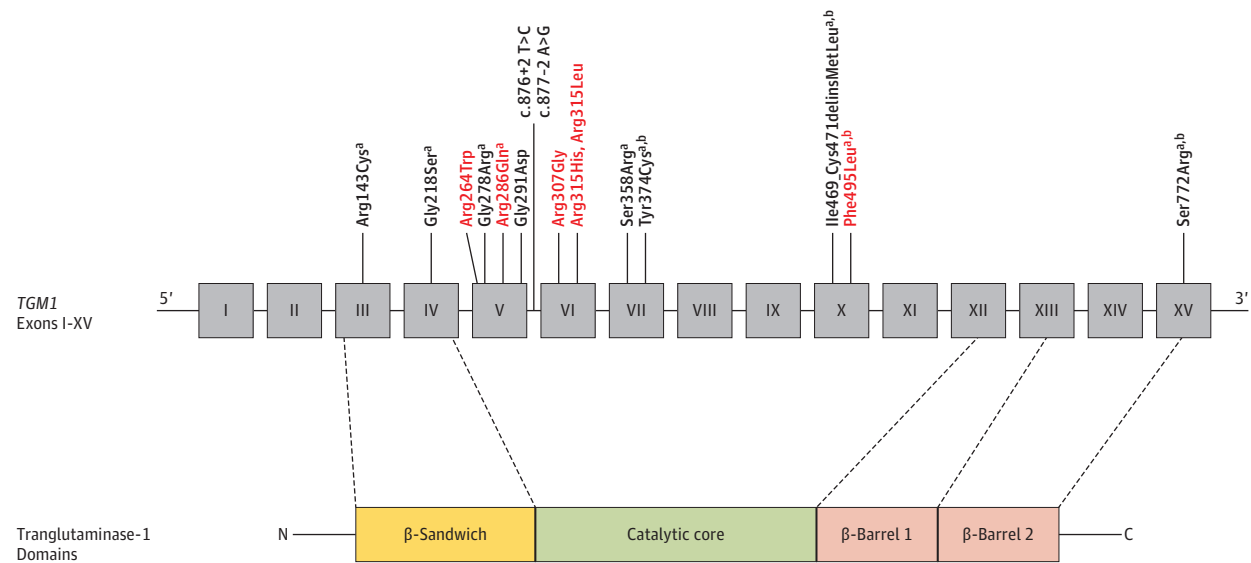
sume that Phe495Leu, which is novel, is the temperature-sensitive mutation in patient 15.

***TGM1* Ile469_Cys471delinsMetLeu: A Novel Mutation in the Catalytic Core**

Patient 16 was born with a collodion membrane. At the time of the study she had scale restricted to the neck, scalp, and trunk. She had *TGM1* mutations Gly291Asp and Ile469_Cys471delinsMetLeu. The Gly291Asp mutation was previously described in a compound heterozygous state in a patient with BSI¹⁶ as well as in a patient with generalized ARCI.¹⁷ The *TGM1* Ile469_Cys471delinsMetLeu is a novel in-frame indel mutation that affects the catalytic core.

Discussion

Bathing suit ichthyosis is a rare ARCI phenotype characterized by presentation at birth with a collodion membrane followed by clinical improvement of ichthyosis on the face and extremities during the first few weeks of life. The resulting phenotype of scaling restricted to the trunk, neck, and scalp is a

Figure 2. Protein Schematic of *TGM1* Mutations Found in Bathing Suit Ichthyosis (BSI)

Thirteen mutations are located in the catalytic core, 2 in the β -sandwich domain, and 1 in the β -barrel 2 domain. Nine mutations lead to substitution of charged residues. Temperature-sensitive mutations are shown in red.

^a Mutations not previously described in BSI.

^b Novel mutations.

distinguishing feature of BSI and can be differentiated from somatic mosaicism by the lack of a distribution pattern along the Blaschko lines.

