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SHORT COMMUNICATION

Novel *TGM1* Missense Mutation p.Arg727Gln in a Case of Self-healing Collodion Baby

Kana Tanahashi[1], Kazumitsu Sugiura[1], Kenji Asagoe[2], Yumi Aoyama[3], Keiji Iwatsuki[3] and Masashi Akiyama[1]*

*[1]Department of Dermatology, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, 466-8550, [2]Division of Dermatology, National Hospital Organization Okayama Medical Center, and [3]Departments of Dermatology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan. *E-mail: makiyama@med.nagoya-u.ac.jp*

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Collodion babies are newborns encased in a glistening membrane that cracks in a characteristic manner within 48 h and desquamates in large lamellae after a few days. Most collodion babies later develop one of the several types of autosomal recessive congenital ichthyoses (ARCI), such as lamellar ichthyosis (LI) or congenital ichthyosiform erythroderma; however, about 10% heal spontaneously (1). This healing condition is known as "self-healing collodion baby" or "self-improving collodion baby" (SHCB/SICB). Raghunath et al. (1) showed that this phenotype is possibly a hydrostatic pressure-sensitive phenotype of *TGM1* mutations. The SHCB/SICB phenotype was subsequently reported in patients with *ALOX12B* and *ALOXE3* mutations (2). To date, few reports on SHCB/SICB cases with *TGM1* mutations have been published (1–4).

TGM1 is the most commonly involved gene in ARCI, and encodes transglutaminase-1 (TGase-1) (1, 5–8). Here, we describe an ARCI patient with a novel *TGM1* mutation who presented at birth with a collodion membrane but spontaneously healed within 2 months without any skin manifestations.

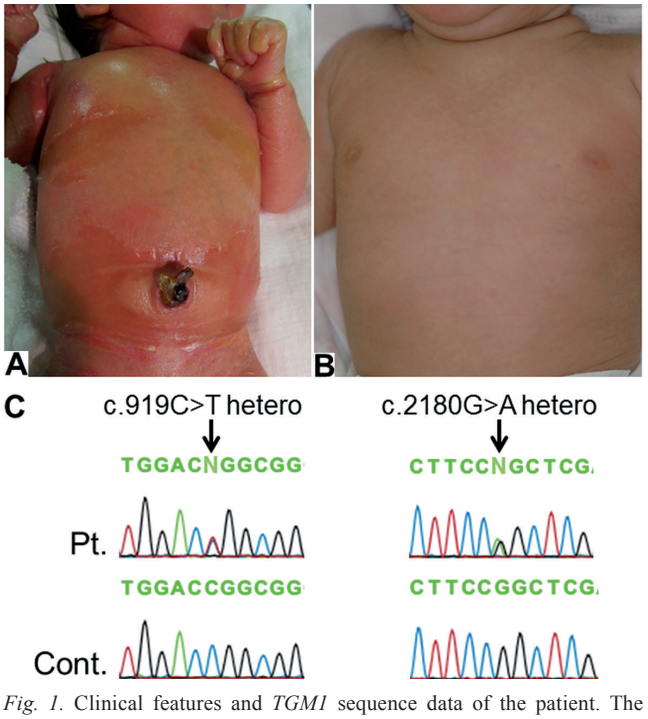

Fig. 1. Clinical features and *TGM1* sequence data of the patient. The patient showed collodion membrane at birth (A). The skin manifestations healed completely by the age of 2 months (B). (C) Sequence data of *TGM1* in the patient in exon 6 (left) and exon 14 (right). Arrows indicate c.919C>T (p.Arg307Trp) (heterozygous) and c.2180G>A (p.Arg727Gln) (heterozygous).

CASE REPORT

A Japanese girl born to nonconsanguineous parents at 40 weeks gestation presented at birth with a collodion membrane but without ectropion or eclabium. Her skin spontaneously healed by the age of 2 months (Fig. 1A and B). The ethics committee of Nagoya University Graduate School of Medicine approved the present studies. The participants gave written informed consent. The coding regions of *TGM1* (GenBank accession No. 359), *ALOX12B* and *ALOXE3* were amplified from genomic DNA by PCR, as described previously (9). Direct sequencing of the patient's PCR products revealed that the patient had the compound heterozygous *TGM1* mutations p.Arg307Trp (c.919C>T) and p.Arg727Gln (c.2180G>A) (Fig. 1C), but had no mutation in *ALOX12B* or *ALOXE3*. The former mutation, p.Arg307Trp, was previously reported as a founder mutation in Japanese LI cases by our group (10, 11). The arginine residue mutated in the other mutation, p.Arg727Gln, in the present case is in the β-barrel 2 domain of TGase-1 (Fig. 2B). This arginine residue was confirmed to be highly conserved in vertebrates. p.Arg727Gln was not detected in the 100 control alleles (Fig. 2A) (data not shown). p.Arg307Trp was present in the mother and p.Arg727Gln was demonstrated as paternal (data not shown). The patient was diagnosed as having SHCB/SICB with compound heterozygous *TGM1* mutations.

