

Bathing-suit ichthyosis: A rare but valuable entity for developing personalised pathogenesis-based therapies for autosomal recessive congenital ichthyosis

Dear Editor,

'Bathing-suit' ichthyosis (BSI) is a rare and mild form of autosomal recessive congenital ichthyosis (ARCI), clinically characterised by a restricted distribution of dark adherent skin scales.¹ *In-situ* and *in-vitro* studies, complemented with digital thermal imaging, deduced that BSI is caused by pathogenic variants in the *TGMI* (transglutaminase-1) gene that decrease the thermostability of the encoded enzyme, particularly at warmer regions of the body.^{1,2} However, such phenotype-genotype correlations are not always straightforward, as the same pathogenic variants can cause other severe ARCI forms, including a dynamic shift from the BSI phenotype over time and *vice-versa*.³ Nevertheless, in the context of incurable diseases like ARCI, identifying naturally occurring mild phenotypes and delving deeper into their underlying molecular mechanisms might provide innovative leads for the development of affordable and indigenous therapeutics. In countries like India, where research studies are largely limited to academic institutions, developing such patient cohorts is challenging due to limited awareness, expertise, financial constraints, and patients with mild phenotypes rarely availing of medical services. Towards this, we wish to report a genetically characterised BSI patient identified at a dermatology outpatient clinic through our collaborative genomics program and provide additional insights that could improve our current understanding of BSI pathogenesis.

A 14-year-old boy, born of consanguineous marriage, was referred to us for genetic evaluation with a provisional diagnosis of mild ARCI and a history of collodion membrane at birth. After obtaining informed consent, whole exome sequencing was performed.⁴ Variant analysis revealed a homozygous 'likely-pathogenic' missense variant in the *TGMI* gene (NM_000359.3: exon3:c.391A>G; p.Thr131Ala). This variant was predicted to be deleterious by *in-silico* softwares, absent in publicly available population databases, including

the Indian population, and was previously reported only once in an Asian patient with an unclassified ARCI phenotype.⁵ No other 'pathogenic' variants were identified in any other known ARCI genes. Clinical re-evaluation of our patient revealed the presence of dark adherent scales restricted to the trunk and neck, with distinct sparing of the face and extremities, confirming a characteristic BSI phenotype [Figure 1]. Further, sanger validation along with family segregation analysis confirmed an autosomal recessive inheritance, and the patient was referred for genetic counselling and enrolled in a follow-up study to understand molecular consequences of the identified variant.

Literature analysis revealed that only 72 genetically characterised BSI patients were reported worldwide, a majority of whom had unique combinations of compound heterozygous *TGMI* pathogenic variants, particularly involving 'arginine' substitutions in at least one allele (85%,



Figure 1: Dark adherent scales on the trunk and neck along with sparing of face and extremities.

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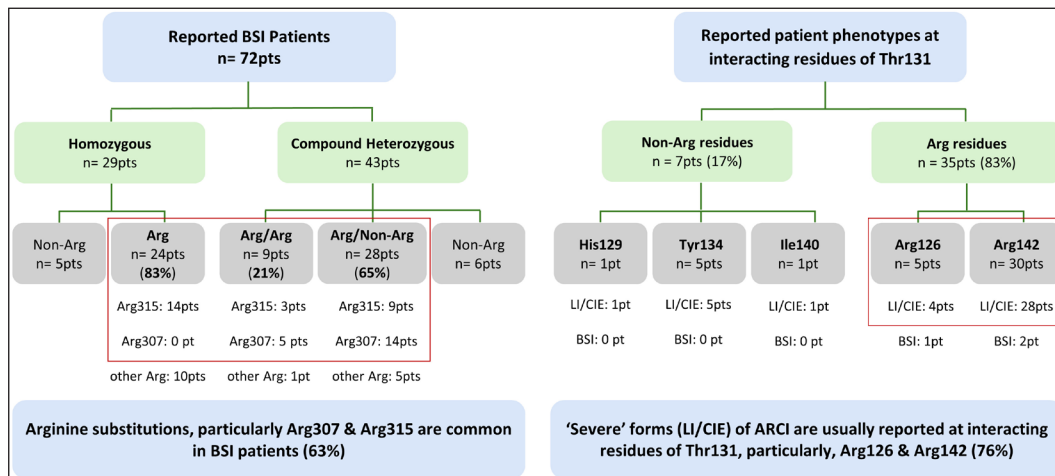


Figure 2: Trends in genotypic alterations in previously reported BSI patients and reported phenotypes associated with the interacting partners of Thr131 (mutated residue in our patient), primarily involving severe forms like lamellar ichthyosis (LI) and congenital ichthyosiform erythroderma (CIE).