Prior to the present report, 21 missense mutations had been reported in patients with BSI. Of these, 9 had been reported exclusively in patients with BSI, while 12 had been observed in both BSI and generalized ARCI.¹⁸ Both truncating mutations (nonsense, splice site, and frameshift) and missense mutations in *TGM1* have been found in individuals with BSI.^{5,9,11,16,18,19} However, while homozygosity or compound heterozygosity for truncating mutations has been observed in generalized forms of ARCI,^{14,20,21} to our knowledge, such a genotype has never been observed in BSI. This is consistent with the hypothesis that near or total loss of TGase-1 function causes generalized forms of ARCI, while genotypes that include a missense mutation resulting in a partially active, temperature-sensitive TGase-1 result in the more limited BSI phenotype.

In 2006, Oji et al⁵ investigated TGase-1 enzymatic activity in BSI tissue, assessing uptake of biotinylated cadaverine into cornified envelopes, and found that areas of healthy skin in patients with BSI show nearly normal TGase-1 activity, while affected areas display clearly reduced and abnormal activity. Furthermore, digital thermal imaging showed close association between skin temperature and the degree of scaling in patients with BSI, with warmer body sites exhibiting greater scaling. Functional TGase-1 testing of normal-appearing skin of a patient with BSI and homozygous for the missense mutation Tyr276Asn showed clear temperature sensitivity, with reduction in enzyme activity at 37°C compared with 25°C. This may explain the increased degree of scaling at sites of relatively higher temperature, such as the trunk.⁵

In addition to the *TGM1* mutation Tyr276Asn, several other mutations have been previously presumed to be temperature

sensitive based on their presence in a homozygous state in individuals with BSI, including *TGM1* mutations Ile304Phe, Arg307Gly, Arg315Leu, Arg315His, Val383Met, and Arg687His.^{5,9-11,16,18,22}

In the present study, we report phenotypic and genotypic data from 16 patients with BSI, the largest known cohort published to date. Aside from a pair of siblings who had normal skin at birth with no collodion membrane (patients 2 and 3), the phenotypes were consistent with prior descriptions of BSI. Of note, while collodion membrane is found in the majority of ARCI due to *TGM1* mutation, this finding is not universal.²³ We identified a total of 16 unique mutations in our cohort, including 13 missense mutations, 2 splice-site mutations, and 1 indel mutation. Eight of the missense mutations have not to our knowledge been previously reported for BSI; of these, 5 have been previously described in generalized ARCI (Arg143Cys, Gly218Ser, Gly278Arg, Arg286Gln, and Ser358Arg), while 3 (Tyr374Cys, Phe495Leu, and Ser772Arg) are novel mutations. The indel mutation *TGM1* I469_C471delinsML is also novel.

Transglutaminase-1 consists of 3 domains: an N-terminal β -sandwich domain, a catalytic core domain, and 2 C-terminal β -barrel domains.²⁴ Most BSI mutations have been located in exons 5 and 6 of *TGM1*, encoding the N-terminal portion of the catalytic core domain.⁵ Of the 13 unique missense mutations reported in the present study, only 2 were within the β -sandwich domain (Arg143Cys and Gly218Ser) and 1 was within the β -barrel 2 domain (Ser772Arg). In stark contrast, 10 were within the catalytic core (Arg264Trp, Gly278Arg, Arg286Gln, Gly291Asp, Arg307Gly, Arg315His, Arg315Leu, Ser358Arg, Tyr374Cys, and Phe495Leu), including all 3 of the mutations in our homozygous participants (Figure 2). All of our participants had at least 1 mutation within the catalytic core,

and catalytic core mutations represent 88% of the mutations in our unrelated probands (23 of 26 alleles). Given that the catalytic core is only 38% of the total protein, our findings underscore a striking clustering of BSI mutations in this domain.

Based on our observation of patients with BSI homozygous for *TGMI* mutations Arg264Trp, Arg286Gln, and Arg315Leu, we conclude that these mutations are temperature sensitive. Furthermore, the recurrence of mutations affecting R307 and R315 in our cohort—which among unrelated probands are present in one-third of homozygotes and seven-tenths of compound heterozygotes, comprising 35% of the mutations (9 of 26 total alleles)—bolsters prior evidence that these mutations are common in BSI (also reported by Bourrat et al¹¹) and that they are temperature sensitive. Finally, we hypothesize that the novel mutation Phe495Leu is also temperature sensitive, given that the *TGMI* genotype of patient 15 included this mutation along with Arg143Cys. The Arg143Cys mutation is presumably not temperature sensitive, given that patients homozygous for Arg143Cys have been described as exhibiting generalized LI.¹³

