Case Report

Deep Phenotyping of Superficial Epidermolytic Ichthyosis due to a Recurrent Mutation in KRT2

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Abstract: Superficial epidermolytic ichthyosis (SEI) is an autosomal dominant inherited ichthyosis. SEI is caused by mutations in KRT2 and frequently shows erythroderma and widespread blistering at birth. We report the clinical manifestations of two patients from a Japanese family with SEI caused by a hotspot mutation, p.Glu487Lys, in KRT2. In addition, we summarize previous reports on SEI patients with the identical mutation. One of the two patients had disease onset at the age of 7 months. The other patient’s age of onset is unknown, but it was in childhood. Neither of the two patients showed erythroderma. To perform deep phenotyping, we studied the age of onset and the frequency of erythroderma in 34 reported SEI cases with the p.Glu487Lys mutation, including the present cases. Among the cases with sufficient clinical information, 44.4% of the cases that were due to p.Glu487Lys in KRT2 occurred at birth. Erythroderma was observed in 11.1% of the cases with p.Glu487Lys in KRT2.

Keywords: genodermatosis; ichthyosis bullosa of Siemens; keratin 2; keratinopathic ichthyoses; superficial epidermolytic ichthyosis

1. Introduction

Superficial epidermolytic ichthyosis (SEI) is an autosomal dominant inherited skin disease caused by mutations in the keratin 2 gene (KRT2). It is characterized by mild epidermal hyperkeratosis of the extremities, very shallow blister formation and superficial denuded areas of the hyperkeratotic epidermis [1]. A large number of SEI patients have been reported to have causative mutations at the 487th glutamic acid in the helix termination motif of keratin 2. Thus, the glutamate is known to be a mutational hotspot [2]. In this article, we report a Japanese family with SEI caused by the recurrent mutation p.Glu487Lys in KRT2. Moreover, we describe clinical, histopathological, and molecular genetic findings in SEI patients in the family and provide a brief review of the literature on cases with the mutation p.Glu487Lys in KRT2.

2. Patients, Materials and Methods

2.1. Case History

2.1.1. Patient 1 (the Proband)

A 40-year-old man from an unrelated Japanese family (the proband in the pedigree, Figure S1) was referred to our dermatology clinic with a history of dry skin and blistering since childhood (specific age unknown). The blisters and erosions were seen until about
12 years of age but they rarely occurred after that age. Even in adulthood, the stratum corneum peeled off easily when tape was applied to the skin, but he was usually suffering from only mild dryness. It is unclear whether he had erythroderma at birth, but he was never aware of erythroderma. His parents and siblings had no similar skin disorders.

2.1.2. Patient 2

The 19-month-old son of the proband (Patient 1) (Figure S1) had a history of recurrent blisters and erosions of the skin since the age of 7 months. The frequency of the symptoms decreased with growth. No abnormalities in growth or development were noted. Patient 2’s mother and father (Patient 1) were unrelated and he had no siblings.

2.2. Histopathological Examination

A punch biopsy was taken from the skin of the anterior lower leg of Patient 1.

2.3. Genetic Testing

Genomic DNA from the peripheral blood mononuclear cells of Patient 1 was used for whole-exome sequencing analysis and Sanger sequencing analysis. Genomic DNA extracted from the saliva of Patient 2 was used for Sanger sequencing analysis. Whole-exome sequencing was conducted. The data were analyzed using Sequence Analysis Software (CLC Main Workbench, Filgen Incorporated, Japan). The transcript ENST00000309680.4 was used as a reference for KRT2. The KRT2 mutation identified by the whole-exome sequencing was verified by Sanger sequencing.

2.4. Literature Review

A literature review was conducted in PubMed (June 1986 to March 2022) using the terms “superficial epidermolytic ichthyosis” or “ichthyosis bullosa of Siemens”. Genetic forms, ages of onset, and presence/absence of erythroderma in SEI patients were examined. Although genotype–phenotype correlations in SEI have not been clarified [3], given the possibility of genotype–phenotype correlations, the present review only includes SEI patients with the KRT2 mutation p.Glu487Lys, identical to the mutation found in the present family.

3. Results

3.1. Clinical Presentations

3.1.1. Patient 1 (the Proband)

On physical examination, he presented with dark, hyperkeratotic skin with scaling on the elbows and the lower extremities (Figure 1A–C). No fresh blisters nor erosions were present.

3.1.2. Patient 2

Physical examination revealed light gray, hyperkeratotic skin at the joints of the extremities (Figure 1D). Superficial denuded areas were also observed where dressings had been applied (Figure 1E). No fresh blisters nor erosions were present.

3.2. Histopathological Examination

A skin biopsy specimen from the anterior lower leg of Patient 1 showed marked hyperkeratosis. Perinuclear vacuoles and basophilic, irregularly sized keratohyaline granules were present within the cytoplasm of keratinocytes from the upper spinous and granular layers of the epidermis (Figure 1F).
As far as we investigated, 20 families with the mutation p.Glu487Lys have been reported, and clinical information has been described in 34 cases, including the present patient.