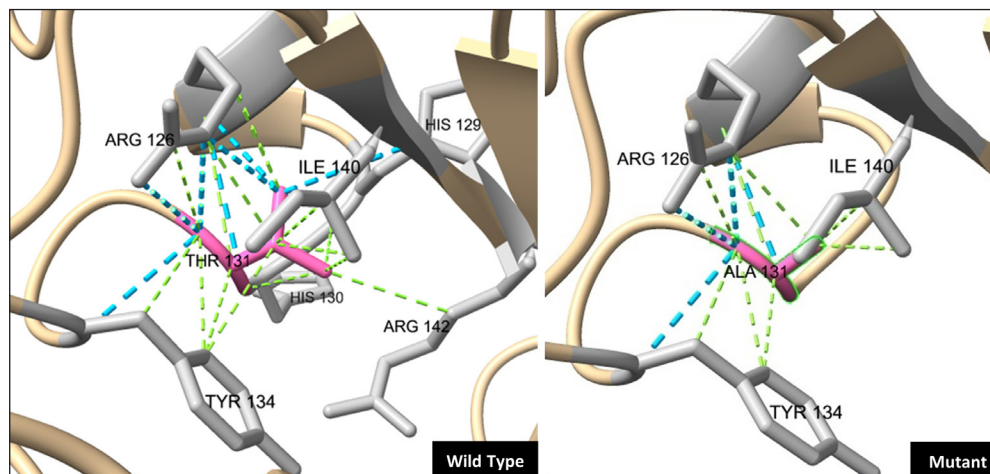


Figure 3: The computational wild-type *TGM1* protein model from Google AlphaFold (ID: P22735), was utilised as a template to generate a mutant protein model (with the p.Thr131Ala variant) and to study interacting partners using the in-built mutagenesis and structure analysis features of the UCSF ChimeraX tool (v1.6.1, <https://www.rbvi.ucsf.edu/chimerax>). The crucial interacting residues (in grey) are shown as ball and stick and the stabilising contacts (Hydrogen and Van der Waals bonds) are shown as blue and green dotted lines, respectively.

n = 61/72), notably at Arg307 and Arg315 (63%, n = 45/72) residues in the catalytic core domain [Figure 2]. Contrary to this general trend, our patient showed a homozygous 'threonine' substitution (Thr131Ala) within the beta-sandwich domain (crucial for protein folding and enzyme stability), adding to the growing list of non-arginine substitutions responsible for the BSI phenotype. Structurally, Thr131 is a highly conserved hydrophilic, polar residue that forms protein-stabilising contacts at the domain interface, like hydrogen bonds (with Arg126, Tyr134, and Ile140) and Van der Waals interactions (with Arg126, His129, His130, Tyr134, Ile140, and Arg142), involving surrounding residues. Substitution of Thr131 with 'alanine' (a hydrophobic, non-polar residue with a compact side chain) disrupts these stabilising contacts, particularly with Arg142, resulting in an altered surface loop that is susceptible to abnormal protein folding and increased proteolytic cleavage [Figure 3]. Although the lack of *TGM1*

enzyme studies preclude us from ascertaining functional significance to the identified variant, such preliminary findings about structural consequences coupled with previous literature evidence shows that severe ARCI phenotypes are more likely to occur due to alterations at these interacting residues [Figure 2].⁶ This raises the question whether the BSI phenotype noted in our patient was an unlikely event.

Given that a majority of BSI-causing *TGM1* variants involve arginine residues at CpG sites and/or NCG-GNN consensus motif,^{3,6} it is plausible that epigenetic regulatory mechanisms like methylation/demethylation (reported to regulate *TGM1* expression⁷) processes might indeed be playing a dominant role in BSI pathogenesis, in addition to reduced thermostability. Bisulfite sequencing using patient skin biopsies from affected and unaffected regions might help in discovering unique molecular signatures, if any. While these

studies are planned in our patient, herein we wish to highlight the importance of identifying such naturally occurring mild phenotypes through collaborative genomics programs. Rapid advances in genomic technologies are enabling us to address complex questions beyond the regular phenotype-genotype correlations, and making them accessible might benefit the development of indigenous pathogenesis-based therapies for incurable diseases like ARCI.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent.

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**Siddhi Tandon^{1,2*}, Sharath Chandra Konda^{3*},
Ramya Kola⁴, Divya Tej Sowpati⁴, Karthik Bharadwaj
Tallapaka⁴, Vamsi Krishna Yenamandra^{1,2}**

¹Division of Disease Biology, CSIR-Institute of Genomics & Integrative Biology, New Delhi, ²Academy of Scientific and Innovative Research, Ghaziabad, ³Department of Dermatology, SVS Medical College, Mahabubnagar, ⁴Division of Genomics & Epigenetic Regulation, CSIR-Centre for Cellular & Molecular Biology, Hyderabad, India,
*contributed equally

Corresponding author:

Dr. Vamsi Krishna Yenamandra,
Division of Disease Biology, CSIR-Institute of Genomics & Integrative Biology, New Delhi, India; Academy of Scientific and Innovative Research, Ghaziabad, India.
vamsi.krishna@igib.res.in

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