Though our findings provide evidence for temperature sensitivity of *TGMI* mutations, clear genotype-phenotype correlations have been difficult to establish because several *TGMI* mutations have been reported in both BSI and generalized ARCI. For example, homozygosity for Arg315Leu has been found in a pair of twins who were described as having LI and whose phenotype at age 2 months included thick platelike scaling on the trunk and extremities but sparing the face.²⁵ Another patient described as having characteristic phenotypic findings of LI was found to be compound heterozygous for *TGMI* mutations, including Arg286Gln,⁶ which we describe here as temperature sensitive.

The presence of these mutations in both BSI and generalized ARCI may represent evolution of the phenotype; patients with BSI can present with more generalized scaling ear-

lier in life and then manifest bathing-suit distribution later in childhood. Thus, phenotypic characterization within the first few months of life may lead to misclassification. This dynamic nature of BSI highlights the importance of continued follow-up of patients with presumed temperature-sensitive mutations, including phenotypic reevaluation at multiple ages. Additional environmental or genetic factors that may determine the level of enzyme activity and response to temperature in patients with *TGMI* mutations remain unclear.

Patients with BSI typically respond well to agents that improve barrier function and promote desquamation, including keratolytics and topical or systemic retinoids. Topical tazarotene led to substantial improvement in 2 of the present study participants.

Limitations

Since BSI is such a rare disorder, we were unable to recruit a large enough cohort to identify additional genetic modifiers that may contribute to temperature sensitivity in BSI due to *TGMI* mutations.

Conclusions

Our findings expand the genotypic spectrum of BSI and provide evidence supporting the temperature sensitivity of specific *TGMI* mutations (Arg264Trp, Arg286Gln, Arg307Gly, Arg315Leu, Arg315His, and Phe495Leu), which are clustered in the catalytic core. Although patients respond well to topical and systemic therapies, further research into the pathogenesis of BSI could lead to the development of novel therapeutic approaches targeting enzymatic stability and consideration of environmental modifications that might modify disease severity.

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NOTABLE NOTES

Tinea in the Time Before Modern Antifungal Agents

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Modernity enjoys a broad and effective arsenal against superficial mycoses. However, the history of social stigma attached to dermatophyte infections, their unusual and often harmful treatments, and the controversial public health efforts designed to limit their spread before the discovery of safe and efficacious antifungal agents is worthy of reflection.

Tinea capitis and corporis were major public health challenges prior to the introduction of oral griseofulvin in 1958. Crowded classrooms were an efficient venue for transmission. In an attempt to mitigate exposure to their classmates, students infected with tinea were excluded from schooling until cured; they fell behind in their education, prompting the creation of special schools where they were able to continue their lessons and receive treatment while being isolated from uninfected children.¹

Therapies for tinea ranged from relatively harmless to downright toxic and included copper coins soaked in vinegar, writing ink, creosote, mercury, carbolic acid, and cantharides. However, that fungal infections of the scalp represented a greater challenge for treatment vs those of the body.² Epilation for treatment of tinea capitis was a common practice, with the rationale being that it simultaneously removed the nidus of infection and increased the penetrance of topical therapies.^{1,2}

In 1904 French dermatologist Raymond Sabouraud popularized the use of radiographic epilation for treatment of tinea capitis, which offered greater efficacy, reduced cost, and less discomfort than the chemical and mechanical methods of epilation available at the time but required having patients sit still for periods as long as 40 minutes while exposed to multiple overlapping fields of radiation.¹

Despite concerns regarding the long-term effects of directing radiation toward children's heads for extended periods of time, radiographic epilation remained a mainstay of treatment until the arrival of griseofulvin in 1958.^{1,3} Numerous reports have described adverse long-term effects associated with radiation therapy for tinea capitis, including permanent hair loss and cancers of the skin, brain, and thyroid.³

Before the discovery of modern antifungal agents, simple dermatophyte infections represented major barriers to education and social acceptance. Patients often underwent treatments more physically harmful than the diseases themselves. The history of tinea corporis and capitis highlights the cultural significance of skin disease throughout the ages and reminds us of the value of the relatively safe and efficacious antimycotic therapeutics available today.

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