### 3.2. Histopathological Examination

A skin biopsy specimen from the anterior lower leg of Patient 1 showed marked hyperkeratosis and granular degeneration restricted to the upper spinous and granular layers of the epidermis (scale bar: 50 μm). No other potentially pathogenic mutations were identified in KRT2, nor in any other gene associated with congenital ichthyoses. Subsequently, genomic DNA from the saliva of Patient 2 was used for Sanger sequencing, and the identical heterozygous missense mutation was identified in Patient 2.

### 3.3. Genetic Testing

Genomic DNA from the peripheral blood leucocytes of Patient 1 was used for whole-exome sequencing analysis. The data revealed a heterozygous missense mutation in KRT2, c.1459G>A (p.Glu487Lys), which was confirmed by Sanger sequencing (Figure 1G). No other potentially pathogenic mutations were identified in KRT2, nor in any other gene associated with congenital ichthyoses. Subsequently, genomic DNA from the saliva of Patient 2 was used for Sanger sequencing, and the identical heterozygous missense mutation was identified in Patient 2.

### 3.4. Literature Review

SEI was first reported by Siemens in 1937 as a mild form of epidermolytic ichthyosis. As far as we investigated, 20 families with the mutation p.Glu487Lys have been reported, and clinical information has been described in 34 cases, including the present ones (Table 1) [1,2,4–17]. Among them, the age of onset and the presence/absence of erythroderma were reported in 27 cases each. In total, 12 of these 27 cases (44.4%) had visible skin symptoms, such as erythroderma, hyperkeratosis, or blistering, when they were born. Three cases occurred at 1 month of age, four cases by 3 months of age, two cases at 4 months of age, two cases at 6 months of age, one case at 7 months of age, one case at 8 months of age, and two cases at 18 months of age. Erythroderma was observed in only 3 of the 27 cases (11.1%). Significantly, there was intrafamilial clinical heterogeneity in the affected family members.
Table 1. Review of published cases of superficial epidermolytic ichthyosis with the identical mutation p.Glu487Lys in KRT2.

| Family-Case No. | Age/Sex | Familial or Sporadic | Age at Onset | Erythroderma Present/Absent | Reference |
|-----------------|---------|----------------------|--------------|---------------------------|-----------|
| 1-1             | 10 yrs./female | familial | within a few months | absent | McLean et al., 1994 [4] |
| 2-1             | —/female | sporadic | — | absent | McLean et al., 1994 [4] |
| 3-1             | 26 yrs./male | familial | at birth | present | Rothnagel et al., 1994 [5] |
| 4-1             | 6 yrs./female | familial | at birth | absent | Rothnagel et al., 1994 [5]; Traupe et al., 1986 [6] |
| 4-2             | 31 yrs./male | familial (father of No. 4-1) | at birth | absent | Traupe et al., 1986 [6] |
| 5-1             | —/female | sporadic | at birth | present | Rothnagel et al., 1994 [5] |
| 6-1             | 32 yrs./female | familial | at birth | absent | Kremer et al., 1994 [7]; Vakilzadeh and Kolde, 1991 [8] |
| 6-2             | 31 yrs./male | familial (brother of No. 8-1) | at birth | absent | Kremer et al., 1994 [7]; Vakilzadeh and Kolde, 1991 [8] |
| 6-3             | 13 yrs./female | familial (daughter of No. 8-1) | at birth | absent | Kremer et al., 1994 [7]; Vakilzadeh and Kolde, 1991 [8] |
| 6-4             | 6 yrs./male | familial (son of No. 8-1) | at birth | absent | Kremer et al., 1994 [7]; Vakilzadeh and Kolde, 1991 [8] |
| 7-1             | —/male | familial | — | absent | Kremer et al., 1994 [7] |
| 7-2             | —/female | familial (daughter of No. 9-1) | — | absent | Kremer et al., 1994 [7] |
| 7-3             | —/male | familial (son of No. 9-1) | — | absent | Kremer et al., 1994 [7] |
| 7-4             | —/female | familial (daughter of No. 9-1) | — | absent | Kremer et al., 1994 [7] |
| 8-1             | 13 yrs./female | familial | 6 months | absent | Mills and Marks, 1993 [10] |
| 9-1             | 3 yrs./male | sporadic | 100 days | — | Yang et al., 1998 [11] |
| 10-1            | 1 yrs./female | familial | at birth | present | Basarab et al., 1999 [12] |
| 10-2            | 11 yrs./male | familial (cousin of No. 12-1) | 6 months | — | Basarab et al., 1999 [12] |
| 10-3            | 9 yrs./female | familial (cousin of No. 12-1) | 4 months | — | Basarab et al., 1999 [12] |
| 11-1            | —/male | familial | at birth | absent | Suga et al., 2000 [2] |
| 12-1            | 56 yrs./female | familial | 8 months | — | Akiyama et al., 2005 [1] |
| 12-2            | 28 yrs./male | familial (son of No. 14-1) | 3 months | — | Akiyama et al., 2005 [1] |
| 13-1            | 3 yrs./male | familial | 1 months | — | Akiyama et al., 2005 [1] |
| 14-1            | 6 yrs./male | familial | at birth | absent | Langan et al., 2010 [13] |
| 14-2            | 20 mo./male | familial (brother of No. 16-1) | at birth | absent | Langan et al., 2010 [13] |
| 15-1            | 2 yrs./male | familial | 3 months | — | Cervantes et al., 2013 [14] |
| 16-1            | 18 mo./female | sporadic | 1 month | absent | Gameiro et al., 2016 [15] |
| 17-1            | 5 yrs./male | sporadic | 40 days | absent | Li et al., 2020 [16] |
| 18-1            | 5 yrs./male | sporadic | 4 months | absent | Diociaiuti et al., 2020 [17] |
| 19-1            | 43 yrs./male | familial | — | absent | Diociaiuti et al., 2020 [17] |
| 19-2            | 7 yrs./male | familial (son of No. 21-1) | 18 months | absent | Diociaiuti et al., 2020 [17] |
| 19-3            | 7 yrs./male | familial (son of No. 21-1) | 18 months | absent | Diociaiuti et al., 2020 [17] |
| 20-1            | 40 yrs./male | familial | — | absent | The present report |
| 20-2            | 19 mo./male | familial (son of No. 22-1) | 7 months | absent | The present report |

