Specific TGM1 Mutation Profiles in Bathing Suit and Self-Improving Collodion Ichthyoses

Phenotypic and Genotypic Data From 9 Patients With Dynamic Phenotypes of Autosomal Recessive Congenital Ichthyosis

Emmanuelle Bourrat, MD; Claudine Blanchet-Bardon, MD; Celine Derbois, MD; Susan Cure, PhD; Judith Fischer, MD, PhD

Background: Bathing suit ichthyosis (BSI) and self-improving collodion ichthyosis (SICI) are 2 minor variants of generalized autosomal recessive congenital ichthyosis. Bathing suit ichthyosis is characterized by scaling of the skin in a bathing suit pattern, mainly limited to the trunk, whereas SICI is characterized by complete disappearance of the skin lesions.

Observations: We report genotypic and phenotypic data from a series of 9 patients who were collodion babies and developed BSI or SICI owing to mutations in the transglutaminase-1 gene (TGM1), including 3 previously unreported missense mutations. All of our patients with BSI or SICI carried at least 1 specific missense mutation in TGM1 concerning an arginine at position 307 or 315. In 2 patients, the disease evolved (BSI to SICI or BSI to autosomal recessive congenital ichthyosis). The remaining 7 patients exhibited a stable BSI phenotype after shedding of the collodion membrane.

Conclusions: This study highlights the possibility of variable evolution of the phenotype of patients with identical mutations in the same gene. Combined with data from the literature, these findings confirm the hypothesis that only a restricted spectrum of TGM1 mutations leads to a BSI and/or an SICI phenotype. This phenotypic variability also depends on other genetic and external factors.


Author Affiliations:
Department of Dermatology, Hôpital Saint-Louis, Paris, France (Drs Bourrat and Blanchet-Bardon); Centre Nationale de Génotypage (Drs Derbois and Fischer) and Centre Nationale de Séquencage, Genoscope (Dr Cure), Commissariat à l’Energie Atomique, Institut de Génomique, Evry, France; and Institute for Human Genetics, University Medical Center Freiburg, Freiburg, Germany (Dr Fischer).
Table. Phenotypes and Genotypes in BSI

<table>
<thead>
<tr>
<th>Patient</th>
<th>Phenotype Progression</th>
<th>Type of Ichthyosis</th>
<th>Treatment</th>
<th>Follow-up, y</th>
<th>PPK</th>
<th>Mutation in Complementary DNA</th>
<th>Effect on Protein</th>
<th>Exon</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F</td>
<td>5/M CB to BSI</td>
<td>Erythema: none, fine pigmented scales</td>
<td>Acitretin</td>
<td>18</td>
<td>Mild</td>
<td>c.944G&gt;A and c.944G&gt;A</td>
<td>p.Arg315His and p.Arg315His</td>
<td>6 and 6</td>
</tr>
<tr>
<td>2/F</td>
<td>6/M CB to BSI</td>
<td>Mild ichthyosis</td>
<td>Topical</td>
<td>7</td>
<td>None</td>
<td>c.1451T&gt;C and c.1451T&gt;C</td>
<td>p.Leu484Pro and p.Leu484Pro</td>
<td>10 and 10</td>
</tr>
<tr>
<td>3/F</td>
<td>7/F CB to BSI</td>
<td>Erythema: slight, fine pigmented scales</td>
<td>Acitretin</td>
<td>19</td>
<td>Mild</td>
<td>c.944G&gt;A and c.944G&gt;A</td>
<td>p.Arg315His and p.Arg315His</td>
<td>6 and 6</td>
</tr>
<tr>
<td>4/F</td>
<td>8/F CB to BSI</td>
<td>Erythema: slight, fine large scales</td>
<td>Acitretin</td>
<td>12</td>
<td>Mild</td>
<td>c.944G&gt;A and c.944G&gt;A</td>
<td>p.Arg315His and p.Arg315His</td>
<td>6 and 6</td>
</tr>
<tr>
<td>5/F</td>
<td>9/F CB to BSI</td>
<td>Lamellar</td>
<td>Acitretin</td>
<td>20</td>
<td>ND</td>
<td>c.944G&gt;A and c.944G&gt;A</td>
<td>p.Arg315His and p.Arg315His</td>
<td>6 and 6</td>
</tr>
<tr>
<td>6/F</td>
<td>10/F CB to BSI</td>
<td>Lamellar</td>
<td>Acitretin</td>
<td>4</td>
<td>Mild</td>
<td>c.944G&gt;A and c.944G&gt;A</td>
<td>p.Arg315His and p.Arg315His</td>
<td>6 and 6</td>
</tr>
<tr>
<td>7/F</td>
<td>11/F CB to BSI</td>
<td>Lamellar</td>
<td>Acitretin</td>
<td>18</td>
<td>ND</td>
<td>c.944G&gt;A and c.944G&gt;A</td>
<td>p.Arg315His and p.Arg315His</td>
<td>6 and 6</td>
</tr>
</tbody>
</table>