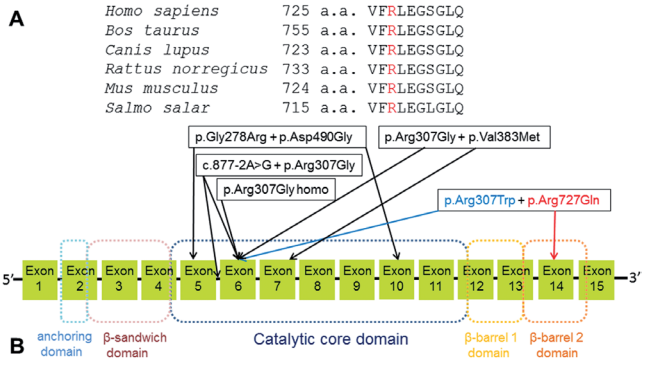

Fig. 2. Sequence alignments around the missense mutation and the summary of *TGM1* mutations in the SHCB/SICB phenotype. (A) The sequence alignment of TGase-1. Arg727 is in red. The leucine residue at codon 727 of human TGase-1 is conserved among the TGase-1 of diverse species. (B) The TGase-1 protein domain structure and *TGM1* mutations in SHCB in this study and in the literature. The present novel missense mutation p.Arg727Gln in the β-barrel domain is in red font. The other mutation in the present case, p.Arg307Trp, is in blue font. It has been reported to be a founder mutation in Japanese LI cases (10, 11).

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DISCUSSION

Previously reported SHCB/SICB cases with *TGM1* mutations had the homozygous mutation p.Arg307Gly, the compound heterozygous mutations p.Arg307Gly and c.877-2A>G, the compound heterozygous mutations p.Arg307Gly and p.Val383Met, or the compound heterozygous mutations p.Gly278Arg and p.Asp490Gly (1–4). Concerning the compound heterozygous mutations p.Gly278Arg and p.Asp490Gly, p.Asp490Gly is considered to be responsible for the SHCB/SICB phenotype because p.Gly278Arg is inactive under any conditions, but p.Asp490Gly has been proven inactive under high hydrostatic water pressure, such as in the uterus, and active under the lower-pressure conditions out of the uterus (1). In the compound heterozygous for p.Arg307Gly and c.877-2A>G, and the compound heterozygous for p.Arg307Gly and p.Val383Met, p.Arg307Gly possibly contributes to the SHCB/SICB phenotype, because the homozygous mutation p.Arg307Gly is known to cause the SHCB/SICB phenotype and c.877-2A>G is considered to bring a splicing error (not analysed in detail). In light of this, the mutations causing SHCB/SICB are limited to substitutions of the 2 residues p.Arg307 and p.Asp490 in the catalytic domains. In our report, one mutation was p.Arg307Trp, which is a founder mutation always associated with typical LI in the Japanese population (10, 11). We do not know the exact reason why p.Arg307Gly is associated with SHCB/SICB, but p.Arg307Trp is associated with typical LI. The difference in the side chain of the amino acid could explain the difference in the phenotype, i.e., tryptophan is the most voluminous amino acid, but glycine has a small side chain. Hence, we attribute the present case of SHCB/SICB to the novel mutation p.Arg727Gln in the β-barrel 2 domain. Several authors suggest that β-barrel domains, which are at the carboxyl-terminus of the gene, increase TGase-1 activity but are not essential for the function of the enzyme (12, 13). Arginine is a polar basic amino acid, but glutamine is a polar neutral amino acid. The reduction of charge in p.727Arg in β-barrel domains may affect the function of TGase-1 slightly. Thus, p.Arg727Gln may contribute to the disease onset and disease healing of SHCB/SICB. Mutations in the β-barrel 1 or β-barrel 2 domains have not been reported in SHCB/SICB. Even in typical LI, mutations in the β-barrel domains have been rarely found (14). Therefore, genotype-phenotype correlations related to the β-barrel domains in TGase-1 have not been determined (14).

In conclusion, we suggest for the first time that the missense mutation in the β-barrel 2 domain of the catalytic domains may cause SHCB/SICB.

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