Abbreviations: yrs., years old; mo., months old; —, not described.

4. Discussion

SEI was previously called ichthyosis bullosa of Siemens and was renamed to its current name at the First Ichthyosis Consensus Conference in Soreze in 2009 [18]. SEI presents clinical features similar to those of epidermolytic ichthyosis, but the clinical symptoms of SEI are milder, without hyperkeratosis of the palms and soles, and they generally improve with age [17].

SEI-causing gene mutations have been identified mostly in the helix initiation and termination motifs of KRT2. The mutations in these helix boundary motifs of keratins affect the assembly of an intermediate filament network more than the mutations occurring at other sites of keratin molecules, which impair the stability of the protein [2,5]. The present variant in KRT2 is predicted to be a disease-causing variant by computational (in silico) predictive programs [19–21]. The major epidermal keratins are keratins 9, 10, 14, and 16 for the type I class and keratins 1, 2, 5, and 6 for the type II class. The expression of each keratin is specific to locations and differentiation stages of epidermal keratinocytes [22]. In keratinocytes of the upper spinous to granular layers, KRT2 expression is upregulated. Thus, in SEI, histopathological findings are characterized by granular degeneration consistent
with the site of KRT2 expression [1]. Consistent with the findings, the skin of SEI patients is usually fragile and the outer layers of the epidermis have the tendency to peel off, producing localized superficial denuded areas. This characteristic clinical feature is called “the Mauserung phenomenon”, or molting [5]. Patient 2 had this symptom (Figure 1E).

SEI was first reported by Siemens in 1937, and the absence of erythroderma was proposed as part of the definition of SEI [23]. However, it has become clear that there are cases of SEI with erythroderma. Thus, at the conference in 2009, erythroderma was added to the list of initial symptoms of SEI [18]. Furthermore, the onset of SEI was considered to be usually at birth. However, no clear statistical data were reported. A search of “The Human Gene Mutation Database” revealed a missense mutation in the 487th glutamate in the helix termination motif of KRT2 to be the most frequently reported among diverse ethnicities and geographic areas, suggesting that the 487th glutamic acid is a mutational hotspot [24]. Thus, we performed deep phenotyping for the age of onset and the presence/absence of erythroderma in the reported SEI cases with the identical KRT2 mutation p.Glu487Lys.

The same genotype has been reported in 22 families, and clinical information has been described in 34 cases in 20 families, including the present patients (Table 1) [1,2,4–17]. Among them, the age of onset and the presence/absence of erythroderma have been reported in 27 cases each. In total, 12 of the 27 cases (44.4%) had the disease at birth. Three cases occurred at 1 month of age, four cases by 3 months of age, two cases at 4 months of age, two cases at 6 months of age, one case at 7 months of age, one case at 8 months of age, and two cases at 18 months of age. Erythroderma was observed in only 3 out of the 27 cases (11.1%) (Figure 2). Significantly, there was intrafamilial clinical heterogeneity in the affected family members. Generally, the number of cases with erythroderma in SEI is small and it was confirmed that the majority of patients with the recurrent KRT2 mutation p.Glu487Lys never showed erythroderma. Moreover, it was found that about half of the patients show the disease at birth and the other half after birth.

![Figure 2](image-url) The age of onset and the presence/absence of erythroderma in SEI patients with the KRT2 mutation p.Glu487Lys. Only the cases with clinical information are included in this figure.

5. Conclusions
Our findings indicate that it was assumed to be difficult to distinguish SEI from epidermolytic ichthyosis only from the presence/absence of erythroderma. When the possibility of epidermolytic ichthyosis cannot be excluded based on the patients’ clinical features, then genetic diagnosis of SEI is important for definite diagnosis and genetic counseling, including the prediction of symptoms and prognosis. We also demonstrated that children at a high risk of SEI from their family history, especially of SEI due to the KRT2 mutation p.Glu487Lys, should be carefully followed up until about 18 months of age, even if they have no symptoms immediately after birth.
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