Abbreviations: ARCI, autosomal recessive congenital ichthyosis; BSI, bathing suit ichthyosis; CB, collodion baby; ND, no data; PPK, palmoplantar keratoderma; SICI, self-improving collodion ichthyosis.

a Indicates before treatment.

b This sibling has generalized ARCI and therefore is not counted as a patient with BSI.

tients with BSI. Two of our patients presented with disease progression in the following 2 phases: an initial BSI phenotype followed by evolution toward an SICI phenotype before 12 months of age in one case (patient 9) and toward a generalized ARCI starting at 12 years of age in the other case (patient 7). The other patients developed a stable BSI phenotype after shedding of the colloid membrane.

RESULTS

Nine patients (4 boys and 5 girls) from 8 families (patients 5 and 6 were brothers) presented with a BSI phenotype a few months after birth. Only patient 1 was from a consanguineous family. The sister of patient 7 was a CB at birth, but the condition progressed directly to generalized ARCI without any specific features of BSI (Table).

PHENOTYPIC DATA

Our phenotypic data are comparable with observations from the literature. All patients were CBs, and the disorder progressed toward a BSI phenotype in a few months, when they were only treated locally with emollients (Table). The BSI phenotype persisted in 7 patients (follow-up ranged from 4 to 28 years), whereas patient 7, a girl who underwent nonsystemic keratolytic treatment since 2 years of age, experienced reversion to a generalized ARCI phenotype at puberty in parallel with the development of obesity. Patient 9 had a typical BSI phenotype at 6 months of age, then was examined at 17 years of age with completely normal skin and thus classified as having SICI retrospectively (Figure 1). The complete disappearance of ichthyosis occurred before 1 year of age according to the parents.

SEQUENCING DATA TABLE

Eight of our patients carried compound heterozygous mutations in TGM1, whereas patient 1 from the consan-
guineous family was homozygous (Figure 2). Nine different mutations of TGM1 were identified. Six of these mutations have been reported before, whereas 3 of the mutations are novel. The novel mutations constitute missense mutations, each of which was only found in 1 patient, that is, p.Leu484Pro (patient 7), p.Gly524Asp (patient 4), and p.Gly524Ser (patient 8). Every BSI patient carried at least 1 missense mutation that replaced an arginine at position 307 or 315.

We herein describe 9 patients with TGM1 mutations and a dynamic ARCI phenotype, including 8 with BSI and 1 with BSI followed by SICI. In 2 patients, progression of the disease occurred in 2 phases. Until 12 years of age, patient 7 exhibited a BSI phenotype that evolved toward a generalized ARCI phenotype in parallel with the development of obesity. This secondary progression toward a generalization of the ichthyosis has already been reported once in the literature in 2 brothers. Family 7 had an intrafamilial discordance because the younger sister of patient 7 developed a generalized ARCI phenotype within the first month of her life, and this phenotype persisted for the duration of follow-up (20 years). Patient 9 was examined at 1 and 3 weeks of age, when he exhibited a BSI phenotype (Figure 1C), but he was completely free of ichthyosis symptoms at 1 year of age, and his status remained stable. Patient 9 was examined again at 19 years of age with a strictly normal skin, not

Figure 1. Typical bathing suit ichthyosis (BSI) phenotypes in 2 patients. Patient 1 at 4 (A) and 6 years of age (B); patient 9 at 3 weeks (C) and 20 years of age (D).

Figure 2. Mutations in our patients with bathing suit ichthyosis (BSI). Schematic presentation of the TGM1 complementary DNA and protein structure include the mutations in our 9 patients with BSI. TGM1 indicates transglutaminase type 1. Adapted from Oji et al.11
dry except for some small scales on the scalp (Figure 1). His diagnosis is therefore SICI with an intermediate BSI phenotype, which has never been reported in the literature, to our knowledge. This lack of reporting could indicate that the condition is rare or that it is unnoticed or not recorded by the physicians because the regression occurs progressively for a few weeks, centripetally from the extremities toward the central part of the body. These dynamic phenotypes in the same patient need to be emphasized because they may explain why the same mutation can be reported in the literature as producing an SICI, a BSI, or a generalized ARCI phenotype.

Bathing suit ichthyosis has always been associated with mutations in TGM1. Twenty-two molecularly characterized cases have been reported to date in the literature,\textsuperscript{11,14-16} in addition to 3 isolated observations under a different nomenclature but with a clinical description that corresponds to the BSI phenotype.\textsuperscript{17,18} The largest ARCI phenotype-genotype correlation study to date included 206 families, of which 104 had mutations in TGM1; none of these patients had a BSI phenotype, indicating a very low frequency for this variant.\textsuperscript{20} Seventeen missense mutations have been reported in BSI patients, to which our 3 new missense mutations must be added. Of these 20 missense mutations, 9 have been reported only in patients with the BSI phenotype, of which 3 have been shown to lead to thermosensitive mutants, and the remaining 11 are common to BSI and ARCI patients. The following 6 of these 20 missense mutations are especially frequent and concern 2 distinct arginine amino acid residues: p.Arg307Gly, p.Arg307Trp, p.Arg315His, p.Arg315Cys, p.Arg315Gly, and p.Arg315Leu, which are all mutations common to BSI and generalized ARCI phenotypes. For example, the p.Arg315Leu mutation, which is the mutation found in the homozygous state in all of the patients in the South African series,\textsuperscript{14,21} has also been reported in the homozygous state in a family with monoyzotic twins with a phenotype of generalized ARCI.\textsuperscript{22} The functional characteristics of the mutated enzyme that is sensitive to atmospheric pressure have been demonstrated for only the p.Asp490Gly mutation, which was reported in the homozygous state in the SICI patient.\textsuperscript{13}

All of our patients harbored at least 1 mutation in an arginine, at position 307 or 315. Two of the second mutations in our compound heterozygous patients (c.877-2A>G and Trp263X) have been described in BSI patients in the same combination with the arginine mutations at positions 307 and 315,\textsuperscript{11} which suggests that these mutations could also have an influence on the determination of the BSI phenotype. The arginine at position 315 in the TGM1 protein is part of a consensus Arg-Gly-Asp tripeptide that may represent part of a functional domain often present in cell adhesion proteins, including fibronectin.\textsuperscript{23}

Self-improving collodion ichthyosis represents another minor variant of ARCI defined by the complete disappearance of the ichthyosis phenotype in the months after the birth of a CB,\textsuperscript{24} an occurrence in 10% of CBs.\textsuperscript{25,26} The SICI phenotype has been reported in association with mutations in TGM1\textsuperscript{13} but also in ALOX12B\textsuperscript{27} and ALOXE3.\textsuperscript{12} Only 4 SICI patients from 3 families have been reported to carry mutations in TGM1.\textsuperscript{12,13} These dynamic clinical variants of ARCI in which the phenotype evolves with age have been explained in certain patients by specific mutations in TGM1 that give rise to a mutant enzyme in which the functional activity is sensitive to the temperature of the skin (BSI phenotype\textsuperscript{11}) or to hydrostatic pressure (SICI phenotype\textsuperscript{12}). Similar findings have been reported in other severe autosomal recessive skin disorders, such as epidermolysis bullosa; spontaneous attenuation of a neonatal dystrophic epidermolysis bullosa has been reported in a 4-year-old Japanese boy.\textsuperscript{28}

The p.Arg307Gly mutation was also found in our SICI patient in the heterozygous state and in another SICI patient in the homozygous state described by Hackett et al.\textsuperscript{15} This mutation, therefore, is common to 3 phenotypes. In keratinocyte cell cultures, Jiang et al.\textsuperscript{29} have recently shown that the TGM1 protein is associated with the endoplasmic reticulum and ultimately delivered to the plasma membrane, the p.Cys377Ala mutation led to the accumulation of the TGM1 protein in the endoplasmic reticulum and the absence of normal trafficking and delivery to the plasma membrane.

In terms of molecular analysis (Table), we are especially interested in the missense mutations, which are more likely than nonsense or splice site mutations to lead to an enzyme that is partially functional. However, the presence of a TGM1 mutation leading to total loss of function is not incompatible with a BSI phenotype (eg, the splice site mutation c.877-2A>G or the nonsense mutation p.Trp263X in Oji et al\textsuperscript{12}).

CONCLUSIONS

The findings on our series of patients favor an ARCI phenotype that evolves over time in certain patients who, beginning with a congenital phenotype of CB, may experience progression toward a stable BSI phenotype, a transitory BSI phenotype with secondary aggravation (return to a generalized ARCI phenotype), or a transitory BSI phenotype with progression to cure (SICI phenotype). The existence of 1 case of intrafamilial phenotypic discordance (one sister with generalized ARCI and the other with BSI) also favors a variable evolving phenotypic spectrum for the same genotype. Finally, certain missense mutations in TGM1 are most often associated with the BSI phenotype, but these same mutations may sometimes be associated with a generalized ARCI or an SICI phenotype in the homozygous or the heterozygous states. This study raises the hypothesis of the existence of modifier genes and/or environmental factors other than temperature and hydrostatic pressure, which could contribute to the extension and severity of the ichthyosis.\textsuperscript{30} The genotype-phenotype correlation has therefore only an imperfect predictive value in terms of the generalized or limited topography of ARCI. These correlations remain indispensable for the comprehension of the pathogenesis of the ichthyosis. Knowledge of the exact pathogenic mechanisms could lead to new therapeutic approaches for TGM1-associated ichthyosis.

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REFERENCES


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